Towards the further understanding of prognosis and outcomes for patients with high grade gliomas:

A randomized phase II study of Carboplatin and Bevacizumab in Recurrent Glioblastoma

(CABARET study)

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Abstract

Glioblastoma (GBM) is the most common, and the most aggressive, adult brain tumour, affecting over one thousand Australians per year. It carries a high mortality burden and a high social burden to both the cancer sufferer and their family. GBM recurs in nearly all patients within months of treatment, and median overall survival from diagnosis remains less than 18 months. At recurrence, no chemotherapy drug has been associated with reliable and meaningful gains in survival, and no new drugs have been added to the Australian Pharmaceutical Benefits Scheme for GBM since temozolomide over a decade ago. We need better treatments for this devastating disease.

Multiple trials have tested the role of targeted therapies – either alone or in addition to chemotherapy – in both the newly diagnosed and recurrent disease settings. Bevacizumab, a vascular endothelial growth factor inhibitor monoclonal antibody, showed promise in early and small clinical trials in recurrent GBM. We developed and conducted a multi-centre, stratified randomized phase II trial comparing bevacizumab monotherapy with bevacizumab + carboplatin chemotherapy in patients with recurrent GBM - the CABARET (Carboplatin And Bevacizumab in REcurrentT glioblastoma) clinical trial.

CABARET represents a substantial achievement in Australian medical research. This is the largest investigator-initiated brain tumour clinical trial in Australia to date. It was conceptualized, developed and conducted entirely within Australia. The primary objective of CABARET was to determine the effect of bevacizumab plus carboplatin versus bevacizumab monotherapy on progression-free survival in patients with recurrent GBM. The trial found that adding carboplatin to bevacizumab resulted in more toxicity without additional clinical benefit: no significant differences in response rate, progression-free or overall survival.

Several secondary and exploratory endpoints have been investigated. This was the first prospective study to assess the role of continuing bevacizumab beyond progression. Albeit with a limited sample size, no differences in survival outcome were noted after patients with progression on study underwent a second randomization to either continue or cease bevacizumab. We measured time to deterioration in health-related quality of life, finding no
difference between the two arms but noting that up to 50% of patients gained some improvements in relevant quality of life parameters while on treatment, suggesting benefit from treatment. We also assessed the role of early MRI after four weeks on study, finding this to be a robust indicator for overall survival in this patient cohort. Finally, we found that using centralized radiology review resulted in significantly earlier time to progression, but the absolute difference for the cohort of 0.3 months was not felt to be clinically relevant.

The study results have significantly improved knowledge regarding the use of bevacizumab in the setting of recurrent GBM. We successfully challenged and refuted the dogma, previously established from either retrospective studies or single arm early phase trials, that bevacizumab should be continued after progression or combined with chemotherapy in GBM. This will have significant impact on both future clinical trial design, and also managing patients with this disease, as we have further insight into anticipated effects and survival in the Australian context.
Declaration

(i) The thesis comprises only my original work towards the Doctor of Philosophy – Thesis with Publication, except where indicated in the preface;

(ii) Due acknowledgement has been made in the text to all other material used;

(iii) The thesis is fewer than the maximum word limit in length, exclusive of tables, maps, bibliographies and appendices
Preface

(i) Work towards the thesis that was carried out in collaboration with others:

Please refer to Table below
This clinical trial is the result of a collaborative effort from many, and with the help of the Co-operative Trials Group for Neuro-Oncology
For all chapters and published papers that form this PhD I have contributed to greater than 50% of the work towards that publication

(ii) Work towards the thesis that has been submitted for other qualifications:
None

(iii) Work towards the thesis that was carried out prior to enrolment in the degree:
   a. CABARET Clinical Trial Protocol (Appendix A)
   b. Oversight as CABARET Principal Investigator of trial conduct, monitoring of Adverse Events from November 2010 to December 2013 (commencement date for PhD)

(iv) Third party editorial assistance:
   No editorial assistance has been sought for the PhD thesis itself.
   Rhana Pike from the NH&MRC Clinical Trials Centre provided editorial assistance with each of the papers submitted – reviewing, cross-checking with journal guidelines for submission, assisting with word counts and ensuring tables, figures and references were submitted in the correct format for the journal each paper was submitted to.

(v) Contributions of all persons involved in any multi-authored publications included in the thesis
   Please refer to Table below

(vi) Acknowledgement of all sources of funding:
   a. Roche: This was an investigator-driven study funded by Roche Products Australia Pty Ltd
   b. Stella Mary Langford Scholarship, University of Melbourne – stipend
   c. NHMRC Clinical Trials Centre
   d. Watt-Geyer Award, Royal Melbourne Hospital – salary support
   e. RMH Research Medal, Royal Melbourne Hospital – salary support
   f. Nick Christopher Scholarship, Royal Melbourne Hospital – salary support
**Table 1: Collaborations and contributions to authorship**

<table>
<thead>
<tr>
<th>Name</th>
<th>Paper/Chapter</th>
<th>Description</th>
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| Trial Management Committee (TMC) | All papers                     | • Protocol development  
|                                |                                | • Overseeing Trial and Trial Conduct  
|                                |                                | • Editing manuscripts |
| Kate Sawkins                  | All papers, Trial conduct      | • Expertise in management  
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| Madeleine King                | HRQL* (Chapter 5)              | • HRQL expertise and guidance for statistical analysis plan  
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|                                |                                | • Editing manuscript drafts |
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|                                |                                | • Assistance with figures |
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*HRQL = health-related quality of life*
**Table 2: Trial Management Committee**

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Acknowledgements

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**Independent Data Safety Monitoring Committee** M Tattersall (Chair), P Kelly, A Hayden

**Clinical Trials Centre** K Sawkins, C Brown, E Barnes, A Livingstone, D Winter, B Tomes, R Pike, J Simes

**Table 3:** Study sites that participated in the CABARET study and randomized at least one patient

<table>
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CABARET Part 1 was reported at the American Society of Clinical Oncology Annual Meeting (2013); the Society for Neuro-Oncology Annual Meeting (2012); the Australian Cooperative Trials Group for Neuro-Oncology annual meetings (2012–2016); the European Association for
Neuro-Oncology and European Society of Medical Oncology annual meetings (2012). The results from CABARET Part 2 were presented at the American Society of Clinical Oncology Annual Meeting (2015).

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Chapter 1: Introduction and literature review

Glioblastoma (GBM)

Glioblastoma (GBM) is the most common adult malignant brain tumour with over 1000 Australians diagnosed with the disease every year. GBM accounts for 60-70% of adult malignant gliomas\(^1\) and is the most aggressive malignant glial tumour, carrying a high mortality burden as well as a high social burden to both cancer sufferer and carers.\(^2,3\) Further, GBM results in high costs for the healthcare system and the community.\(^4,5\) In fact, an Australian health economics report placed brain cancer as the highest cost of any cancer when considering the total expected lifetime economic cost per person.\(^6\) For those diagnosed with this disease, the median overall survival is approximately 15 months for patients suitable for post-surgery radiotherapy and chemotherapy.\(^7,8\) However, for patients who did not receive this treatment, a Victorian population data documented overall survival of only six to nine months.\(^8\)

For the most part, the aetiology of GBM is unknown and this is a sporadic disease. A small minority, less than 5%, are associated with a familial genetic syndrome such as Li-Fraumeni syndrome, Turcot syndrome or neurofibromatosis.\(^9\) High radiation exposure in childhood has been associated with an increased incidence of GBM.\(^10\) While reports exist of GBM being more common in industrialized and higher socio-economic countries, this observation is affected by the increased likelihood and availability of sophisticated investigation for symptoms in such countries compared with developing nations.\(^11\) GBM is more common in people over 50 years old, with the median age at diagnosis 64 years.\(^12\) GBM is rare in children, representing less than 10% of all CNS malignancies in the paediatric cohort.\(^13\) There is a slight male preponderance, and the disease seems more common in Caucasians compared with other ethnicities,\(^12\) although again diagnostic availability could bias this finding.

There are no screening tests available for GBM, with the exception of those individuals previously diagnosed with low grade glioma, for whom surveillance Magnetic Resonance Imaging (MRI) aims to detect recurrence and possible transformation to ‘secondary’ GBM. Typically, patients with GBM present to emergency departments with headache or first onset seizure, or are investigated for rapid onset of personality changes. Depending on the location of the tumour, other presenting symptoms may include visual field loss, speech, motor or
sensory deficits. Typically symptoms are present for only days or weeks prior to diagnosis. Patients with a radiological diagnosis of likely high grade glioma are referred emergently to centres with neurosurgical expertise, and surgery typically occurs within days of a radiological finding consistent with high grade glioma. This is both for diagnostic purposes (to obtain a histological diagnosis) and therapeutic purposes (to relieve increased intracranial pressure, and to obtain maximal surgical resection which is generally felt to be associated with a survival benefit).

**Pathology of GBM**

GBM is derived from malignant growth of astrocytes, star-shaped glial cells which form part of the structural and metabolic supportive environment for neurons within the central nervous system. The tumour is associated with typical histological features including high cellularity, microvascular proliferation and palisading necrosis. An infiltrative growth pattern into the surrounding healthy brain tissue is considered one of the hallmarks of GBM.14

GBM may be “primary” (arising de novo, in older patients, representing around 90% of all GBM) or the much less common “secondary GBM” (arising from a prior lower grade glioma). These express different molecular markers and, in general, secondary GBMs are associated with better prognosis.

**Molecular Characteristics**

Increasingly, the molecular characteristics of GBM are being elucidated. The Cancer Genome Atlas Research Network was developed to enable a comprehensive catalogue of genetic abnormalities across multiple cancer types including GBM.15 Patterns of gene abnormalities include EGFR amplification/mutation and PTEN mutations in de novo GBM,16-18 and isocitrate dehydrogenase-1 (IDH1) mutations and TP53 mutations in secondary GBMs.19-23 Other important genetic changes in malignant glioma include mutations of the alpha-thalassemia/mental retardation syndrome X-linked (ATRX) gene,24 methylation status of O6-methylguanine-DNA-methyltransferase (MGMT)25-27 and co-deletion of chromosomes Ip19q.28 Importantly, MGMT methylation status appears provide both prognostic and predictive information.25,26

Increasingly, the assessment of the genetic changes within the tumour influence treatment decisions, particularly as the 2016 WHO grading system for gliomas places more emphasis on molecular characteristics of gliomas rather than simply the histopathological grade.29 As an
example, patients with unmethylated tumours do poorly on standard treatment regimens, so an Australian clinical trial (VERTU) is examining a new treatment regimen in these patients. The range of gene alterations in GBM offer opportunity to develop new therapeutic agents. These include Epidermal Growth Factor Receptor (EGFR), a splice variant (EGFRv3), TP53, PTEN, Telomerase Reverse Transcriptase (TERT) and many others.

Management of newly diagnosed GBM
The treatment of GBM includes surgical resection, radiotherapy, chemotherapy and novel therapies with the optimal management of patients facilitated through a multidisciplinary approach. Treatment is determined by a number of factors including age, performance status, neurological status, location and extent of the cancer. For patients under the age of 70 years and of good performance status, ‘standard’ treatment incorporates surgery (maximum safe resection) followed by concurrent radiotherapy and temozolomide chemotherapy, followed by at least six months of post-irradiation temozolomide. This is based on the landmark EORTC/NCIC trial of Stupp et al, published in 2005, that demonstrated the addition of concurrent and adjuvant temozolomide to radiotherapy resulted in a significant improvement in overall survival against radiotherapy alone. However the median overall survival was only 14 months with two and five-year survival of 27% and 10% respectively. In the Australian context, comparisons between two retrospective cohort studies of patients diagnosed with GBM before and after the advent of the EORTC results documented a significant improvement in overall survival for patients treated as per the EORTC protocol, compared with those who received radiotherapy alone.

The EORTC treatment strategy was not formally tested in the Stupp et al trial for patients over the age of 70 years, who represent over 30% of all patients, and those of poor performance status. Thus, optimal treatment for elderly patients or younger patients with poor performance status has been less certain, as the therapeutic ratio between efficacy and toxicity is narrow. A randomized phase III trial for elderly patients, published in 2017, randomized 562 patients with newly diagnosed GBM over 65 years old to either short course radiotherapy alone (40Gy in 15 fractions), or short course radiotherapy plus concurrent and adjuvant temozolomide chemotherapy. The trial found in favour of the combination arm, with improved progression-free and overall survival, and acceptable toxicity parameters, without significant deterioration in quality of life when adding chemotherapy. This
represents a new standard of care when managing elderly patients considered suitable for active treatment of their GBM.

A number of International Phase III studies have assessed the benefit of adding additional therapies to the EORTC protocol for newly diagnosed GBM. Despite strong pre-clinical rationales and encouraging early trial data, drugs such as Cilengitide (an integrin inhibitor), Cediranib (pan-VEGF receptor tyrosine kinase inhibitor) and Bevacizumab (VEGF inhibitor) added no overall survival benefit to the standard EORTC protocol in newly diagnosed GBM.\textsuperscript{34-37} More recently, the NovoTTF (Tumour Treating Fields) medical device that delivers alternating electrical fields has shown overall survival benefit in newly diagnosed GBM (post initial chemoradiation) in a randomized phase III trial.\textsuperscript{38} Despite the lack of a placebo arm, the results were nevertheless compelling. In 695 randomized patients, median overall survival was 20.8 versus 16 months (HR 0.65, p=0.0006) and 2 year survival 43% versus 30% favouring the experimental arm.\textsuperscript{38} Based on these findings the United States National Comprehensive Cancer Network now includes NovoTTF among their recommended options for the management of newly diagnosed GBM.\textsuperscript{39} The treatment is not yet available in Australia and is extremely expensive to deliver.

**Recurrent GBM**

Relapse, disease progression and death is almost inevitable for patients with GBM. Usually recurrence is close to the site of the original tumour; less often elsewhere within the brain or ‘drop metastases’ to the spinal cord. Systemic metastases outside the central nervous system are exceedingly rare.\textsuperscript{40} The management of recurrent GBM mirrors the approach to newly diagnosed disease with surgery, radiation and chemotherapy considered on a case-by-case basis with no clinical trial data to guide decision making. With respect to systemic therapies for recurrent disease: chemotherapy, bevacizumab, and novel therapies including those accessible via clinical trials are all potential options in the setting of recurrent disease. Irrespective of treatment choices, the median survival for a patient with recurrent GBM is usually measured in months.\textsuperscript{41}

An Australian patterns of care study for patients diagnosed with GBM between 2006 and 2008 in Victoria, Australia, showed that close to 50% of patients have active treatment at first recurrence, and patients who received any treatment at progression had a significantly higher median overall survival than those who do not (7 versus 3 months, p<0.001).\textsuperscript{42} A variety of chemotherapy drugs were used by clinicians over this time period, including temozolomide, carmustine, carboplatin and etoposide.
Systemic therapies for recurrent GBM

Treatment with chemotherapy at relapse aims to prolong progression-free and overall survival, reduce morbidity, and restore or preserve neurological function and quality of life. The efficacy of chemotherapy for GBM is limited by the blood-brain barrier, which restricts the entry of many drugs to the site of the malignancy. As such, there is a paucity of agents available for use in GBM. For those patients with recurrent disease, arguably no chemotherapy regimen has provided reliable substantive clinical benefit. Commonly used chemotherapy agents include nitrosoureas (CCNU/BCNU), temozolomide, and carboplatin. Phase II data provides some support for each of these approaches.\textsuperscript{43,44} A summary by Wong et al 1999, suggested the six month PFS was approximately 15% and response rate only around 5% for chemotherapy in the setting of recurrent disease.\textsuperscript{45} This is often the historical standard by which newer agents are compared to in early phases of drug development.

Carboplatin, the chemotherapy drug selected for use in the CABARET clinical trial, is a platinum analogue that works by causing inter- and intra-strand cross-links in DNA, inhibiting DNA synthesis. Carboplatin has been studied in the phase II setting for recurrent GBM in small numbers of patients.\textsuperscript{46,47} Response rates in this setting are around 14%. It is generally well tolerated and is a reasonable second line chemotherapy choice for patients with GBM whose disease is refractory to temozolomide. In addition, the drug can be given over long periods of time (assuming response/stable disease/clinical benefit), unlike nitrosoureas that are limited by progressive bone marrow toxicity. At the time of the CABARET trial design, many Australian oncologists routinely used carboplatin in this second-line setting.\textsuperscript{48} Lomustine, a commonly used alternative second-line agent in this context, was not readily available in Australia at the time and is not on the Australian Pharmaceutical Benefits Scheme.

In addition to, or in place of chemotherapy, multiple pathways have been targeted in targeted therapy clinical trials for GBM including: EGFR, VEGF and its receptor, integrins, PDGFR, PI3K/AKT/mTOR inhibitors, RAS/RAF/<AP-kinase inhibitors, and HDAC inhibitors.

Most of these drugs have ceased investigation for GBM due to futility or toxicity; or remain in phase I/II trial stages of development.

More recent experimental therapeutics include:
• Dendritic cell (DC) vaccines
• Rindopepimut, a peptide vaccine containing EGFR vIII peptide conjugated with keyhole limpet hemocyanin (KLH) (Phase III study ceased early due to lack of efficacy)\textsuperscript{49}
• EGFR targeted therapy: ABT-414 antibody-drug conjugate (Phase III trial is underway)
• NovoTTF (Tumor Treating Fields)\textsuperscript{38}
• Immune checkpoint inhibitors

Bevacizumab

Anti-angiogenic therapy for GBM has been under investigation for several years, as GBM is a highly vascular tumour and a pre-clinical rationale exists for the use of anti-angiogenic agents. Bevacizumab (Avastin\textsuperscript{®}) is a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF) by binding to and neutralizing it. Bevacizumab is administered intravenously, with a half-life of approximately 20 days. Its mechanism of action in GBM is poorly understood. It is postulated that by vascular normalization and reduction of tumour interstitial pressure, bevacizumab enhances the delivery of chemotherapy\textsuperscript{1,50}; direct antitumour activity by its anti-VEGF activity is also possible.\textsuperscript{51} Unlike other tumour types, bevacizumab seems to have some activity as monotherapy in GBM, indicating anti-cancer activity beyond simply as an adjunct to chemotherapy by enhancing drug delivery.

Bevacizumab has been used in several other tumour types since 2004, but its investigation and development for patients with brain tumours occurred later. There were concerns about its use in GBM patients because of the known side-effect of bleeding and, in particular, central nervous system haemorrhage. As such, early clinical trials for other solid organ tumours excluded patients with untreated CNS disease.

However, GBM, being a highly vascular tumour with high levels of expression of VEGF, was recognized to be an ideal target for anti-angiogenic drugs such as bevacizumab. It is known that microvessel density and the amount of VEGF expression is correlated with the level of aggressiveness in malignant gliomas and is a prognostic factor.\textsuperscript{52-54} As such, the angiogenesis pathway has been thought to be a good target for therapy against GBM.

To date, no validated predictive biomarker for bevacizumab has been elucidated in any tumor type although some promising signals have been identified. Many potential markers have been
Bevacizumab in recurrent GBM

Reports of dramatic radiologic responses and clinical benefit began to surface in the mid-2000s. Promising results from single-arm, non-comparative Phase II studies were reported in the recurrent disease setting with improvement in response rates and 6-month progression-free survival (PFS) compared with historical controls. The pivotal AVF3708g/"BRAIN" study of Friedman et al followed: a randomized, non-controlled phase II study evaluating the activity of bevacizumab monotherapy and bevacizumab plus irinotecan, reporting a 42.6% and 50.3% 6 month PFS respectively. Kreisl et al, during the same time period, published another non-comparative trial, without a non-bevacizumab comparator arm, reporting favourable outcomes with bevacizumab. In retrospect, these early results were likely confounded by the phenomenon of "pseudo-response". Bevacizumab is known to decrease contrast enhancing disease on MRI, due to its anti-angiogenic effect, hence decreasing perfusion and the appearance of contrast on MRI sequencing. Nevertheless, on the basis of these studies, the US Food and Drug Administration (FDA), as well as the Australian Therapeutic Goods Administration (TGA) approved the use of bevacizumab in recurrent GBM on the basis of these studies that, collectively, documented partial responses in up to 26% and a six month PFS of 36%.

Bevacizumab remains a commonly used second-line agent for recurrent GBM. It improves progression-free survival compared with historical controls, and although it has not been shown to improve overall survival in any phase III clinical trial, at least some patients derive durable benefits from the drug. In Australia bevacizumab is approved by the Therapeutic Goods Administration (TGA) as monotherapy for recurrent GBM. It is not, however, approved by the Australian Pharmaceutical Benefits Scheme and results in considerable out-of-pocket patient cost (approximately $20,000 AUD for a 12-week course).

Bevacizumab in newly diagnosed GBM

Given the initial data in recurrent GBM, Investigators were encouraged to test Bevacizumab in the de novo setting. Two pivotal studies demonstrated that the addition of bevacizumab to the standard EORTC protocol for de novo GBM resulted in no discernable benefit. These two large-
scale first-line randomized phase III studies – AVAglio and RTOG 0825 - represent significant achievements in terms of size, accrual and conduct.\textsuperscript{36,59}

The AVAglio trial (n=961) met its predefined progression-free survival (PFS) endpoint, with a median PFS of 10.6 versus 6.2 months, [HR 0.64, 95%CI (0.55-0.74) p<0.0001], but not the overall survival (OS) co-primary endpoint.\textsuperscript{36} The median overall survival between arms was 16.8 versus 16.7 months [HR 0.88, 95% CI (0.76-1.02), p=0.0987]). Although crossover on progression was not permitted on AVAglio, it is estimated that up to 30% of participants not randomized to receive bevacizumab ultimately did receive the drug on progression, thus potentially distorting any potential OS benefits.

While the trial protocol was slightly different from AVAglio, including crossover being permitted, the RTOG 0825 study (n=637 randomized) had similar co-primary endpoints of PFS and OS.\textsuperscript{59} Although PFS was longer for the bevacizumab arm (10.7 versus 7.3 months, p=0.004), this did not meet the predefined PFS significance level of 0.002. Similar to the AVAglio study, no difference in OS was seen between arms (median OS 15.7 versus 16.1 months, p=0.11). The authors also noted increased risks of grade 3 or more toxicity in the bevacizumab arm, including neutropenia, hypertension and venous thromboembolic events.

Several other, smaller, prospective clinical trials have been reported in newly diagnosed GBM. The GLARIUS trial randomized 182 patients with unmethylated MGMT to standard treatment with temozolomide versus bevacizumab with radiotherapy, then bevacizumab + irinotecan.\textsuperscript{60} While 6-month PFS was significantly improved (42.6% versus 79.3%), there were no differences in OS, although crossover was given to 82% of patients who had not initially received bevacizumab, likely diluting any potential overall survival difference. Given the lack of OS benefit observed in the above studies, bevacizumab is not recommended in the setting of newly diagnosed GBM.

Table 1 outlines the prospective clinical trials that existed at the time of the CABARET trial concept and development. Subsequent trials including the BELOB study and the EORTC 26101 trial have further informed the use of bevacizumab in recurrent disease; however these were reported after CABARET and will be discussed in the conclusion section of this thesis. The table is notable for the lack of robust data supporting the use of bevacizumab in this context: No randomized comparative studies had been conducted; sample sizes for each trial were small; and the earlier trials used MacDonald criteria, failing to appreciate the significance of T2/FLAIR signal change as representing disease progression.
**Table 1:** Prospective phase II/III clinical trials of bevacizumab in recurrent GBM to 2010 (contemporary at the time of CABARET trial design)

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Trial design</th>
<th>Treatment</th>
<th>Patients (n)</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR (%)</td>
<td>6m PFS (%)</td>
</tr>
<tr>
<td>Vredenburgh, 2007</td>
<td>Phase II</td>
<td>Bev + Irinotecan</td>
<td>35</td>
<td>57%</td>
</tr>
<tr>
<td>Kreisl, 2009</td>
<td>Phase II</td>
<td>Bev then Bev + Irinotecan</td>
<td>48</td>
<td>35%</td>
</tr>
<tr>
<td>Friedman, 2009</td>
<td>Phase II</td>
<td>Bev or Bev + Irinotecan</td>
<td>167</td>
<td>28%</td>
</tr>
<tr>
<td>Raizer, 2010</td>
<td>Phase II</td>
<td>Bev monotherapy</td>
<td>50</td>
<td>25%</td>
</tr>
</tbody>
</table>

*Bev = bevacizumab; RR = Response Rate; PFS = Progression-Free Survival; OS = Overall Survival*
MRI assessment of GBM

An increased understanding of imaging features and the nature of progression of GBM has resulted in better appreciation of the indistinct, infiltrative nature of disease progression of this malignancy. This, coupled with the advent of targeted therapies including those which affect vascular permeability and thus radiographic contrast delivery to the tumour site, has resulted in the need for more sophisticated radiological imaging criteria for disease assessment.

The MacDonald criteria were traditionally used for disease assessment in clinical trials and routine clinical practice. These were developed nearly 25 years ago, in 1990, and were a step forward in neuro-oncology imaging at the time, with the ability to take into consideration steroid dosing and the patient’s neurological status into disease assessment; and requiring confirmation of response on serial imaging; thus improving the scientific rigour of determining response to therapies.

The Response Assessment in Neuro-Oncology (RANO) criteria have been developed to incorporate changes in T2/FLAIR (Fluid Attenuated Inversion Recovery) seen characteristically as part of the infiltrative nature of GBM. These changes can occur in the absence of changes in contrast enhancing disease and thus represent an aspect of tumour progression that would not be accounted for by MacDonald criteria. Additionally, given the possible effect of anti-angiogenic therapies such as bevacizumab on reducing vascular permeability and thus contrast enhancement, using MacDonald criteria alone may not suffice in adequately assessing response to, or progression on, anti-angiogenic therapies.

As the RANO criteria are relatively new, validation of their use and applicability remains ongoing. A retrospective comparison of RANO and MacDonald methods of assessment in patients who participated in the BRAIN trial (AVF3708g) found that using RANO resulted in a small but statistically significant lowering of median progression-free survival (PFS) and response rates. Both MacDonald and RANO-assessed response and PFS significantly correlated with overall survival, suggesting that these endpoints measured as per either criteria may be able to be used as surrogate endpoints for overall survival.

CABARET was one of the first prospective clinical trials world-wide to formally incorporate RANO criteria into assessment of disease.

Imaging biomarkers include enhancing tumor volume measurements, relative cerebral blood volume variation, perfusion maps, and contrast-enhanced T1-weighted subtraction maps. These are all potential methods to enhance MRI interpretation of tumor that show promise in
improving accuracy of response assessment and potentially use as predictors of response to bevacizumab.

**Quality of life testing in GBM**

In the setting of incurable disease, health-related quality of life (HRQL) is a key endpoint in clinical trials, in order to ensure that palliative-intent treatment is not increasing morbidity.

HRQL has been a recent contentious issue when considering bevacizumab in the field of GBM. The two large scale randomized phase III studies in patients with newly diagnosed GBM, reported conflicting HRQL outcomes for patients receiving bevacizumab. The AVAglio study reported improved time to deterioration of HRQL in bevacizumab-treated patients, whereas the RTOG 0825 trial conversely reported that bevacizumab-treated patients had worse HRQL outcomes. There has been much discussion surrounding these conflicting results; the different statistical methodology between studies is thought to be one of the reasons for the discrepant findings. The issue of whether or not bevacizumab may benefit or worsen HRQL is an important one in light of now more modest effects on PFS in recent studies than previously reported, and more uncertainty in the recurrent disease setting as to the overall survival benefits of the drug. As such, any beneficial or detrimental effects of bevacizumab on HRQL become a critical aspect of determining the merit of the drug in this setting.
Chapter 2: Methods

CABARET – Rationale and its beginnings

CABARET is Australia’s largest investigator-initiated trial in central nervous system oncology. It was designed in 2010 at a time when there were no prospective comparative randomized trials for bevacizumab in recurrent GBM. It was the first trial to compare bevacizumab monotherapy with combination therapy, and has received intense international attention.

It is important to understand the role of bevacizumab and data that existed at the time of the CABARET trial design. Figure 1 shows a historical timeline of bevacizumab development in GBM and Figure 2 shows the increase in abstracts and manuscripts related to bevacizumab and GBM over this time frame. At the time of design of the CABARET clinical trial, there were no prospective clinical trials or data reporting the efficacy of bevacizumab when compared with chemotherapy; and there had been no formal comparisons between bevacizumab monotherapy and bevacizumab plus chemotherapy.

Bevacizumab was (and is) available for patients with recurrent GBM in Australia, for use as monotherapy. However, although TGA approved, the drug was (and is) not PBS approved, and via Roche’s access program is available to patients at a cost of approximately $20,000 for the first 12 weeks of therapy. If patients are responding or stable at this point, the remainder of their treatment until disease progression is provided at no additional cost. However, this is understandably a large and unattainable cost for many.

In early 2010, recognizing an opportunity, a group of lead neuro-oncology clinicians from Australia under the auspices of the Co-Operative Trials Group for Neuro-Oncology (COGNO), met with Roche Australia to discuss the potential for a funded investigator-initiated randomized clinical trial in recurrent GBM. This group later became the Trial Management Committee (TMC), with COGNO as the trial’s sponsor and providing statistician support. I was invited to be part of this initial development of the trial and to take the role of Study Chair. Initial meetings surrounded trial design and endpoints of interest.
Initially a three-arm randomized phase II trial was proposed, comparing bevacizumab monotherapy, carboplatin monotherapy, or the combination. Testing the combination compared with either monotherapy arm was proposed in order to determine whether an additive or synergistic effect was present. This has subsequently been the subject of a later European trial BELOB; see discussion section, Chapter 9, for detail.

Ultimately a decision was made to proceed with a two-arm trial (bevacizumab versus bevacizumab plus carboplatin chemotherapy). The trial was designed to address two crucial aspects of the use of bevacizumab that had arisen largely from single-arm trials or retrospective single-centre studies. Firstly, no prospective randomized data comparing bevacizumab monotherapy with bevacizumab plus chemotherapy existed. Secondly, despite the paucity of evidence, it had become common to continue using bevacizumab beyond disease progression, supported entirely by small retrospective studies that seemed to suggest accelerated disease progression if the drug was stopped. It is remarkable that this dogmatic approach has arisen in the context of modern-day medicine without any prospective clinical data to suggest that there is an issue.

CABARET provided 122 Australians access to a drug that would have otherwise been prohibitively expensive. While the aim of the trial was to answer valid, important and novel clinical research questions, the access to the drug and the opportunity to participate in a clinical trial was also felt to be of value to the neuro-oncology patient population.

The trial progressed from early discussion, through protocol writing and revision, to first patient randomized in approximately eleven months, which represents a substantial effort by many involved in the process. CABARET then recruited all 122 patients over a 14-month time period, many months ahead of schedule.
### Figure 1: Timeline of bevacizumab development in GBM

<table>
<thead>
<tr>
<th>Year</th>
<th>Key Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980s</td>
<td>Vascular endothelial growth factor (VEGF) discovered</td>
</tr>
</tbody>
</table>
| 1997 | • Bevacizumab (humanized version of anti-VEGF monoclonal antibody) produced  
      • First Phase I clinical trials commenced |
| 2004 | Bevacizumab first approved for metastatic colorectal cancer |
| 2005 | Bevacizumab activity in recurrent GBM reported in retrospective series. Dramatic responses seen (Stark-Vance, Neuro-oncology 2005) |
| 2007 | First Phase II trial of bevacizumab in recurrent GBM published (Vredenburgh et al). PFS benefit compared with historical data |
| 2009 | • Pivotal recurrent GBM randomized Phase II study published (AVF3708G/BRAIN study, Friedman et al). PFS benefit compared with historical data  
      • US FDA accelerated approval for recurrent GBM  
      • TGA approval in Australia for bevacizumab monotherapy in recurrent GBM |
| 2010-2012 | • CABARET clinical trial concept development, protocol drafting and finalization, first patient randomized to Part 1 November 2010  
           • Last patient randomized to Part 1 March 2012 |
| 2013 | • Randomized Phase III first-line bevacizumab studies (AvaGlio and RTOG 0825) reported. Both show benefit in PFS; neither shows OS increment  
      • 1st line bevacizumab in GBM no longer recommended (outside of clinical trial)  
      • CABARET clinical trial ongoing |
| 2014-2015 | • BELOB randomized phase II study in recurrent GBM indicated OS benefit for bevacizumab + lomustine combination over either monotherapy arm  
           • Formal CABARET study closure December 2014 |
**Figure 2:** Graphs showing number of abstracts and publications related to bevacizumab and GBM: American Society of Clinical Oncology (ASCO) annual meeting and PubMed searches

Red arrow indicates CABARET trial protocol writing and commencement period
Unanswered questions relevant to trial design

The trial was designed to provide access to, and answer several research questions related to the use of bevacizumab in recurrent GBM. These included:

- Whether bevacizumab in combination with carboplatin chemotherapy provided any additional benefit compared with bevacizumab monotherapy (Chapter 3).
- Whether continuing bevacizumab beyond disease progression in GBM provided any additional benefit to patients compared with ceasing the drug at progression (Chapter 4).
- The effect of bevacizumab on quality of life (chapter 5) and neurocognitive function.
- Whether early MRI (at 4 weeks post commencement of treatment) was predictive for outcome and could help determine likelihood of benefit from bevacizumab therapy (chapter 6).
- Comparing central radiology review with site-based radiology review to determine whether significant differences in response rates and progression-free survival were obtained when comparing the two, using RANO criteria (chapter 7).

Primary aim of the CABARET study

Our primary aim was to determine the effect of the combination of bevacizumab plus carboplatin versus bevacizumab alone on progression-free survival in patients with recurrent GBM. (Chapter 3)

We tested whether bevacizumab plus chemotherapy resulted in any difference in efficacy (measured by response rate, progression-free and overall survival) when compared with monotherapy. In other tumour types such as colorectal cancer where bevacizumab is now part of standard therapy, prior trials have indicated that bevacizumab monotherapy has no role and it is only when used in combination with chemotherapy that additional efficacy is seen. This relates back to the theory that a major effect of bevacizumab is to ‘normalize’ tumour vasculature and hence enhance delivery of chemotherapy to tumour cells. Secondly, in the ‘BRAIN’ randomized non-comparative study of bevacizumab versus bevacizumab plus irinotecan, PFS was 43% (monotherapy) and 50% (combination) and response rates 28% (monotherapy) and 38% (combination). While not formally compared statistically, this was a potential signal that combination therapy may provide an advantage in GBM. Thus, there was good rationale to test this in a formalized comparative clinical trial, and CABARET was the first study worldwide to do this.
Secondary and exploratory endpoints

**Whether continuing bevacizumab beyond disease progression in GBM provided any additional benefit to patients compared with ceasing the drug at progression (Chapter 4)**

Despite no prospective data supporting this practice in recurrent GBM had existed prior to CABARET, continuing bevacizumab beyond progression was a relatively common practice at the time. This was based largely on data from other tumour types including colorectal cancer, where bevacizumab beyond progression has been associated with survival advantages; and partly on retrospective series. The use of bevacizumab beyond progression in GBM had never been prospectively tested prior to the CABARET study.

**The effect of bevacizumab on quality of life (QOL) (Chapter 5)**

Without a chemotherapy-only comparator arm we were unable to determine whether bevacizumab results in improved or stable QOL compared with chemotherapy alone. Nevertheless, the QOL analysis for patients with recurrent GBM on bevacizumab is important especially in the context of the conflicting reports from the two large first-line (newly diagnosed GBM) bevacizumab studies, where one reported maintenance of QOL while on bevacizumab but the other reported the reverse.

**The utility of an early (4-week) MRI to predict outcomes (Chapter 6)**

Our hypothesis was that a 4-week MRI would correlate well with the ‘standard’ (8 week) MRI result, and would reliably predict survival outcome. This is important in that currently patients need to pay for bevacizumab therapy for recurrent GBM in Australia. If a reliable early radiological finding could accurately predict the likelihood of durable benefit from the drug, it would be useful in order to avoid unnecessary cost and toxicity in patients who are unlikely to derive clinical benefit. Such a study had never been prospectively conducted.

**The use of the new Response Assessment in Neuro-Oncology (RANO) criteria in a prospective clinical trial setting, comparing site and central radiological review (Chapter 7)**

We hypothesized that using RANO would result in a shorter PFS time than historical PFS data for bevacizumab in recurrent GBM. This was because RANO criteria take into consideration the T2/FLAIR (Fluid attenuated Inversion Recovery) appearance of MRI scans. Increases in T2/FLAIR signal abnormality are classified as recurrent disease by RANO criteria but are not measured
using Macdonald criteria. This may be one reason why the older studies of bevacizumab, using Macdonald criteria, reported significantly improved PFS times without translating to OS benefit. Bevacizumab is known to decrease contrast enhancement, termed ‘pseudoresponse’.9

We also hypothesized that the central radiological review date of progression may precede the site’s determination of disease progression, based on neuroradiological expertise and precision at determining disease progression.

**Additional endpoints of the CABARET trial**

The following endpoints are currently under analysis but are ongoing, and the results do not form part of this Thesis.

*The utility of CogState neurocognitive testing in patients with recurrent GBM*

CogState ClinicalTrials® is a range of computerised cognitive tasks able to measure baseline and change in all cognitive domains. The CogState testing method has been validated in peer-reviewed journals10 and has been used extensively in phase I to IV trials with both healthy volunteers and patient groups, including dementia studies and studies of drug effects. It is sensitive to changes over time and is reproducible. At the time of trial design it had not been used in brain tumour clinical trials for monitoring of neurocognitive function. In this first prospective neuro-oncology trial to use CogState, we aimed to determine the potential utility in this setting by measuring completion/participation rates, as well as conduct exploratory comparisons between randomized arms for time to deterioration in neurocognitive function, together with a comparison between CogState and mini-mental state examination (MMSE).

*Prognostic and/or predictive biomarkers in the setting of bevacizumab for glioblastoma.*

To date, there are no validated predictive biomarkers for bevacizumab response in any tumour type.11,12 There are several promising biomarkers and in the small percentage of people who have a sustained response to bevacizumab, it would be ideal to identify a predictive biomarker. Both blood and tissue biomarkers were evaluated by senior scientific investigators as a component of the CABARET trial.

The biomarker tissue and blood sub-studies were conducted by experienced scientists with expertise in brain tumour basic research, and I have not been directly involved with any of the
laboratory work related to these sub-studies. I was involved in protocol and informed consent writing, and helping to secure funding for the biomarker sub-studies. However, they do not form part of this PhD Thesis.

While COGNO facilitated most of the discussion and paperwork regarding funding, intellectual property, ethics and governance, an additional face-to-face meeting in the United States between Roche Global, myself, and several other TMC members, was required to discuss and facilitate funding of the biomarker component of the study. Two lead Australian scientists were involved in the design of the biomarker tissue and serum analysis plans. Ultimately the trial commenced prior to formal biomarker agreements were in place; so the biomarker component of the trial commenced after approximately 50% of patients had already been randomized, limiting the number of samples that could be obtained.

**CABARET design and accrual**

CABARET was a randomized two part, two-arm, non-blinded non-placebo-controlled multicentre phase II study, conducted at 18 sites around Australia. The trial was designed and revised during 2010; the first patient was recruited in November 2010, and all 122 patients were enrolled by April 2012. The trial was formally closed in December 2014 with two patients still receiving Part 1 treatment; they continued to receive bevacizumab with compassionate access beyond the time of study closure with no progression (as determined by the sites) at the time of study closure.

**Figure 3:** Recruitment timeline, CABARET study
Choice of anti-cancer agents

Bevacizumab was known to have activity in patients with GBM and had been shown to have efficacy both as a single agent and in combination with chemotherapy. Given the results of the Vredenburgh trial of bevacizumab +/- irinotecan\textsuperscript{13}, and the Kreisl phase II study of single agent bevacizumab with irinotecan at progression\textsuperscript{14} demonstrating efficacy of bevacizumab as a single agent, it was felt acceptable to randomise patients to receive bevacizumab as a single agent in this setting. We postulated that the combination of bevacizumab with carboplatin may add clinical benefit. Prior animal model research had demonstrated that the combination of carboplatin and bevacizumab was superior for survival and asymptomatic tumour volume over bevacizumab or carboplatin monotherapy\textsuperscript{15}.

Bevacizumab at a dose of 10 mg/kg every two weeks was chosen for development in malignant gliomas, because:

- This is the approved dose according to the Australian Product Information.
- Clinical studies in the setting of relapsed GBM have been performed with a dose of 10 mg/kg, two-weekly bevacizumab and demonstrated clinical activity and acceptable safety\textsuperscript{13}.
- The two-weekly schedule was convenient considering that carboplatin was dosed every four weeks for patients who were randomized to receive the combination.

Summary of work on trial design, development and data analysis

This trial has been a collaborative effort and would not have occurred without the assistance of members of the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, the Co-operative Trials Group for Neuro-Oncology (COGNO), and the Trial Management Committee (TMC). Figure 4 summarizes the steps involved in the development and conduct of the trial.
**Figure 4:** Summary of steps in the development and management of the CABARET clinical trial

- **Development**
  - Trial concept and design
  - Protocol and PICF writing, editing, revision
  - CRF development
  - Trial site selection

- **Conduct**
  - Study Chair and Principal Investigator
  - Trial recruitment
  - Decisions re eligibility
  - Review of SAEs and world toxicity data
  - Decisions re continuing or stopping treatment
  - Logistics of trial closure

- **Analysis**
  - Checking and categorizing adverse events
  - Determining central versus site dates of radiological progression
  - Statistical analysis plans
  - Review and interpretation of all data analysis
  - Paper writing and editing

**PICF** = patient information and consent form

**CRF** = Case Report Form
i. **Trial concept and design**

I was involved from the outset in trial concept and design, together with members of the TMC and COGNO. As a result of several face to face meetings and email as well as teleconference communication, the trial concept and design was established in early 2010. I was nominated as the Study Chair and Principal Investigator for the trial. I also attended a meeting in the USA with Roche global executives in June 2010 to help move the biomarker component of the study forward.

ii. **Protocol and Patient information and consent form (PICF) writing**

In the first half of 2010 I wrote and revised the CABARET protocol and PICFs for Part 1 and 2 of the study, as well as the PICFs for the optional biomarker component of the study. These were revised several times with the assistance of the trial’s sponsor, COGNO under the auspices of the NHMRC Clinical Trials Centre. TMC members also assisted with protocol drafting and revision but ultimately as the Study Chair I was principally responsible.

iii. **Trial site selection**

Together with COGNO staff, I was responsible for selection of Australian sites to participate in the trial. This was determined by track record and ability to recruit adequate numbers of patients; adequate resources; and also consideration given to ensuring that patients from many parts of Australia would be able to participate.

iv. **Trial recruitment**

Within Royal Melbourne Hospital, one of the 18 participating sites, I was the site Principal Investigator and responsible for recruitment of participants as well as oversight of the trial progress at Royal Melbourne Hospital.

v. **Trial oversight**

I was responsible for oversight of the trial at all participating centres. This included:
• Making decisions regarding eligibility criteria and addressing queries from sites about this.
• Reviewing serious adverse events (SAE) within a 24 hour time frame and attributing cause (drug-related or not drug-related).
• Regular review of world-wide toxicity data about bevacizumab from other clinical trials, in order to determine whether the CABARET trial was directly affected by emerging safety data.
• Decisions regarding continuing/stopping treatment in ambiguous situations
• Helping to navigate the logistics of trial closure.
• Up to 30 days after the last study drug dose on 5th December 2014, I was responsible for monitoring all safety issues and serious adverse events.

vii. Communication
Regular communication was required as part of the running of this clinical trial. This included communication with:
• The TMC, via regular teleconferences and emails.
• Other investigators: Trial progress and updates were communicated by emails and sometimes by telephone conversations for any challenging issues.
• The oncology community: Trial progress was reported at several national and international conferences including the COGNO annual meetings; Society for Neuro-Oncology and American Society of Clinical Oncology annual meetings.
• The pharmaceutical company (Roche Australia) regarding trial progress, and discussions re timing of closure. Initially there was also extensive discussion about a biomarker component of the study that was to enable samples being sent to the Roche Clinical Repository in Europe; however, this component of the trial ultimately did not proceed.

vii. Data analysis
My role in data analysis included:
• Design of case report forms (CRFs) to ensure appropriate and analyzable data collection occurred during the conduct of the trial.
• Formulating a priori statistical analysis plans for each of the sub-studies, and working with statisticians to refine these.
• Checking and categorizing/coding adverse events.
• Determining date of progression for central radiology review based on review of all RANO criteria radiological endpoints for each patient’s series of scans.
• Comparing site with central radiology reviews.
• Assisting the COGNO statistician with data analysis methodology.
• Reviewing all preliminary data analyses; identifying anomalies and unexpected results to enable further data checking and cleaning where relevant.

viii  Paper writing

I have been directly involved with the writing and drafting of each paper, as well as abstracts that have been presented at local and international conferences.
Chapter 3: Primary Endpoint publication (Part 1)
Randomized phase 2 study of carboplatin and bevacizumab in recurrent glioblastoma

Kathryn M. Field, John Simes, Anna K. Nowak, Lawrence Cher, Helen Wheeler, Elizabeth J. Hovey, Christopher S.B. Brown, Elizabeth H. Barnes, Kate Sawkins, Ann Livingstone, Ron Freilich, Pramit M. Phal, Greg Fitt, CABARET/COGNO investigators, and Mark A. Rosenthal

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Corresponding Author: Kathryn Field, MBBS, Department of Medical Oncology, Royal Melbourne Hospital, Grattan Street, Parkville, Victoria 3050, Australia (kathryn.field@mh.org.au).

Background. The optimal use of bevacizumab in recurrent glioblastoma (GBM), including the choice of monotherapy or combination therapy, remains uncertain. The purpose of this study was to compare combination therapy with bevacizumab monotherapy.

Methods. This was a 2-part randomized phase 2 study. Eligibility criteria included recurrent GBM after radiotherapy and temozolomide, no other chemotherapy for GBM, and Eastern Cooperative Oncology Group performance status 0–2. The primary objective (Part 1) was to determine the effect of bevacizumab plus carboplatin versus bevacizumab monotherapy on progression-free survival (PFS) using modified Response Assessment in Neuro-Oncology criteria. Bevacizumab was given every 2 weeks, 10 mg/kg; and carboplatin every 4 weeks, (AUC 5). On progression, patients able to continue were randomized to continue or cease bevacizumab (Part 2). Secondary endpoints included objective radiological response rate (ORR), quality of life, toxicity, and overall survival (OS).

Results. One hundred twenty-two patients (median age, 55y) were enrolled to Part 1 from 18 Australian sites. Median follow-up was 32 months, and median on-treatment time was 3.3 months. Median PFS was 3.5 months for each arm (hazard ratio [HR]: 0.92, 95% CI: 0.64–1.33, P = .66). ORR was 14% (combination) versus 6% (monotherapy) (P = .18). Median OS was 6.9 (combination) versus 7.5 months (monotherapy) (HR: 1.18, 95% CI: 0.82–1.69, P = .38). The incidence of bevacizumab-related adverse events was similar to prior literature, with no new toxicity signals. Toxicities were higher in the combination arm. Part 2 data (n = 48) will be reported separately.

Conclusions. Adding carboplatin resulted in more toxicity without additional clinical benefit. Clinical outcomes in patients with recurrent GBM treated with bevacizumab were inferior to those in previously reported studies.

Clinical trials registration nr. ACTRN12610000915055.

Keywords: bevacizumab, carboplatin, glioblastoma.

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agent, effective both as monotherapy and in combination with traditional chemotherapy drugs, in early-phase clinical trials in the setting of recurrent GBM. Encouraging results from phase 2 studies in recurrent disease were reported in 2007 and 2009, with response rates up to 50% and progression-free survival (PFS) up to 9 months, representing a substantial improvement on historical data for chemotherapy alone.7,8 This led to US FDA approval in 2009 for use of bevacizumab in recurrent GBM and widespread uptake of the drug on that continent.9

Despite this, there remain several unanswered questions, which include the use of bevacizumab as monotherapy versus in combination with chemotherapy, the potential utility of continuing bevacizumab beyond disease progression, and comparison of the recently developed Response Assessment in Neuro-Oncology (RANO) guidelines10 with the Macdonald criteria used to interpret MRI changes in earlier studies.11 RANO criteria place emphasis on fluid attenuated inversion recovery (FLAIR) sequence abnormalities, which were not considered in the traditional Macdonald criteria and may be more relevant in the setting of antiangiogenic agents (eg, bevacizumab) that may affect T1 contrast enhancement. In addition, the effect of bevacizumab on quality of life (QOL) and neurocognitive function (NCF) has been questioned, with limited existing information at the time of study design and now controversial findings in the first-line setting for bevacizumab use in GBM.12–14

We report the primary endpoint for Part 1 of “A randomized phase 2 study of carboplatin and bevacizumab in recurrent glioblastoma multiforme” (CABARET) in which we compared the effect of bevacizumab plus carboplatin with bevacizumab monotherapy on progression-free survival (PFS) in patients with recurrent GBM. At the time of protocol development, carboplatin was a commonly used second-line chemotherapy drug for recurrent GBM in Australia based on previous studies showing modest benefit, with response or stabilization of disease in approximately 50% of patients and median time to progression of 19–26 weeks.15,16 Carboplatin had also been used in combination with other cytotoxics and bevacizumab in 2 single-arm phase 2 studies.17,18 At the time of study design, chemotherapy alone was regarded as standard therapy for recurrent GBM in Australia; while bevacizumab monotherapy was approved for use in this context, it was not funded by the Australian Pharmaceutical Benefits Scheme (PBS) and thus was not standard second-line therapy. A control arm using chemotherapy alone was not included in the trial design due to lack of funding support for this comparator.

While efficacy was the primary endpoint, important secondary endpoints, including toxicity and QOL, were evaluated to help determine whether the combination of bevacizumab and carboplatin warranted further evaluation.

Materials and Methods

Study Objectives

The primary objective was to determine the effect of bevacizumab plus carboplatin versus bevacizumab monotherapy on PFS in patients with recurrent GBM, using modified RANO criteria. Secondary objectives included objective radiological response rate, neurocognitive function, health-related QOL, corticosteroid use, toxicity, OS, and time to treatment failure (TTF). In Part 2, we aimed to determine the effect of continuing or stopping bevacizumab after disease progression on the above parameters and on subsequent PFS.

Exploratory objectives included correlation between steroid dose and clinical outcome, correlation of MRI response at 4 weeks with clinical outcome, comparison between Macdonald and modified RANO criteria for assessment of disease response or progression, documenting the location and type of radiological progression on and after bevacizumab discontinuation, and correlation between blood and tissue biomarkers and clinical outcome.

Patient Eligibility

Eligible participants were adults >18 years with Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and a histological diagnosis of GBM (WHO grade IV glioma) following resection or biopsy, who had received treatment with both radiotherapy and temozolomide (concurrently and/or sequentially). Patients with first or subsequent recurrences were eligible to participate, provided that prior therapy had only included radiotherapy and temozolomide. This was to enable inclusion of the patients with recurrent GBM often seen in routine practice with more than one recurrence, who would potentially benefit from bevacizumab therapy, recognizing that other prominent contemporary studies such as the BRAIN trial also permitted patients beyond first recurrence to participate.8 The prior dosing schedule of temozolomide was not stipulated, and prior metronomic temozolomide was permitted (including in the recurrent setting). At least 12 weeks must have elapsed since the cessation of radiotherapy. Recurrent or progressive disease had to be confirmed by MRI showing measurable disease according to RANO criteria10 or surgical resection of recurrent disease. The baseline or eligibility MRI was performed within 14 days prior to randomization. The craniotomy or biopsy site had to be adequately healed. Other key inclusion criteria were adequate renal function (including <2+ urine protein on dipstick or urine protein/creatinine ratio ≤1.0) and adequate hematological parameters (including neutrophil count ≥1.5 × 10^9/L and platelets ≥100 × 10^9/L). Anticoagulation was permitted if required; low molecular-weight heparin was the preferred approach.

Exclusion criteria included prior chemotherapy other than temozolomide, prior bevacizumab or other investigational agent for the treatment of glioma, surgery within 4 weeks before treatment commencement, evidence of recent hemorrhage on MRI with the exception of asymptomatic punctate hemorrhage or resolving postsurgical change, inability to undergo MRI, inadequately controlled hypertension, clinically significant cardiovascular disease, history of coagulation disorder, prior or concurrent malignancy (except nonmelanomatous skin cancer or malignancy treated and disease-free for >5 years), pregnancy or lactation, or other concurrent physical, psychological, or sociological condition that could jeopardize patient safety or compliance.

Study Design

This was a multicenter, sequential, stratified, nonblinded, randomized phase 2 study in 2 parts, recruiting from 18 Australian
sites (Supplementary Fig. S1). Eligible patients were randomized in a 1:1 to receive bevacizumab 10 mg/kg IV every 2 weeks plus carboplatin AUC 5 every 4 weeks (4 weeks was deemed to be the length of one cycle), or bevacizumab monotherapy at the same dose (Part 1). Study therapy continued until progressive disease, unacceptable toxicity, participant withdrawal, noncompliance with protocol guidelines, or death. Following disease progression, participants considered suitable for further treatment, and who consented to further treatment on the trial, were then randomized to cease or continue bevacizumab using the same dose and schedule, in addition to further chemotherapy dependent on clinician preference (Part 2). Details and results from Part 2 will be reported separately as part of a planned and separate analysis of the 48 participants randomized to Part 2.

**Dose Modification**

The causative drug was discontinued for any grade 3 or 4 hypersensitivity reaction. No bevacizumab dose reductions were permitted at any time. For grade 2 neutropenia, bevacizumab was continued, but carboplatin was withheld until resolution to grade 1. For grade ≥3 neutropenia, both drugs were withheld until resolution to grade 1 and then resumed with a carboplatin dose reduction to AUC 4. For grade 2 thrombocytopenia, carboplatin was withheld until platelet counts improved to ≥100 × 10^9/L and recommenced at the same dose; bevacizumab was continued. For grade 3 thrombocytopenia, once platelet counts were ≥100 × 10^9/L, carboplatin was restarted at AUC 4; for grade 4, carboplatin was permanently discontinued. For both grade 3 and 4, bevacizumab was restarted once platelet counts were ≥75 × 10^9/L. For grade 2–3 increase in ALT or AST, carboplatin was withheld until grade ≤1 and restarted at the same dose (for grade 2) or AUC 4 (for grade 3); bevacizumab was withheld until grade ≤2. Both drugs were discontinued if AST or ALT toxicity was grade 4. Bevacizumab was discontinued for grade 4 hypertension and delayed for grade 2–3 hypertension until blood pressure was ≤150/100 mmHg. Bevacizumab was also discontinued for any grade CNS hemorrhage (with the exception of clinically asymptomatic hemosiderin or punctate hemorrhage) and for nephrotic syndrome. For grade 3 proteinuria, bevacizumab was delayed until grade ≤2. Bevacizumab was delayed if a grade 3–4 venous thromboembolic event occurred and was restarted once resolution or full-dose anticoagulation was established. A maximum of 8 weeks delay was permissible for either drug.

**Response Evaluation and Radiological Assessments**

The primary criterion for assessment of efficacy was PFS. PFS was defined as time from randomization to disease progression based on centrally reviewed modified RANO criteria or death from any cause. OS was defined as the time of randomization to the date of death from any cause. Participants who were alive at their last follow-up were censored at that date. Both PFS and OS were estimated using the Kaplan-Meier method.

Response evaluation was determined by MRI, clinical and neurological examination, and steroid use, which are incorporated in the RANO criteria. The primary endpoint, as well as the secondary and exploratory radiological endpoints, were assessed by blinded central radiology review. Cerebral MRI including pre- and postgadolinium T1, T2/FLAIR was performed at baseline and then every 8 weeks or more frequently if clinically indicated during study treatment. An additional MRI was performed 4 weeks after randomization for an exploratory endpoint but was not used by site investigators for decision-making except when safety concerns arose.

Responses were defined by modified RANO criteria, and any response needed to be sustained at the subsequent scan for the purpose of confirmation. In the setting of resected recurrent disease with no baseline measurable disease, the best response was stable disease. Because the existing RANO criteria are not specific regarding extent of FLAIR changes warranted to be labeled as progressive disease, a novel 5-point scale was devised by several neuroradiologists and neuro-oncologists for the purpose of this study, in order to quantify T2/FLAIR abnormality, and added to the existing RANO criteria; hence, modified RANO criteria were used (Supplementary Table S1). Further details about the use of the 5-point scale and its use compared with standard RANO criteria, as well as a comparison between RANO and Macdonald criteria for disease assessment on this trial, will be the subject of a separate paper.

Site investigators assessed disease progression for the purpose of eligibility for continuing participation in Part 1 of the study. For the purpose of trial reporting, the date of the MRI at which the central radiology review detected progression was used as the progression date. Participants were censored if they commenced any new anticancer treatment.

Clinical assessments, including QOL and NCF testing for those participants able to complete them, were performed at the start of each 4-week cycle. Laboratory assessments, including urinalysis for patients receiving bevacizumab, were performed every 2 weeks. All participants were assessed at the cessation of study treatment and then every 4 weeks until death, loss to follow-up, or withdrawal of consent. QOL was measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire (QLQ-C30) and BN20 validated measurement tools. The EQ-5D health outcome measure was also obtained. Neurocognitive function testing was measured by the Mini-Mental status examination and CogState neurocognitive function testing, and will be reported separately for the subset of patients able to participate in this testing modality beyond baseline.

**Safety**

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 was used to classify and grade adverse events. Safety data were collected for all participants until at least 30 days after their last study drug dose.

**Study Oversight**

The study protocol was written by members of the trial management committee and approved by the relevant human research ethics committees for participating sites. All participants provided written informed consent before commencement of study procedures. Data for each participant were collected.
using an InForm clinical trial database (Oracle). The study was conducted under the auspices of the Cooperative Trials Group for Neuro-Oncology (COGNO), coordinated at the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney. The Clinical Trials Centre was responsible for the collection, maintenance, integrity, and confidentiality of all data. The trial management committee was responsible for all aspects of the conduct of the study. An independent data safety monitoring committee (IDSMC) monitored the progress of all safety aspects of the study. The statistical analysis was performed at the Clinical Trials Centre. While Roche Products, Pty Limited (Australia) provided funding for the trial and access to bevacizumab, the company was not involved in data monitoring, analysis, or manuscript preparation.

**Statistical Analysis**

The intention-to-treat population of all randomly assigned participants was used for survival analysis. Toxicities, treatment details, and QOL were reported for participants receiving at least one dose of study treatment. For Part 1 sample size calculations, 6PFS was assumed to be 35% for bevacizumab monotherapy and 50% for the combination of bevacizumab and carboplatin, based on data for the bevacizumab-irinotecan combination. At the time of protocol writing, only retrospective data existed for the bevacizumab-carboplatin combination. We sought to detect a HR of approximately 0.6 to consider the combination clinically significantly different from monotherapy.

The sample size of 120 participants was chosen to provide 70% power at a 2-sided alpha = 0.1 to detect a HR of 0.62. Time to progression, OS, and time on treatment were measured from the date of randomization, estimated using the non-parametric Kaplan-Meier method including 95% CIs, and proportional-hazards regression was used to compare the 2 arms of the study. Randomized treatment arms were compared for overall response and best response using chi-square tests. No interim analyses were planned or conducted, with the exception of safety monitoring.

Patient randomization for Part 1 used the method of minimization, stratified by site, sex, age >65 years, and ECOG performance status. For Part 2, the same factors plus previous diagnosis of grade I-III glioma were used to stratify the participants. Bevacizumab-related adverse events, as well as hematologic adverse events, were specifically reported. No formal statistical comparisons between arms were made for adverse events. All reporting of adverse events and QOL included participants who continued to receive Part 1 treatment on the basis of site radiology and clinical reviews, even if central radiology review had deemed progression to be earlier.

**Results**

**Patient Baseline Characteristics**

Characteristics of the 122 participants enrolled in the study between November 2010 and March 2012 are summarized in Table 1. The median time from initial GBM surgery to randomization was 11 months for both arms. Most participants (87%, n = 106) had an initial diagnosis of GBM; the remainder had been diagnosed with an earlier grade I-III glioma that had subsequently progressed to histologically confirmed GBM. Sixty-six percent (n = 80) were enrolled at first disease recurrence. Forty-four percent (n = 54) had undergone surgery for recurrent disease. Baseline demographic data were comparable between the 2 groups (Table 1).

**Study Treatment**

One hundred twenty-two participants were registered and randomized to the trial (enrolled population) (Fig. 1). In total, 120 participants received at least one dose of study treatment.

### Table 1. Baseline characteristics of participants; n (%) or median (range)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bevacizumab + Carboplatin (N = 60)</th>
<th>Bevacizumab (N = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>55 (32–79)</td>
<td>55 (25–82)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>26 (43%)</td>
<td>29 (47%)</td>
</tr>
<tr>
<td>Male</td>
<td>34 (57%)</td>
<td>33 (53%)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (12%)</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>1</td>
<td>35 (58%)</td>
<td>35 (56%)</td>
</tr>
<tr>
<td>2</td>
<td>18 (30%)</td>
<td>16 (26%)</td>
</tr>
<tr>
<td>KPS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90–100</td>
<td>21 (35%)</td>
<td>22 (35%)</td>
</tr>
<tr>
<td>70–80</td>
<td>28 (47%)</td>
<td>28 (45%)</td>
</tr>
<tr>
<td>&lt;70</td>
<td>11 (18%)</td>
<td>10 (16%)</td>
</tr>
<tr>
<td>Not done</td>
<td>0 (0%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Prior diagnosis of grade I-III glioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>54 (90%)</td>
<td>52 (84%)</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (10%)</td>
<td>10 (16%)</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>39 (65%)</td>
<td>41 (66%)</td>
</tr>
<tr>
<td>Second or more</td>
<td>21 (35%)</td>
<td>19 (31%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Initial surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>6 (10%)</td>
<td>9 (15%)</td>
</tr>
<tr>
<td>Debulking</td>
<td>21 (35%)</td>
<td>16 (26%)</td>
</tr>
<tr>
<td>Resection</td>
<td>33 (55%)</td>
<td>37 (60%)</td>
</tr>
<tr>
<td>Surgery for recurrent disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>37 (62%)</td>
<td>29 (47%)</td>
</tr>
<tr>
<td>Yes</td>
<td>23 (38%)</td>
<td>31 (50%)</td>
</tr>
<tr>
<td>Corticosteroid use at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10 (17%)</td>
<td>16 (26%)</td>
</tr>
<tr>
<td>Yes</td>
<td>50 (83%)</td>
<td>46 (74%)</td>
</tr>
<tr>
<td>Months from last radiotherapy to randomization</td>
<td>9 (3–61)</td>
<td>9 (3–101)</td>
</tr>
<tr>
<td>Months from initial glioblastoma surgery to randomization</td>
<td>11 (1–48)</td>
<td>11 (1–43)</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG, Eastern Cooperative Oncology Group; y, years.
(toxicity-evaluable population). Two participants, both assigned to bevacizumab plus carboplatin, did not receive study treatment. These participants were included in the survival analysis as part of the intention-to-treat population; sensitivity analyses excluding both patients did not change the primary outcome. The study was closed on December 5, 2014. At the time of study closure, 2 participants were receiving Part 1 study treatment, none were receiving Part 2 study treatment, 2 participants (2%) were in follow-up; 117 (96%) were deceased, and one (<1%) had withdrawn consent to follow-up.

The median number of treatment cycles per participant was 4 (range: 1–40) for the combination arm and 4 (range: 1–35) for the monotherapy arm. Carboplatin dose reductions were required in 21 of 58 participants (36%). In the combination arm, 12 of 58 participants (21%) ceased carboplatin during the trial but were able to continue bevacizumab; and one participant (2%) ceased bevacizumab but continued carboplatin.

Among the 118 participants who received at least one dose of treatment and were off-study at the time of analysis, Part 1 study treatment was discontinued because of disease progression (as determined by the local investigator) or death in 102 participants (86%); adverse events in 9 participants (8%, 5 in the combination arm and 4 in the monotherapy arm); participant preference in 5 participants (4%, all in the combination arm); and clinician preference in 2 participants (2%, 1 from each arm).

**Efficacy**

The median follow-up was 32 months (Fig. 2). The central radiology review-determined endpoint of 6PFS for Part 1 was 15% (combination) and 18% (monotherapy). Median PFS was 3.5 months (95% CI: 2.2–3.7 mo) (combination) and 3.5 months (95% CI: 1.9–3.7 mo) (monotherapy), (HR: 0.92, 95% CI: 0.64–1.33, P = .66) (Fig. 2A). Progression was determined clinically for 30 of the 118 participants who had completed Part 1 (25%) without radiological confirmation at the time of progression. For the remaining participants, central radiological confirmation of disease progression included increased enhancement on the postcontrast T1-weighted images, T2/FLAIR increase, a new lesion, or a combination of these radiologic findings, with no single imaging technique predominating in terms of determining disease progression (Supplementary Table S2). In particular, T2/FLAIR changes alone were the stated reason for progression in only 11.6% (n = 14) of participants.

No participant had a complete response (Table 2). Of the 120 participants who received at least one dose of study treatment, 8 (14%) in the combination arm and 4 (6%) in the
monotherapy arm had a RANO-defined partial response. Overall, 44 participants (76%) in the combination arm and 40 (65%) in the monotherapy arm had an initial response or stable disease before progressing. Median OS was 6.9 months (combination) versus 7.5 months (monotherapy), (HR: 1.18, 95% CI: 0.82–1.69, \( P = .38 \)) (Fig. 2B). Comparison between participants who participated in CABARET with first versus second or subsequent recurrence did not show any statistically significant difference in PFS or OS outcomes.

**Quality of Life Analysis**

Analysis of QOL data comparing change scores (mean across all treatment cycles minus baseline score, using a 0–100 scale transformation) for the QLQ-C30 overall QOL responses during Part 1 treatment indicated no significant differences between arms. The mean of the change scores was \(-0.2\) for the combination arm and \(-5.2\) for bevacizumab monotherapy (difference between arms \(-5.0\), 95% CI: \(-14.1\) to 4.1, \( P = .28 \)). More detailed QOL analyses will be reported separately.

**Safety**

Safety data are summarized in Tables 3 and 4. Events are presented here as the combination versus monotherapy arm, but the groups were not statistically compared. The most common adverse events (all grades) included fatigue, neurological symptoms or signs, hypertension, nausea and vomiting, thrombocytopenia, and constipation. Hematologic adverse events were more common in the combination arm. In addition to the grade 3 events documented in Tables 3 and 4, several other grade 3 events were reported, including headache, seizures, weight gain, dyspnea, and joint pain.

There was one death related to CNS hemorrhage and one death related to bowel perforation; both participants were receiving bevacizumab and carboplatin. One suspected unexpected serious adverse reaction (SUSAR) occurred in a male patient receiving bevacizumab monotherapy who developed acute renal failure and biopsy-proven acute interstitial nephritis. Four months earlier, this participant had also commenced carbamazepine, which is known to be associated with this complication, and it could not be discerned whether bevacizumab was the causative agent.

**Discussion**

In this large, multicenter randomized phase 2 study, no obvious clinically significant benefit for the combination of bevacizumab and carboplatin was detected, and CABARET provides no support for further study of this combination. The efficacy of bevacizumab in both arms was lower than in previous reports available at the time of trial design.\(^8,^{21}\)

Previous studies of bevacizumab monotherapy or bevacizumab plus chemotherapy in recurrent GBM have resulted in somewhat varied findings, with 6PFS ranging from 19% to 50%. Further, combination therapy does not appear superior to monotherapy in cross-trial comparisons but does seem to result in greater toxicity.\(^8,^{21–23}\) At the time the CABARET trial was designed, the only evidence that combining bevacizumab with chemotherapy might improve outcomes relative to bevacizumab alone came from the BRAIN study, published in 2009.\(^8\)

In this trial, bevacizumab plus irinotecan resulted in 6PFS of...
50% versus 43% for monotherapy and median PFS of 5.6 versus 4.2 months.8

More recently, the BELOB randomized phase 2 study results showed 6PFS of 42% for bevacizumab plus lomustine versus 16% for bevacizumab monotherapy and 13% for lomustine monotherapy.24 The BELOB study has been the first and only prospective trial to date to show a potential survival advantage of combination therapy over bevacizumab monotherapy or chemotherapy alone. Following on from the BELOB study, the EORTC 26101 randomized phase 3 clinical trial compares bevacizumab + lomustine combination therapy with lomustine monotherapy; the trial is now closed, and results are being eagerly awaited as to whether the promising results from the combination in the BELOB phase 2 study will be sustained in the larger phase 3 clinical trial design setting. This will help to definitively determine the role of bevacizumab in the setting of recurrent glioblastoma.

In the CABARET trial, adding carboplatin to bevacizumab did not provide additional efficacy when compared with bevacizumab monotherapy. The combination of carboplatin and

Table 3. Adverse events (Number [%] of participants experiencing adverse event, by treatment group)a

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>Bevacizum + Carboplatin (N = 58)</th>
<th>Bevacizum (N = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>All grades</td>
<td>16 (28%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥ 3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>All grades</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥ 3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Neutrophil count decreased (without fever)</td>
<td>All grades</td>
<td>14 (24%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥ 3</td>
<td>4 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>All grades</td>
<td>32 (55%)</td>
<td>14 (23%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥ 3</td>
<td>9 (16%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>All grades</td>
<td>29 (50%)</td>
<td>24 (39%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥ 3</td>
<td>0 (0%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>All grades</td>
<td>15 (26%)</td>
<td>15 (24%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥ 3</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>All grades</td>
<td>26 (45%)</td>
<td>18 (29%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥ 3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>All grades</td>
<td>50 (86%)</td>
<td>52 (84%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥ 3</td>
<td>5 (9%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>Grade ≥ 3</td>
<td>37 (64%)</td>
<td>36 (58%)</td>
</tr>
<tr>
<td>Causing death</td>
<td></td>
<td>2 (3%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

aFor the 120 participants who had at least one dose of study medication, from the first treatment dose through to 30 days after the last treatment dose on Part 1 of the study.

Table 4. Adverse events (Number [%] of participants experiencing a bevacizumab-related adverse event, by treatment group)a

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Any</th>
<th>Bevacizum + Carboplatin (N = 58)</th>
<th>Bevacizum (N = 62)</th>
<th>Grade ≥ 3</th>
<th>Bevacizum + Carboplatin (N = 58)</th>
<th>Bevacizum (N = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal perforation</td>
<td>1 (2%)</td>
<td>0</td>
<td>1 (2%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS hemorrhage</td>
<td>3 (5%)</td>
<td>3 (5%)</td>
<td>1 (2%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding (other)</td>
<td>17 (29%)</td>
<td>16 (26%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>4 (7%)</td>
<td>6 (10%)</td>
<td>2 (3%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>2 (3%)</td>
<td>0</td>
<td>2 (3%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis and pulmonary embolus</td>
<td>0</td>
<td>1 (2%)</td>
<td>0</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolic other</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound healing complication</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>7 (12%)</td>
<td>4 (6%)</td>
<td>0</td>
<td>2 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>36 (62%)</td>
<td>51 (82%)</td>
<td>10 (17%)</td>
<td>10 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscesses or fistulae</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aFor the 120 participants who had at least one dose of study medication, from the first treatment dose through to 30 days after the last treatment dose on Part 1 of the study.

50% versus 43% for monotherapy and median PFS of 5.6 versus 4.2 months.8

More recently, the BELOB randomized phase 2 study results showed 6PFS of 42% for bevacizumab plus lomustine versus 16% for bevacizumab monotherapy and 13% for lomustine monotherapy.24 The BELOB study has been the first and only prospective trial to date to show a potential survival advantage of combination therapy over bevacizumab monotherapy or chemotherapy alone. Following on from the BELOB study, the EORTC 26101 randomized phase 3 clinical trial compares bevacizumab + lomustine combination therapy with lomustine monotherapy; the trial is now closed, and results are being eagerly awaited as to whether the promising results from the combination in the BELOB phase 2 study will be sustained in the larger phase 3 clinical trial design setting. This will help to definitively determine the role of bevacizumab in the setting of recurrent glioblastoma.

In the CABARET trial, adding carboplatin to bevacizumab did not provide additional efficacy when compared with bevacizumab monotherapy. The combination of carboplatin and
bevacizumab in recurrent glioma has been reported in small retrospective series with 6PFS rates up to 50% and median OS up to 40 weeks.20,25 A prospective cohort study of 61 participants, 7 of whom had carboplatin and bevacizumab for recurrent GBM, reported a median PFS of 5 months and OS of 9 months with no significant differences between treatment groups, although the small sample size and nonrandomized design preclude robust conclusions.26 Recommended practice in Australia does not include carboplatin in the GBM management algorithm, with the drug not being listed in the Australian evIQ Cancer Treatments Online options for management of GBM. Both irinotecan and lomustine, when used in combination with bevacizumab, have resulted in better efficacy outcomes than those in the CABARET study.7,8,24 However, irinotecan is not routinely available in Australia for recurrent GBM, and the BELOB trial, which included lomustine monotherapy as a comparator arm, also did not suggest that lomustine monotherapy was particularly efficacious with 6PFS of only 13%.24 Again, results from the EORTC 26101 study will be extremely informative.

The fact that a third (33%) of our participants were enrolled at their second or subsequent recurrence may have also impacted the response rates and survival outcomes, as these patients were further down the disease pathway and were more heavily pretreated. In the BRAIN study only 19% of participants were enrolled at second/subsequent recurrence.8 The higher number of multiple progressions included in the CABARET study may partly account for the lower OS compared with prior studies.

Of interest, we observed lower than expected response rates, PFS, and OS for bevacizumab in patients compared with several previous trials. Vredenburgh, in the first prospective clinical trial of bevacizumab in GBM, reported 46% 6PFS and 9.7 month median OS in a single-arm phase 2 study of bevacizumab plus irinotecan.7 The BRAIN study had similar outcomes.8 More recently though, lower response rates and survival outcomes have been noted. The BELOB study documented only 16% 6PFS with bevacizumab monotherapy.24 A single-arm bevacizumab monotherapy phase 2 trial in 2010 reported 6PFS of 25%, which was also lower than expected.27 In our study, the 6PFS was 15%–18%, in keeping with these more recent trials. The lower apparent benefits in more recent years could be attributable to several variables including a better appreciation of the significance of T2/FLAIR abnormalities on radiological imaging, how heavily patients had been pretreated, and performance status inclusion criteria among others. ECOG performance status is a relatively subjective criterion; we allowed patients with ECOG 2 or better into the study, but assigning a PS of 2 is always subject to investigator discretion, and it is possible that some participants were more unwell than those recruited to earlier studies. It is possible that more contemporary studies, such as CABARET and BELOB, provide a more accurate representation of disease progression times for this cohort of patients compared with older studies. Notably though, fewer than 12% of the participants were deemed to have progressed on T2/FLAIR signal change alone, suggesting that the incorporation of T2/FLAIR in RANO criteria for disease assessment may not have substantially affected the PFS endpoint of this trial compared with the more traditional approach of measuring contrast enhancement alone.

Since the CABARET trial did not include a chemotherapy-alone arm, it does not provide any direct evidence of the effectiveness of bevacizumab compared with chemotherapy, as the BELOB study did. While our study has shown that neither PFS nor OS is improved when carboplatin is added to bevacizumab, it did not explore whether bevacizumab results in greater benefit than carboplatin monotherapy. To date, aside from the BELOB study, no other clinical trial in recurrent GBM can answer the question of whether bevacizumab is truly superior to chemotherapy, aside from historical comparisons.

Where should bevacizumab sit in the recurrent glioblastoma setting? Recent nonrandomized cohort studies have suggested no disadvantage in introducing bevacizumab later, after initial chemotherapy for disease progression or recurrence.28,29 Whether chemotherapy alone, followed by subsequent bevacizumab, is an acceptable strategy has not been addressed by CABARET with the lack of a chemotherapy-only arm. At present the most common time to deliver bevacizumab, assuming it is available, is at first recurrence after temozolomide therapy since this is the setting of the majority of available clinical trial evidence.

In summary, we did not find that the combination of bevacizumab and chemotherapy resulted in additional PFS or OS benefit compared with bevacizumab monotherapy in recurrent GBM. Hematologic toxicities were more common in the combination arm but were generally manageable, and preliminary analysis of QOL data suggests no differences between arms while patients are on treatment. Overall response rates and survival outcomes, using modified RANO criteria, were somewhat inferior to those in several previously reported studies. Despite this, a small proportion of patients clearly responded, and some derived prolonged clinical benefit from therapy. We await biomarker studies, which will search for signals to discern the patients who are most likely to benefit from bevacizumab.

Supplementary Material

Supplementary material is available at Neuro-Oncology Journal online (http://neuro-oncology.oxfordjournals.org/).

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Acknowledgments

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Trial Management Committee: K. Field (Chair), J. Simes, E. Hovey, A. Nowak, L. Cher, H. Wheeler, C. Brown, E. Barnes, K. Sawkins, A. Livingstone, and M. Rosenthal.

Independent Central Radiological Review Committee: P. Phal, G. Fitt, and C. Goh.

Independent Data Safety Monitoring Committee: M. Tattersall (Chair), P. Kelly, and A. Hayden.

The following study sites participated in the CABARET study and randomized at least one patient (principal investigator and site coordinator):

Monash Medical Centre, Victoria: R. Freilich and I. Arzhintar (17); Royal Melbourne Hospital, Victoria: K. Field, M. Rosenthal, and L. Garrett (16); Royal Prince Alfred Hospital, New South Wales: J. Simes and A. Byrne (13); St Vincent’s Hospital, Victoria: A. Dowling and N. Ranieri (11); Epworth HealthCare Richmond, Victoria: R. Jennens and F. Osmond (9); The Queen Elizabeth Hospital, South Australia: W.K. Patterson and A. Phoy (8); Calvary Mater Newcastle, New South Wales: F. Abell and L. Ploowman (7); Austin Hospital, Victoria: L. Cher and J. Flynn (7); Prince of Wales Hospital, New South Wales: E. Hovey and H. Kilby (6); Royal North Shore Hospital, New South Wales: H. Wheeler and S. Kirby-Lewis (6); Royal Adelaide Hospital, South Australia: N. Singhal, S. Smith, and M. Whelan (5); Royal Brisbane and Women’s Hospital, Queensland: P. Inglis and A. Ives (5); Sir Charles Gairdner Hospital, Western Australia: A. Nowak and S. Lobb (5); Port Macquarie Base Hospital, New South Wales: S. Begbie and P. Williams (4); Mater Adult Hospital, Queensland: Z. Lwin, N. Woodward, and G. Crosbie (1); Royal Hobart Hospital, Tasmania: R. Harrup and L. Pyszkowski (1); Launceston General Hospital, Tasmania: S. Gauden and A. Neville (1).

This trial has previously been reported at the American Society of Clinical Oncology Annual Meeting (2013), the Society for Neuro-Oncology Annual Meeting (2012), the Australian Cooperative Trials Group for Neuro-Oncology Annual Meetings (2012–2014), the European Association for Neuro-Oncology and the European Society of Medical Oncology Annual Meetings (2012).

Conflict of interest statement. K.F. has received conference travel grants and honoraria from Roche for speaking invitations. E.H. has been a member of a Roche Advisory Board 2009–2013. A.N. has been a member of a Roche Advisory board 2013 and received honoraria from Roche for speaking invitations. M.R. has been a member of a Roche Advisory Board. J.S. has received research funding from Roche. H.W. has received research funding from Roche and has been a member of a Roche Advisory board. E.B., G.F., P.P., K.S., C.B., A.L., and L.C. declare no conflict of interest. There is no stated conflict of interest for R.F.

References


**Supplementary Table 1**: 5-point scale for T2/FLAIR used in ‘modified’ RANO criteria

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>&gt;50% decrease in size of T2 / FLAIR abnormality</td>
</tr>
<tr>
<td>-1</td>
<td>25-50% decrease in size of T2 / FLAIR abnormality</td>
</tr>
<tr>
<td>0</td>
<td>Stable (+/- 25% from nadir T2/FLAIR appearance)</td>
</tr>
<tr>
<td>+1</td>
<td>25-50% increase in size of T2 / FLAIR abnormality</td>
</tr>
<tr>
<td>+2</td>
<td>&gt;50% increase in size of T2 / FLAIR abnormality</td>
</tr>
</tbody>
</table>
**Supplementary table 2: Reasons for progression (Central radiological review, n=120)**

<table>
<thead>
<tr>
<th>Reason(s)</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical only</td>
<td>30 (25%)</td>
</tr>
<tr>
<td>T1 only</td>
<td>18 (15%)</td>
</tr>
<tr>
<td>T2 / FLAIR only</td>
<td>14 (12%)</td>
</tr>
<tr>
<td>T1 + New lesion</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>T1 + Clinical</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>T1 + T2/FLAIR</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>T1 + T2 / FLAIR + New lesion + Clinical</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>T2 / FLAIR + Clinical</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>New lesion only</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>T1 + T2 / FLAIR + Clinical</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>T1 + New lesion + Clinical</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>T1 + T2 / FLAIR + New lesion</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>New lesion + Clinical</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Other*</td>
<td>13 (11%)</td>
</tr>
</tbody>
</table>

*Censored for PFS at commencement of new therapy or death without centrally determined radiological progression*
Chapter 4: Bevacizumab after progression publication (Part 2)
Continuing or ceasing bevacizumab beyond progression in recurrent glioblastoma: an exploratory randomized phase II trial

Elizabeth J Hovey,* Kathryn M Field,* Mark A Rosenthal, Elizabeth H Barnes, Lawrence Cher, Anna K Nowak, Helen Wheeler, Kate Sawkins, Ann Livingstone, Pramit Phal, Christine Goh, and John Simes, on behalf of CABARET/COGNO investigators

Abstract

Background. In patients with recurrent glioblastoma, the benefit of bevacizumab beyond progression remains uncertain. We prospectively evaluated continuing or ceasing bevacizumab in patients who progressed while on bevacizumab.

Methods. CABARET, a phase II study, initially randomized patients to bevacizumab with or without carboplatin (Part 1). At progression, eligible patients underwent a second randomization to continue or cease bevacizumab (Part 2). They could also receive additional chemotherapy regimens (carboplatin, temozolomide, or etoposide) or supportive care.

Results. Of 120 patients treated in Part 1, 48 (80% of the anticipated 60-patient sample size) continued to Part 2. Despite randomization, there were some imbalances in patient characteristics. The best response was stable disease in 7 (30%) patients who continued bevacizumab and 2 (8%) patients who stopped receiving bevacizumab. There were no radiological responses. Median progression-free survival was 1.8 vs 2.0 months (bevacizumab vs no bevacizumab; hazard ratio [HR], 1.08; 95% CI, 0.59–1.96; P = .81). Median overall survival was 3.4 vs 3.0 months (HR, .84; 95% CI, .47–1.50; P = .56 and HR .70; 95% CI .38–1.29; P = .25 after adjustment for baseline factors). Quality-of-life scores did not significantly differ between arms. While the maximum daily steroid dose was lower in the continuation arm, the difference was not statistically significant.

Conclusions. Patients who continued bevacizumab beyond disease progression did not have clear survival improvements, although the study was not powered to detect other than very large differences. While these data provide the only randomized evidence related to continuing bevacizumab beyond progression in recurrent glioblastoma, the small sample size precludes definitive conclusions and suggests this remains an open question.

Key words
bevacizumab | carboplatin | glioblastoma | phase II trial
Glioblastoma has a universally poor prognosis, a high morbidity and mortality burden, and the highest average years lost for any tumor type. Management approaches for recurrent glioblastoma are limited. Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF) is commonly used, having received accelerated approval from the Food and Drug Administration (FDA) in 2009 on the basis of radiological response rates (up to 50%) and progression-free survival (PFS) (up to 9 months) in phase 2 trials. However, no phase 3 study has demonstrated an overall survival (OS) benefit. Most recently, the phase 3 EORTC 26101 study did not find an OS benefit when using bevacizumab in combination with lomustine over lomustine monotherapy, despite initial enthusiasm and a reported survival benefit from the phase 2 BELOB study. Bevacizumab use in the recurrent glioblastoma setting is not universal: the European Medicines Agency did not approve it, in part due to the absence of chemotherapy-alone comparative data at that time.

The role of continuing bevacizumab beyond initial progression remains controversial. Some clinicians favor continuing bevacizumab on the basis of metastatic colorectal cancer studies indicating benefit beyond progression. and small retrospective glioblastoma studies have suggested that cessation may result in accelerated disease progression, rapid revascularization, and rebound edema. Conversely, a retrospective review of 54 glioblastoma patients reported a 6-month PFS of only 2% for patients continuing with a second bevacizumab-containing regimen.

Despite a relative lack of prospective supportive data, the current National Comprehensive Cancer Network guidelines for recurrent glioblastoma specifically indicate support for continuing bevacizumab beyond progression. Reasonable preclinical rationale has existed for this practice. Although the drug’s exact mechanism of action in glioblastoma is poorly understood, its antiangiogenic effects are thought to contribute directly. These effects, as well as possible enhanced delivery of chemotherapy to the tumor site through vascular normalization, should in theory be maintained throughout different lines of chemotherapy. The antiedema effect of bevacizumab is also well documented. This, together with published benefits in administering the drug beyond progression in colorectal cancer and the lack of randomized data in the setting of glioblastoma, provided the rationale for this study.

The two-part, stratified, nonblinded, randomized phase 2 study, Carboplatin and Bevacizumab in Recurrent Glioblastoma (CABARET), was conducted in Australia. In Part 1 of CABARET, 120 patients were randomized to bevacizumab plus carboplatin or bevacizumab alone. The primary objective was to determine the effect of bevacizumab plus carboplatin, versus bevacizumab monotherapy on PFS using modified Response Assessment in Neuro-Oncology (RANO) criteria. Published outcomes showed no PFS or OS benefit from adding carboplatin to bevacizumab.

We report here results from Part 2 of CABARET, in which, at progression, eligible patients were randomized to continue or cease bevacizumab in addition to a specified chemotherapy regimen or best supportive care. The objectives were to determine the effect of continuing or stopping bevacizumab after progression.

Methods

Patient Eligibility

Eligibility criteria for CABARET Part 1 have been previously described. Eligibility criteria for entry onto Part 2 included: patients with RANO-defined (radiological or clinical) progression on Part 1 of CABARET; considered appropriate by the site investigator to undergo further active therapy; and did not have contraindications to the ongoing use of bevacizumab. Reasons for patients not continuing on to Part 2 were documented (Supplementary Table 1).

Part 2 Study Design

The study design is outlined in Fig. 1. Following progression on Part 1 and prior to Part 2 randomization, patients continuing to Part 2 could elect to receive specified chemotherapy or best supportive care without chemotherapy at clinician discretion in consultation with the patient. After this decision had been recorded, eligible patients were then randomized 1:1 to continue bevacizumab 10 mg/kg intravenously 2-weekly, or to cease bevacizumab. Part 2 randomization was stratified by center, age, sex, performance status, and Part 1 treatment allocation. The randomization occurred after the decision about additional therapy in order to avoid bias from the possibility of patients subsequently choosing not to remain on trial if they chose no chemotherapy and were randomized to receive no bevacizumab.

Patients who had received bevacizumab monotherapy in Part 1 were treated with either carboplatin (AUC 5) 4-weekly, or best supportive care without chemotherapy. Patients who had received bevacizumab plus carboplatin in Part 1 could receive: etoposide (50 mg/m² daily for 20 days every 28 days); temozolomide (150–200 mg/m² daily for 5 days every 28 days, or 75 mg/m² daily for 20 days every 28 days), or best supportive care without chemotherapy. These drug choices were limited by safety recommendations from Roche: availability of safety data was required for use of these agents in combination with bevacizumab, and at the time data existed to support the use of temozolomide rechallenge or etoposide in this setting. Additional limitations included unavailability of
lomustine and irinotecan on the Australian Pharmaceutical Benefits Scheme for this indication at the time of study design, and the safety and efficacy of bevacizumab in combination with lomustine had not been reported at the time of study design.

Supportive care was permitted throughout for all patients including concomitant antibiotics, analgesics, corticosteroids, transfusions, and other necessary symptomatic therapy, except other investigational antitumor agents, chemotherapy, hormonal therapy, or immunotherapy.

**Part 2 Outcomes**

The primary outcome was median PFS. Response rate, OS, health-related quality of life (QOL), cognitive function, corticosteroid dose, and toxicities were also assessed.

**Dose Modification**

The toxicity criteria for discontinuing or suspending treatment have been previously reported. To summarize: no bevacizumab dose reductions were permitted, but bevacizumab was discontinued for clinically relevant central nervous system hemorrhage, nephrotic syndrome, or grade 4 hypertension. The causative drug was discontinued for any grade 3 or 4 hypersensitivity reaction. Any drug could be delayed for up to 8 weeks for lesser adverse events. In Part 2, modifications to the specified chemotherapy regimen were at clinician discretion.

**Response Evaluation**

Response evaluation was determined by magnetic resonance imaging (MRI), clinical status, and steroid dosing, according to RANO criteria and incorporated a modification using a 5-point scale to define the extent of T2/FLAIR signal abnormality (modified RANO criteria). PFS for Part 2 was defined as the time between date of progression on Part 1 treatment determined at the trial site (using RANO criteria) and the date of disease progression on Part 2 treatment as determined by central radiology review, or death from any cause. Patients were censored at commencement of any other anticancer therapy or if alive and progression-free at last assessment. Overall survival for Part 2 was calculated from the date of Part 1 site-determined progression to date of death from any cause. The date of progression on Part 1 of the study served as the baseline for patients who participated in Part 2 as in clinical practice this is also likely to be the date at which decisions about further treatment are made, and thus most relevant to comparing survival between alternative treatments. Response rates and progression were determined by central radiology review according to modified RANO criteria.

Precontrast and postcontrast T1 and T2/FLAIR MRI were performed 8-weekly during Part 2, the baseline MRI being defined as the MRI that confirmed Part 1 progression. MRIs were reviewed both by site investigators and centrally. The radiological and clinical assessment of progression at the trial site was used to make decisions about study treatment continuation or cessation. Central radiology review was used for reporting trial endpoints.

Clinical assessments, including physical examination and neurocognitive and QOL assessments, were performed 4-weekly. Following Part 2 progression, monthly follow-up assessments were conducted until the patient died or withdrew from the trial.

**Safety**

Adverse events were classified and graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, and safety data were collected until at least 30 days after the last study treatment. The protocol was approved by all relevant human research ethics committees. Written informed consent was required before any study procedure commencement. Cooperative Trials Group for Neuro-Oncology
Statistical Design and Analysis

We compared two arms: patients randomized to continue bevacizumab versus patients randomized to cease bevacizumab, irrespective of additional treatment received. It was anticipated that approximately 60 patients (50 percent of the Part 1 cohort) would be randomized to Part 2, and as such, Part 2 was powered to detect only a large difference between arms. A sample of 30 patients per group would have provided 80% power to detect a large difference in survival (hazard ratio [HR] of 2, median survival 2 versus 4 months) and a one-sided alpha of 5%. At the time of study design in early 2010, retrospective data reported a median PFS of 2 months for 19 patients with recurrent glioblastoma who discontinued bevacizumab and received other salvage therapies.28

For safety assessments, all patients, except one who withdrew prior to receiving any Part 2 treatment, were included. Efficacy assessments comparing continuing versus ceasing bevacizumab included the intention-to-treat (ITT) population of all randomized patients, using the Kaplan-Meier method to estimate median survival and 6-month survival percentage and proportional hazards regression to calculate the HR. The best responses in each patient were compared between treatments using a chi-square test. In addition, a Cox regression analysis of treatment effect on survival was undertaken with adjustment for key baseline factors: age, sex, performance status, prior recurrence, and planned chemotherapy regimen, as a sensitivity analysis.

The EORTC QLQ-C30 social functioning, overall QOL, role functioning, physical functioning, cognitive functioning, and fatigue, drowsiness, communication deficit and motor dysfunction symptom scales were compared between arms. QOL is reported as time to deterioration, measured as time between the end of Part 1 and first recorded deterioration on the global QOL scale. Deterioration was defined as a decline of ≥10 points on a 0–100 scale persisting for 2 consecutive assessments; or a single decline of ≥10 points on a 0–100 scale where further measurements were not obtained because of progression or death; disease progression on central review without QOL decline or completion; or inability to complete assessments because of neurological deterioration or death. The median and interquartile range (IQR) of time to deterioration was calculated using the Kaplan-Meier method, and the HR for deterioration was calculated using proportional hazards regression.

Mean and maximum daily steroid doses in the first 30 days of treatment were calculated for each patient; the mean calculated by summing total steroid intake divided by 30 or the number of days the patient was on Part 2 treatment, whichever was lower. The medians of these values were compared between arms using the Wilcoxon rank-sum test.

Results

Baseline Characteristics

Characteristics of patients who continued to Part 2 are shown in Table 1. In total, 48 patients (80% of the anticipated n = 60 from Part 1) were recruited to Part 2. There were some differences between the two arms with respect to number of relapses at the time of Part 1 recruitment, with 48% (n = 11) of patients randomized to continue bevacizumab having more than one recurrence, compared with 20% (n = 5) of those randomized to cease bevacizumab (P = .05). Patients with ECOG performance status of 2 and 3 were equally balanced between arms, but with a higher proportion of patients with undocumented status in the bevacizumab continuation arm.

Characteristics of patients who did not continue to Part 2 are shown in Table 1 for comparison. These patients tended to be older, with a poorer performance status and a shorter OS (median 2.0 versus 3.3 months for those randomized). The most common reasons for decisions not to continue onto Part 2 were that the patient was not considered appropriate to receive further chemotherapy or bevacizumab (n = 34); and patient preference (n = 14). Other reasons included death while on Part 1 (n = 5); surgery for recurrence (n = 4); and withdrawal from bevacizumab during Part 1 (n = 4) (Supplementary Table 1). Supplementary Table 2 shows the treatment received after Part 1 for patients who did not continue to Part 2, and for those who had treatment beyond Part 2.

Treatment

Forty-eight of the 120 patients who received at least one dose of study treatment in Part 1 were randomized to Part 2 between July 2011 and September 2013, from 15 of the 18 participating sites (Fig. 2). Of these, 48% were randomized to continuing bevacizumab and 52% to ceasing bevacizumab. Two patients were still receiving treatment on Part 1 at the time of study closure, so were not eligible to participate in Part 2, and received ongoing compassionate access to bevacizumab. The median time from discontinuing Part 1 to randomization to Part 2 was 2.5 days. Chemotherapy choices for both arms were similar (Table 1). One patient randomized to cease bevacizumab chose to discontinue participation, dying 24 days after Part 2 randomization, and is included in the ITT analysis.

Median time on study was 1.5 months for bevacizumab continuation and 1.1 months for bevacizumab cessation. The mean number of bevacizumab doses was 3 (range, 1–14). Reasons for ceasing Part 2 treatment (site-determined) were progression (65%, n = 31), patient choice (23%, n = 11), clinician preference (6%, n = 3), death from cancer (4%, n = 2), and adverse event (2%, n = 1; grade 2 elevated alanine transaminase).
Efficacy

No patients had an objective response, as determined by central radiology review. The best response by site review was stable disease in 30% (n = 7) of those continuing bevacizumab and 8% (n = 2) of those ceasing (P = .047). Only 30 of 48 patients (63%) underwent MRI on Part 2; thus progression was determined clinically for a substantial proportion. There was no difference in median PFS between arms: 1.8 months in the continuation arm and 2.0 months in the cessation arm (HR, 1.08; 95% CI, .59−1.96; P = .81) (Fig. 3a). Six-month PFS was 5% (n = 1) for bevacizumab continuation and 0% for cessation. Progression was determined clinically or as death without documented radiological progression in 22 of 48 participants: 9 (39%) in the continuation arm and 13 (52%) in the cessation arm. In the remainder, a combination of radiological and clinical progression was seen, with no clear differences between arms, and specifically no abundance of nonenhancing T2 progression in the bevacizumab cessation arm (Table 2).

Median OS was 3.4 months (bevacizumab continuation) versus 3.0 months (bevacizumab cessation) (HR, .84; 95% CI, .47−1.50; P = .56) (Fig. 3b). After adjustment for baseline factors, HR, .70; 95% CI .38–1.29; P = .25. Four patients who participated in Part 2 died within 1 month of completing

| Table 1 | Baseline characteristics of patients participating in Part 2 of the CABARET trial |
|-----------------|---------------------------------|---------------------------------|---------------------------------|
| Characteristic                                           | Value                  | Continued bevacizumab (n = 23) | Ceased bevacizumab (n = 25) | Did not continue to Part 2 (n = 74) |
| Age (years) at Part 2 randomization                      | 50 (30–70)             | 54 (34–74)                      | 57 (25–82)                     |
| Sex                                                     | Female 9 (39%)          | 12 (48%)                        | 34 (46%)                       |
|                                                          | Male 14 (61%)           | 13 (52%)                        | 40 (54%)                       |
| ECOG performance status at Part 2 baseline/end Part 1   | 0/1 8 (35%)             | 12 (48%)                        | 13 (18%)                       |
|                                                          | 2 7 (30%)               | 8 (32%)                         | 12 (16%)                       |
|                                                          | 3 3 (13%)               | 3 (12%)                         | 10 (14%)                       |
|                                                          | 4 0                    | 0                               | 5 (7%)                         |
|                                                          | Not recorded 5 (22%)    | 2 (8%)                          | 34 (46%)                       |
| Time on CABARET Part 1 (median months, range)           | 3.6 (1.3–12.9)         | 4.1 (1.7–20.3)                  |                                 |
| Reasons for Part 1 progression                          | T1 MRI changes 4 (17%) | 2 (8%)                          | NA                             |
|                                                          | T2 MRI changes 1 (4%)   | 3 (12%)                         |                                 |
|                                                          | New lesion on MRI 2 (9%)| 1 (4%)                          |                                 |
|                                                          | Clinical only 6 (26%)   | 4 (16%)                         |                                 |
|                                                          | Combination of above 10 (43%) | 15 (60%)                      |                                 |
| Prior diagnosis of grade I–III astrocytoma,             | No 19 (83%)             | 21 (84%)                        | 66 (89%)                       |
| oligoastrocytoma, or oligodendroglioma                  | Yes 4 (17%)             | 4 (16%)                         | 8 (11%)                        |
| Relapse at time of Part 1 recruitment                   | First 12 (52%)          | 19 (76%)                        | 49 (66%)                       |
|                                                          | Second or more 11 (48%) | 5 (20%)                         | 24 (32%)                       |
|                                                          | Unknown 0 (0%)          | 1 (4%)                          | 1 (1%)                         |
| Initial surgery                                          | Biopsy 2 (9%)           | 3 (12%)                         | 10 (14%)                       |
|                                                          | Debulking 6 (26%)       | 8 (32%)                         | 23 (31%)                       |
|                                                          | Resection 15 (65%)      | 14 (56%)                        | 41 (55%)                       |
| Surgery for recurrent disease                           | Unknown 0 (0%)          | 1 (4%)                          | 1 (1%)                         |
|                                                          | No 11 (48%)             | 13 (52%)                        | 42 (57%)                       |
|                                                          | Yes 12 (52%)            | 11 (44%)                        | 31 (42%)                       |
| Corticosteroid use at Part 2 randomization              | No 3 (13%)              | 4 (16%)                         | NA                             |
|                                                          | Yes 20 (87%)            | 21 (84%)                        | NA                             |
| Cytotoxic drug selected for Part 2                      | Carboplatin 13 (57%)   | 13 (52%)                        | NA                             |
|                                                          | Temozolomide 2 (9%)     | 6 (24%)                         |                                 |
|                                                          | Etoposide 7 (30%)       | 5 (20%)                         |                                 |
|                                                          | No chemotherapy 1 (4%)  | 1 (4%)                          |                                 |
Part 1; 3 in the cessation arm and 1 in the continuation arm. All 4 patients were reported as dying from cancer but none were able to undergo MRI showing RANO progression. These patients are included in all analyses.

Exploratory sensitivity analyses using date of randomization as the baseline date instead of date of progression on Part 1 to calculate PFS and OS also did not result in differences in survival times between arms (data not shown).

Median survival for the cohort of 48 patients who continued to Part 2 was 3.3 months (95% CI, 2.5–3.9) and median survival for the 64 patients who did not go on to Part 2 was 2.0 months (95% CI, 1.4–2.9).

Safety

Treatment-related adverse events are shown in Table 3. There were no unexpected toxicities and no grade 5 toxicities. Ten patients (43%) who continued and 8 (33%) who ceased bevacizumab experienced grade 3 or 4 toxicities. The most common toxicities in both arms were hypertension and fatigue. Specific bevacizumab-related toxicities, including bleeding, deep-vein thrombosis, proteinuria, and hypertension, occurred more frequently in the continuation arm and were uncommon, with the exception of low-grade hypertension, in both arms.

Quality of Life

Some patients in Part 2 did not complete QOL questionnaires beyond baseline, largely because they were too unwell. Completion rates in both arms were similar, with 37 (77%) completing QOL assessment at Part 2 baseline, 24/28 (86%) at 4 weeks, 8/8 (100%) at 8 weeks, and 4/4 (100%) at 12 weeks. The median (IQR) time to deterioration in overall QOL for patients who continued bevacizumab was 1.15 (0.89–1.64) months, and 1.64 (0.85–2.04) months for those who ceased bevacizumab (HR = 1.25 for the continuation arm relative to the cessation arm, 95% CI, .70–2.24, \( P = .45 \)). This takes into consideration all patients on study including those who did not complete questionnaires beyond baseline (which was classified as a deterioration for the purposes of the trial). Median times were similar, and there were no clinically or statistically significant differences between arms in any of the subscales tested. For most patients, QOL deterioration was attributed to not completing QOL tools because of neurological deterioration, progression, or death (as specified as a determinant of QOL deterioration) rather than to completed QOL questionnaires having a decrease of 10 points or more.

Steroid Dosing

Mean daily steroid doses in the first 30 days of treatment were similar in both arms, ranging from 0 to 16 mg/day for patients in the continuation arm and 0 to 18 mg/day in the cessation arm (median 4 mg/day in both arms, \( P = .6 \)). Maximum daily dose per patient ranged from 0 to 16 mg/day in the continuation arm (median 4 mg/day) and 0 to 36 mg/day in the cessation arm (median 8 mg/day), although the higher maximum daily dose in the cessation arm was not statistically significantly different from the continuation arm (\( P = .55 \)).
Discussion

In this first prospective, randomized clinical trial of continuing versus ceasing bevacizumab beyond progression in recurrent glioblastoma, we were not able to show a significant difference in PFS or OS between arms. However, with the small sample size, the confidence intervals on survival benefits are wide, ruling out only very large effects. Further, an analysis adjusted for some imbalances in baseline factors suggests that moderate effects of continuing bevacizumab are possible. Consequently, this remains an open question, and ultimately a phase 3 study would be required to demonstrate smaller but important benefits of continuing bevacizumab are possible. Nevertheless, Part 2 of CABARET has demonstrated that randomizing patients to continue or cease bevacizumab in this context is indeed feasible and in the absence of a clear effect, further study of the question is warranted.

Median OS for both arms on Part 2 of CABARET was short, and poorer than reported in similar study settings.\textsuperscript{28,29} No radiological responses were seen, and the higher proportion with recorded stable disease in the continuation arm did not translate to any survival benefit, although it is important to note that many patients did not actually receive their first planned Part 2 MRI and many who did, did not have a subsequent one. From the limited results using the MRIs that were performed, ceasing bevacizumab on progression did not appear detrimental, with no overabundance of rebound effects radiologically in the discontinuation arm. Nevertheless, with the large proportion of patients who did not undergo MRI we are unable to conclude that this does not occur.

Two other important study endpoints, QOL and corticosteroid use, have also been reported. There was no evidence that bevacizumab continuation was associated with better QOL; but we cannot exclude the possibility of a difference that was simply not detected, owing to the low statistical power of this study. The maximum recorded steroid dose included up to 36 mg per day in the cessation arm compared with up to 16 mg per day in the continuation arm, which is a clinically relevant difference. While there was no statistically significant difference in median values for maximum or mean daily steroid dose, again this may relate to the small sample. In retrospective studies, conflict surrounds the merits of continuing or ceasing bevacizumab. While rapid rebound is a noted concern in some studies,\textsuperscript{14,16,17} others have indicated it may be safe to discontinue bevacizumab for some patients. A small retrospective series of 7 patients discontinuing bevacizumab for reasons other than progression demonstrated a median time to recurrence after discontinuation of 4 months (range 1–26) and a 6-month PFS as high as 43%.\textsuperscript{30} Three of five patients who resumed bevacizumab had a partial response.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Reason for progression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Continued bevacizumab (n = 23)</td>
</tr>
<tr>
<td>T1 + T2 + clinical</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>clinical only; MRI completed but not showing progression</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>T1 + T2 + new lesion + clinical</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>T1 + T2 + new lesion</td>
<td>0</td>
</tr>
<tr>
<td>T1 + T2</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>T2 + new lesion + clinical</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>T2 + clinical</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>T1 + new lesion + clinical</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>T1 + new lesion</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>T1 + clinical</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>T2 only</td>
<td>0</td>
</tr>
<tr>
<td>Clinical deterioration or death without MRI completed to confirm progression</td>
<td>9 (39%)</td>
</tr>
<tr>
<td>Censored*</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

* Commenced other anticancer treatment
Several publications specifically addressing the role of bevacizumab beyond progression in glioma have been reported since CABARET was designed. Reardon et al published a retrospective pooled analysis of 99 participants in single-arm, phase 2 studies of bevacizumab, comparing outcomes after on-trial progression for those who did and did not continue bevacizumab.31 Median OS was longer for those continuing bevacizumab (5.9 versus 4.0 months), and bevacizumab was an independent predictor of survival in multivariable analysis. Other retrospective series indicate at best a modest effect of continuing bevacizumab beyond progression,17,18,32 including a retrospective review of 42 patients receiving ongoing bevacizumab plus nitrosourea chemotherapy after bevacizumab failure, which did not show any benefit in continuation; response rate was 0% and 6-month PFS was 3%, in keeping with our findings.33 Several prospective phase 2, single-arm studies of bevacizumab continuation after progression have similarly shown no responses, and PFS and OS data together demonstrate doubtful clinically meaningful benefit.7,28,29

The TAMIGA study, a prospective randomized phase 2 trial is yet to report results but will be the only other prospective study to compare continuation and cessation of bevacizumab.34

There are a number of important limitations to this study. First, the small sample size and that the lower number of patients recruited than anticipated meant that it is not possible to draw definitive conclusions on the effectiveness of continuing bevacizumab. Median OS was longer for those continuing bevacizumab (5.9 versus 4.0 months), and bevacizumab was an independent predictor of survival in multivariable analysis. Other retrospective series indicate at best a modest effect of continuing bevacizumab beyond progression,17,18,32 including a retrospective review of 42 patients receiving ongoing bevacizumab plus nitrosourea chemotherapy after bevacizumab failure, which did not show any benefit in continuation; response rate was 0% and 6-month PFS was 3%, in keeping with our findings.33 Several prospective phase 2, single-arm studies of bevacizumab continuation after progression have similarly shown no responses, and PFS and OS data together demonstrate doubtful clinically meaningful benefit.7,28,29

The TAMIGA study, a prospective randomized phase 2 trial is yet to report results but will be the only other prospective study to compare continuation and cessation of bevacizumab.34

There are a number of important limitations to this study. First, the small sample size and that the lower number of patients recruited than anticipated meant that it is not possible to draw definitive conclusions on the effectiveness of continuing bevacizumab. But Part 2 of CABARET was only intended as an exploratory study of this question to rule out very large effects and to demonstrate the feasibility of a larger trial subsequently. Second, only 80% of the planned 60 patients were able to be enrolled. This partly represents the difficulties of recruiting patients with more than one recurrence of glioblastoma, the disease not uncommonly rendering them too unwell for participation in a clinical trial. Indeed, beyond Part 2, only 10 of 48 patients then went on to receive any further therapy (Supplementary Table 2).

### Table 3  Toxicity

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade</th>
<th>Continued bevacizumab (n = 23)</th>
<th>Ceased bevacizumab (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>All grades</td>
<td>1 (4%)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>All grades</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Neutropenia (without fever)</td>
<td>All grades</td>
<td>3 (13%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>All grades</td>
<td>7 (30%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>2 (9%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>All grades</td>
<td>7 (30%)</td>
<td>8 (33%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>All grades</td>
<td>3 (13%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>All grades</td>
<td>6 (26%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>All grades</td>
<td>20 (87%)</td>
<td>13 (54%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>2 (9%)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Central nervous system hemorrhage</td>
<td>All grades</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>All grades</td>
<td>3 (13%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>All grades</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>All grades</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>All grades</td>
<td>19 (83%)</td>
<td>17 (71%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Abscess</td>
<td>All grades</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* One patient declined to participate after randomization and no further toxicity data are available.
We had already anticipated a 50% drop-out from Part 1 to Part 2, and were aware that, given this was a phase 2 study, Part 2 was aimed mainly to provide information on potential signals for efficacy that might warrant further investigation. Regarding reasons why participants did not continue on to Part 2, usually this was because they were considered not well enough for additional therapy; this is reflected in lower ECOG performance status and lower median survival (2 months in this group versus 3.3 months).

A further limitation is related to chance imbalances in baseline factors at the time of randomization to Part 2, with more patients having more than one recurrence among those assigned to the continuing-bevacizumab arm. Survival analysis with adjustment for this and other baseline factors did not show a significant survival effect between treatments, but confidence intervals did suggest that an even larger effect of continuing bevacizumab could have been missed (compared with the unadjusted analysis).

One concern raised has been whether patients randomized are representative, with many patients being considered to be uncomfortable about ceasing bevacizumab; however, bevacizumab was not otherwise available in Australia for such patients other than on compassionate use, and after ceasing Part 1 of CABARET, only 2 went on to receive further bevacizumab (Supplementary Table 2).

An additional limitation is the restricted chemotherapeutic choices (temozolomide, etoposide, or carboplatin) for patients after recurrence on Part 1, and the unavailability of the nitrosourea lomustine as an option. These choices available to clinicians at that time were pragmatic and represented standard (Australian) second- and third-line approaches at the time of study design, but have not been shown to improve survival, and rechallenge with temozolomide would generally only be considered from a clinical perspective if progression has not occurred during prior therapy with the drug. Lomustine is now used more commonly in this setting, both in Australia and elsewhere, and has been the reference arm for several prominent clinical trials, none of which had been presented or published by the time of study design. The choice of chemotherapeutic regimen is less critical to the trial question, since chemotherapy choices were made before randomization and were well balanced between the 2 arms of the trial, which examined the additional value of continuing or stopping bevacizumab on the background of whatever other therapy was chosen.

This study represented a real-world patient cohort. Patients with multiple relapses were eligible; and while performance status was stipulated for Part 1, for Part 2, 6 patients with ECOG 3 were eligible to participate on the basis of their clinician’s decision that they were suitable for additional active treatment. The second randomization itself selected for relatively well patients, that is, those who were considered well enough to continue therapy for their disease, which may limit the generalizability of our findings to the broader population of patients with recurrent glioblastoma but may be very applicable to a population considering continuation or cessation of bevacizumab following progression on this agent.

A substantial proportion of patients in each treatment arm died without documented radiological progression, presumably being too unwell to undergo MRI. This highlights the limitations of using PFS as an endpoint compared with the unequivocal endpoint of OS. It is possible that differences in radiological outcomes between continuing and ceasing bevacizumab were not adequately documented, and radiological PFS has not been captured for all patients in this study. While there were no signals suggesting obvious differences between the 2 arms for those completing scheduled imaging, the proportion who did not have follow-up MRI means that we cannot conclusively state that there is no difference in types of radiological progression. However, in patients with glioblastoma, death almost invariably is a consequence of disease progression. Thus, clinical progression without MRI documentation is still true progression. MRI testing every 4 weeks may have increased the proportion of patients with documented radiological progression, but was not feasible.

In conclusion, Part 2 of the CABARET clinical trial provides the first randomized evidence on the value of continuing or stopping bevacizumab after progression in patients with recurrent glioblastoma. The study has not been able to demonstrate any significant benefits of continuing bevacizumab, but on the basis of its small sample, only very large benefits have been excluded, and the value of such treatment remains a very open question. The trial does suggest that randomizing patients to this question is challenging, but provides evidence that it is feasible, and further pursuit of this question in a future phase 3 trial should be supported.

Supplementary Material
Supplementary material is available at Neuro-Oncology Practice online.

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This trial was conducted under the auspices of the Cooperative Trials Group for Neuro-Oncology (COGNO), coordinated at the NHMRC Clinical Trials Centre, University of Sydney, and supported by Roche Products Pty Limited (Australia). Rhana Pike from the Clinical Trials Centre edited the paper.

Trial Management Committee K Field (chair), J Simes, E Hovey, A Nowak, L Cher, H Wheeler, C Brown, E Barnes, K Sawkins, A Livingstone, M Rosenthal
Hovey et al. Bevacizumab after glioblastoma progression

Independent Central Radiological Review Committee
P Phal, G Pitt, C Goh

Independent Data Safety Monitoring Committee
M Tattersall (Chair), P Kelly, A Hayden

Clinical Trials Centre
K Sawkins, E Barnes, D Espinoza, C Brown, A Livingstone, D Winter, B Tomes, R Pike, J Simes

The following study sites participated in the CABARET study and randomized at least one patient to Part 2 (principal investigator and site coordinator):
Royal Melbourne Hospital, Victoria—K Field/M Rosenthal, L Garrett (7); Prince of Wales Hospital, New South Wales—E Hovey, H Kilby (6); Monash Medical Centre, Victoria—R Freilich, I Arzihant (5); St Vincent’s Hospital, Victoria—A Dowling, N Ranieri (4); Epworth HealthCare Richmond, Victoria—R Jennens, F Osmond (4); The Queen Elizabeth Hospital, South Australia—WK Patterson, A Phay (4); Royal Prince Alfred Hospital, New South Wales—J Simes, A Byrne (3); Port Macquarie Base Hospital, New South Wales—S Begbie, P Williams (3); Royal North Shore Hospital, New South Wales—H Wheeler, S Kirby-Lewis (2); Calvary Mater Newcastle, New South Wales—F Abell, L Plowman (2); Austin Hospital, Victoria—L Cher, J Flynn (2); Royal Brisbane and Women’s Hospital, Queensland—P Inglis, A Ives (2); Sir Charles Gairdner Hospital, Western Australia—A Nowak, S Lobb (2); Mater Adult Hospital, Queensland—Z Lwin/N Woodward, G Crosbie (1); Royal Adelaide Hospital, South Australia—N Singhal, S Smith and M Whelan (1).

CABARET Part 1 was reported at the American Society of Clinical Oncology Annual Meeting (2013); the Society for Neuro-Oncology Annual Meeting (2012); the Australian Cooperative Trials Group for Neuro-Oncology annual meetings (2012–2014); the European Association for Neuro-Oncology and European Society of Medical Oncology annual meetings (2012). The results from CABARET Part 2 were presented at the American Society of Clinical Oncology Annual Meeting (2015).

CABARET was prospectively registered with the Australian New Zealand Clinical Trials Registry (ANZCTR), ACTRN12610000915055 (anzctr.org.au).

Conflict of interest statement. EJH has had consulting or advisory roles for Bayer, Janssen Oncology, Pfizer, and Roche, and has received travel grants from GlaxoSmithKline and Sanofi. KMF has received travel grants from Roche.

LC has received honoraria from and has had consulting or advisory roles for Roche Pharma AG, and has received institutional research funding from Celldex, Lilly, Merck, and Roche.

AKN has had consulting or advisory roles for Boehringer Ingelheim and Roche and has received research funding from Boehringer Ingelheim.

JS and KS have received institutional research funding from Roche through the Clinical Trials Centre.

References

**Supplementary Table 1: Reasons for not continuing onto Part 2 (n=72)**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not suitable for further chemotherapy</td>
<td>22 (31%)</td>
</tr>
<tr>
<td>Patient preference</td>
<td>14 (19%)</td>
</tr>
<tr>
<td>Not suitable for further bevacizumab</td>
<td>12 (17%)</td>
</tr>
<tr>
<td>Disease progression/death</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Withdrawn from bevacizumab in Part 1</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Surgery/likely surgery</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Withdrew from Part 1 prior to commencing treatment</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Receiving compassionate bevacizumab</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Cognitive decline</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Family decision</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Commenced carboplatin/etoposide</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>No site-determined progressive disease on Part 1</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>
**Supplementary Table 2a:** Treatment after CABARET Part 1 for patients who did not go on to Part 2 (n=72)

<table>
<thead>
<tr>
<th>Anti-cancer treatment</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>None</td>
<td>46 (64%)</td>
</tr>
<tr>
<td>Treatment</td>
<td>23 (32%)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>5 (22%)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Carboplatin/etoposide, irinotecan</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Radiotherapy, surgery, carboplatin, temozolomide</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>
**Supplementary Table 2b: Treatment after CABARET Part 2 (n=48)**

<table>
<thead>
<tr>
<th>Anti-cancer treatment</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>38 (79%)</td>
</tr>
<tr>
<td>Treatment</td>
<td>10 (21%)</td>
</tr>
<tr>
<td>BCNU/carmustine</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Lomustine</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>1 (10%)</td>
</tr>
</tbody>
</table>
Chapter 5: Quality of life in patients on the CABARET Trial
Health-related quality of life outcomes from CABARET: a randomized phase 2 trial of carboplatin and bevacizumab in recurrent glioblastoma

Kathryn M. Field1,2 · Madeleine T. King3 · John Simes4 · David Espinoza4 · Elizabeth H. Barnes4 · Kate Sawkins4 · Mark A. Rosenthal1,2 · Lawrence Cher5 · Elizabeth Hovey6,7 · Helen Wheeler8 · Anna K. Nowak9,10

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Abstract In recurrent glioblastoma, health-related quality of life (HRQL) is a crucial trial endpoint. We examined HRQL outcomes as a secondary endpoint for patients in the CABARET randomized phase 2 trial. 122 patients were randomly allocated to bevacizumab monotherapy or bevacizumab plus carboplatin. We calculated change scores from baseline for each HRQL measure on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the Brain Cancer Module (QLQ-BN20), together with time to deterioration in HRQL, and the proportion of participants with clinically meaningful improvements in specific disease-related symptoms. At baseline, 117 of 122 randomized patients (96%) attempted questionnaires. Questionnaire participation rates were >90% for patients continuing on treatment, however at the end-of-treatment visit only 72 (64% of eligible participants) returned a form. There were no differences between arms in change scores over the treatment period. Time to ≥10 point deterioration in scores from baseline was also similar between arms. HRQL deterioration occurred largely before progression for the domains tested, but scores in HRQL domains specifically relevant to symptoms of recurrent glioblastoma also improved for about 50% of patients with symptoms at baseline. Neither detrimental nor beneficial effects on HRQL were seen with carboplatin added to bevacizumab, with a proportion of patients on both arms experiencing symptomatic benefit. Given the reduced questionnaire completion at end of treatment, time to HRQL deterioration is a feasible and robust clinical trial endpoint in this patient population. Clinical trials registration number: ACTRN12610000915055.

Keywords Glioblastoma · Quality of life · Bevacizumab · Carboplatin · QLQ-C30 · BN20 · Clinical trial

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Trial registration Clinical trials registration number: ACTRN12610000915055.

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Introduction

Recurrent glioblastoma is associated with a grim prognosis. Despite global research efforts, no treatments have been shown to confer substantial survival benefit in large-scale clinical trials, and progression within weeks to months of commencing any second line treatment is almost inevitable. It is therefore crucial to ensure that treatment is not increasing morbidity by adversely affecting health-related quality of life (HRQL), and further, to establish whether any treatment could improve HRQL for individuals affected by this devastating cancer.

In the CABARET randomized phase 2 clinical trial, we compared bevacizumab monotherapy with bevacizumab plus carboplatin in adult patients with recurrent glioblastoma [1]. The primary outcome of the study, progression-free survival, showed no difference between arms [1]. A secondary endpoint was to compare HRQL outcomes between the two arms, which was particularly important given the potential for an additional cytotoxic drug to add to toxicity and consequent HRQL losses.

Here we present HRQL results for Part 1 of the CABARET study, in which patients were randomized to receive either bevacizumab or bevacizumab plus carboplatin. For the smaller Part 2 of the trial (a second randomization assessing continuation vs. cessation of bevacizumab after recurrence on Part 1), HRQL outcomes, already reported, showed no difference in time to deterioration in overall HRQL for patients who continued and those who ceased bevacizumab [2]. In this paper, we describe HRQL in the study population and assess whether adding carboplatin to bevacizumab resulted in either improvement in or detriment to HRQL. At the trial outset, we postulated that any PFS benefit of adding carboplatin may also translate to improvement in HRQL. Given the negative primary results of the study, we then wished to understand whether the addition of carboplatin resulted in worse HRQL outcomes due to additional treatment side effects, or whether HRQL changes were largely determined by disease status. The trial design also allowed us to gain understanding of the proportion of patients experiencing symptomatic benefit when exposed to bevacizumab treatment on either study arm.

Methods

Eligibility

The eligibility criteria for the CABARET clinical trial have been described in detail previously [1]. Briefly, consenting adults (over 18 years) with recurrent glioblastoma who had previously been treated with radiotherapy and temozolomide chemotherapy, with Eastern Cooperative Oncology Group (ECOG) performance status 2 or better, and adequate hematological and other organ function, were eligible to participate. Patients with more than one recurrence and no prior treatment other than radiotherapy or temozolomide were eligible.

Trial design and treatments

Patients in Part 1 of CABARET were randomly assigned to receive either intravenous bevacizumab monotherapy (5 mg/kg every 2 weeks), or intravenous bevacizumab at the same dose plus intravenous carboplatin (area under the curve (AUC) = 5, every 4 weeks). Randomization was stratified by treatment center, age, sex, and ECOG performance status. The efficacy endpoints of the trial and its conduct have been published [1]. Written consent was obtained from each participant. Patients were expected to complete planned HRQL assessments while on the study, and were considered off-study when treatment ceased owing to site-determined disease progression, unacceptable toxicities, or death.

HRQL assessment and scoring

We used the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 Version 3.0 (QLQ-C30) and Brain Cancer Module (QLQ-BN20); both are well-validated instruments and have been used in many clinical trials [3, 4]. The QLQ-C30, the core questionnaire of the EORTC’s modular HRQL suite, covers core domains of HRQL and symptoms common to all cancer. It is designed to be complemented by site-specific modules, such as the QLQ-BN20, designed specifically for brain cancer patients. Together, they cover a comprehensive set of HRQL issues pertinent to patients in the CABARET trial, and enable comparison with other trials.

The QLQ-C30 contains 30 items covering five aspects of functioning (physical, role, emotional, cognitive, social), eight symptoms (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea), financial impact, and global health status/quality of life (global HRQL). The QLQ-BN20 covers future uncertainty, visual disorder, motor dysfunction, communication deficit, headache, seizures, drowsiness, hair loss, itching, difficulty with bladder control, and weakness of both legs. Patients respond by self-report, with most items rated on a 4-point scale, from 1 “not at all” to 4 “very much”, except for the two global health status/quality of life items, which are measured on a 7-point Likert scale (“very poor” through “excellent”). Patient responses are scored on HRQL measurement scales according to standard algorithms [5]. Some scales represent the average of several items, while others
contain only a single item. All scales have a 0–100 range, but the direction differs, with a higher score representing better outcomes for functioning domains and global HRQL, while for symptoms, a higher score represents greater frequency and/or impact of the symptom. Improvement in function is represented by an increase in score, whereas improvement in symptoms is represented by a decrease in score.

Six domains from the QLQ-BN20 were identified by clinician consensus to potentially represent baseline symptoms of progressive glioblastoma, specifically: cognitive functioning (2 items), communication deficit (3), drowsiness (1), headaches (1), motor dysfunction (3), and visual disorder (3). The number of patients with baseline deficits with potential for at least 10-point improvement in each domain were identified.

HRQL assessments occurred at baseline (before treatment), on day 1 or up to 3 days before each 4-week treatment cycle, and at the end of treatment. Wherever possible, the HRQL questionnaires were completed before the patient was reviewed and underwent treatment for that cycle in order to avoid potential bias from patients being aware of their disease status at the time of progression. Questionnaires were completed on day 1 of each cycle, as this was the day patients were in hospital. No further HRQL testing was conducted after 30 days beyond the date of trial closure (December 2014).

Participation in HRQL assessment was mandatory; the site research nurse administered the questionnaires at each relevant time point. Additional explanation or reading instructions and questions aloud for patients with visual or reading difficulty was allowed; however, only the patient could complete the questionnaire. Reasons for non-completion were documented wherever possible.

### Statistical analysis

A prespecified HRQL statistical analysis plan was developed before the database was interrogated for the purpose of the HRQL analysis. All statistical analyses were conducted in SAS9.3 (SAS Institute Inc., Cary, NC, USA.), with no adjustment for multiple statistical comparisons.

HRQL assessment participation rate (‘Participation’) was calculated as the number of patients who were administered the questionnaires at designated time points divided by the total number of patients still on the study and expected to complete at each time point (the ‘number expected’ population) [6]. Additionally, for participating patients, we calculated the proportion of items completed of the total of 50 items in the QLQ-C30 and QLQ-BN20 (‘Completion’).

The sample size of 120 for the CABARET trial was determined by the primary endpoint of progression-free survival; analyses of HRQL and other secondary endpoints are exploratory in this phase 2 study. Eight domains were prespecified in the HRQL analysis plan, selected on the basis of clinical rationale and their representativeness of the effect of glioblastoma on function and symptoms: global HRQL, social functioning, role function, physical function, cognitive function, drowsiness, communication deficit, and motor dysfunction. Descriptive analyses are presented for baseline scores and the mean difference from baseline at each time point. Mean change scores were calculated as the difference between a patient’s baseline score and their average score on treatment. This was calculated for all patients remaining progression-free who had two or more HRQL results for each domain, and then combined as the mean of all participants’ mean change scores from baseline for each domain tested. The treatment effect on the change scores was assessed using a two sample t test, as a difference in means between treatment arms. This was exploratory and uncorrected for multiple comparisons. We also assessed the proportions of patients who improved and who deteriorated from baseline [6]. A 10-point change was selected, as it is commonly considered to be the minimum clinically relevant change in a 0–100 HRQL scale [7]. For each of the eight selected domains, logistic regression was used to estimate odds ratios to compare trial arms for the effect of treatment on the proportions of patients with a ≥ 10 point improvement, and separately for a ≥ 10 point deterioration. The models included randomized treatment only and were not adjusted for any other risk factors.

The Kaplan–Meier method was used to determine the median time to HRQL scale deterioration (≥10 points), progression or death, whichever came first, for the same eight domains. Proportional-hazards regression models were used to determine hazard ratios for the effect of treatment on this outcome. Time to deterioration in HRQL was measured as the time between randomization and the first recorded deterioration in that scale or item. Deterioration was defined as a worsening of ≥10 points on a 0–100 scale persisting for at least 4 weeks, or a single worsening of ≥10 points on a 0–100 scale where further measurements had not been obtained because of progression, death, or inability to complete the questionnaires due to clinical deterioration. Patients whose HRQL did not deteriorate and remained alive or were lost to follow-up were censored at the date of last contact.

### Results

Between November 2010 and March 2012, 122 patients were enrolled in the CABARET trial from 18 sites across Australia, with 120 receiving at least one study treatment and two patients declining participation after
randomization. At baseline, 117 of the 122 randomized patients (96%) participated in HRQL questionnaires, and 116 provided analyzable data. Baseline characteristics of these patients, which were similar in the two randomized arms, are shown in Supplementary Table 1.

**Participation and completion**

Participation and completion rates for scheduled assessments and items within questionnaires were over 90% at baseline and the majority of treatment cycles, and similar in the two arms of the study (Table 1). From cycle 9 (approximately week 36) onwards, reported participation and completion was, at almost all time points, 100% for the small number of patients who continued on treatment beyond that point. At the end-of-treatment timepoint, 113 of the 122 randomized patients were potentially able to complete HRQL questionnaires, after exclusion of two who withdrew before starting treatment, five who died without progression, and two who continued treatment without site-determined progression. Participation rates were lower at this timepoint: \( n = 72, 64\% \). Reasons for non-participation at the end of treatment were documented and are shown in Supplementary Table 2. Twenty-three (56% of the 41 eligible patients who did not fill out HRQL questionnaires at end of treatment) did not so because they were too unwell at the time.

**Baseline and change scores**

Scores at baseline for all domains of the EORTC QLQ-C30 and QLQ-BN20 questionnaires are available in Supplementary Table 3. QLQ-C30 scores were similar to expected reference values for patients with brain cancer [5, 8]. Mean change scores for global QOL are depicted in Fig. 1, and for each domain in Supplementary Table 4. There was no evidence of a difference between the two arms for the overall mean of the mean changes from baseline for any domain of the QLQ-C30 or QLQ-BN20. In both arms of the trial, physical functioning and role functioning (QLQ-C30) and future uncertainty and headaches (QLQ-BN20) were associated with the largest negative change in score from baseline, the largest of which was 13.3 points (mean, for future uncertainty, combination arm) (Supplementary Table 4).

**Clinically significant changes**

Results for proportions of patients with a \( \geq 10 \) point change (improvement or deterioration) are shown in Table 2. There was no evidence of any difference in the odds of improvement or deterioration between treatment groups. Results from both arms combined are henceforth discussed, where appropriate, in this paper.

All but 1 of 116 patients with analyzable data for these domains reported baseline scores with potential for at least 10-point improvement in at least one of six domains from

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**Table 1** Participation in testing for health-related quality of life (HRQL) by patients in the CABARET trial, Part 11

<table>
<thead>
<tr>
<th>Cycle number (^a)</th>
<th>Patients still on the study (n)</th>
<th>Survey participation (^b) ((n%))</th>
<th>Completion, (^c) bevacizumab monotherapy (%)</th>
<th>Completion, (^c) bevacizumab + carboplatin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>122</td>
<td>117 (96)</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>115</td>
<td>111 (97)</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>89</td>
<td>86 (97)</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>68 (97)</td>
<td>99</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>48 (96)</td>
<td>99</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>41</td>
<td>41 (100)</td>
<td>99</td>
<td>99</td>
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<tr>
<td>7</td>
<td>31</td>
<td>30 (97)</td>
<td>100</td>
<td>99</td>
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<td>8</td>
<td>29</td>
<td>27 (93)</td>
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<td>9</td>
<td>18</td>
<td>18 (100)</td>
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<td>6 (100)</td>
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<td>5 (100)</td>
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<td>100</td>
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<tr>
<td>30</td>
<td>5</td>
<td>4 (80)</td>
<td>100</td>
<td>100</td>
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<tr>
<td>35</td>
<td>2</td>
<td>2 (100)</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>End of treatment</td>
<td>113</td>
<td>72 (64)</td>
<td>97</td>
<td>98</td>
</tr>
</tbody>
</table>

\(^a\) After cycle 10, every fifth cycle is shown

\(^b\) Participation is defined as having received and attempted HRQL questionnaires

\(^c\) Completion is defined as the total number of questionnaire items completed divided by the expected number of items, for participants who received and attempted HRQL questionnaires
the QLQ-BN20 prespecified to represent symptoms of progressive glioblastoma, specifically: cognitive functioning (24%), communication deficit (23%), drowsiness (15%), headaches (28%), motor dysfunction (25%), and visual disorder (39%). Most patients reported multiple symptoms with potential for improvement: 79 (68%) reported four or more. Almost half (53/115, 46%) reported an improvement of ≥10 points in at least one of these domains, with 19 (17%) improving in one domain, 12 (10%) in two domains, 15 (13%) in three domains, and 7 (6%) in four domains.
There was no discernible pattern to improvements, which varied in keeping with the unique pattern of symptoms experienced by individual patients. These results suggest that approximately half of all patients treated on either arm experienced a clinically relevant improvement during treatment in one or more domains that were likely to represent symptoms or signs of their disease.

Sustained improvements over baseline (≥10 points for at least two time points) were most commonly reported in motor dysfunction and cognitive, role, and social function in both arms, possibly reflecting a therapeutic effect of treatment in either study arm.

**Time to deterioration**

Overall, for Part 1 of CABARET, the median progression-free survival was 3.5 months for each arm as determined by central radiological review. Comparison between arms for time to HRQL deterioration, disease progression, or death for the eight selected domains are shown in Table 3. The hazard ratios (HR) are for the combination arm relative to bevacizumab monotherapy. Deterioration in HRQL was seen earlier than the reported median progression-free survival (as defined by the RANO criteria) of 3.5 months, in all prespecified domains, with no evidence of differences between arms, although deterioration across most domains was somewhat slower for the combination arm. Post hoc analysis combining the two treatment arms showed that across the eight prespecified domains, approximately two-thirds of patients had a single or sustained (over 2 or more questionnaire time points) deterioration of HRQL that preceded radiological or clinical disease progression and cessation of treatment. In total, 43 of 122 patients (35%) had a sustained ≥10 point deterioration in the overall QOL score over two or more visits before disease progression; and another 34 (28%) a decrease at a single time point before progression, death, or inability to complete further assessments. Figure 2 shows the Kaplan–Meier survival curve for time to deterioration for global QOL, with no evidence of any difference in event rates between the two arms.

**Table 3** Months to deterioration in score or disease progression or death

<table>
<thead>
<tr>
<th>Domain</th>
<th>Treatment group</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bevacizumab monotherapy median (IQR)</td>
<td>Bevacizumab + carboplatin median (IQR)</td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>2.1 (1.8–2.9)</td>
<td>3.0 (2.0–3.7)</td>
<td>0.84 (0.58–1.21)</td>
</tr>
<tr>
<td>Quality of life</td>
<td>2.0 (1.8–2.9)</td>
<td>3.4 (2.2–3.7)</td>
<td>0.83 (0.58–1.20)</td>
</tr>
<tr>
<td>Role function</td>
<td>1.9 (1.2–2.8)</td>
<td>2.2 (1.9–3.5)</td>
<td>0.77 (0.54–1.11)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>2.0 (1.8–2.8)</td>
<td>2.1 (1.8–2.9)</td>
<td>0.93 (0.65–1.34)</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>2.3 (1.8–3.5)</td>
<td>2.2 (1.9–3.3)</td>
<td>1.07 (0.74–1.53)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>2.1 (1.8–2.8)</td>
<td>2.8 (2.0–3.5)</td>
<td>0.95 (0.66–1.36)</td>
</tr>
<tr>
<td>Communication deficit</td>
<td>2.0 (1.8–2.8)</td>
<td>3.1 (2.1–3.8)</td>
<td>0.79 (0.55–1.13)</td>
</tr>
<tr>
<td>Motor dysfunction</td>
<td>2.0 (1.8–2.8)</td>
<td>3.2 (2.2–3.8)</td>
<td>0.82 (0.57–1.18)</td>
</tr>
</tbody>
</table>

*IQR* Interquartile range, *HR* Hazard ratio

*aHazard ratio for bevacizumab + carboplatin relative to bevacizumab monotherapy

**Discussion**

In this randomized phase 2 study comparing bevacizumab monotherapy with bevacizumab plus carboplatin chemotherapy, we did not observe any clear differences between arms with respect to HRQL outcomes. While adding carboplatin to bevacizumab did not result in improved PFS, neither was it associated with worse HRQL in patients who received chemotherapy in addition to bevacizumab. While there was a >10 point difference between arms at some
time points for global QOL (Fig. 1), the wide confidence intervals reflect the small sample size at these times, and no statistically significant differences occurred in mean change scores overall for any domain. HRQL participation rates were excellent except at the end-of-treatment visit.

For all eight prespecified domains, the median time to deterioration was shorter than the median time to clinical or radiological progression, and for each of these domains more than 50% of patients experienced at least one deterioration in score before disease progression was documented. This could potentially signify an effect of treatment itself on the domains, but alternatively could represent subtle, subclinical disease progression before a formal radiological or clinical finding of progressive disease. Similar observations of deteriorating neurocognitive function prior to, and heralding, radiological progression have been reported [9, 10]. This may be particularly pertinent in the setting of bevacizumab treatment, where the antiangiogenic effects can reduce perfusion, thus obscuring contrast enhancement and clear evidence of radiological progression [11].

HRQL assessment provides valuable information in many clinical trials, especially where overall survival is poor and therefore an individual’s remaining life must be optimized for quality. In CABARET, we were able to achieve excellent HRQL compliance, with the exception of the end-of-treatment visit, which usually coincided with radiological or clinical progression (or both). This supports the feasibility of including HRQL assessment in clinical trials in advanced glioma after first-line therapy, and demonstrates that patients are able to complete a 50-item questionnaire in this setting. Our excellent completion rates may also reinforce the importance of staff training and a protocol requiring patients to complete HRQL questionnaires before receiving information on treatment response or discontinuation; these were issues that received attention in CABARET. Completion rates for patients on treatment were similar to or better than those from the BELOB study, a contemporary randomized trial in a similar recurrent-glioblastoma population [12]. In the BELOB HRQL study, compliance at the end of treatment dropped significantly. While missing data will continue to be an issue in such trials, especially at the time of disease progression, we postulate that a tight window in which to complete HRQL questionnaires and protocol-mandated conduct of HRQL testing with careful instructions for research nurses contributed to the excellent completion rates during treatment.

There are several possible approaches to the analysis of HRQL results. This has been a contentious issue recently, particularly when trials of bevacizumab in glioblastoma are considered. Two large-scale phase 3 studies in patients with newly diagnosed glioblastoma, both randomizing patients to standard treatment with or without bevacizumab, reported conflicting HRQL outcomes for patients receiving bevacizumab [13–15]. This has incited debate and discussion; differences in statistical methods and differences in data interpretation are among the purported reasons for such discrepancies [16]. The handling of missing data, in particular, remains an ongoing challenge in HRQL analysis, especially in populations with rapidly progressive disease such as glioblastoma. This requires careful consideration and a priori decisions when formulating a statistical analysis plan. The obvious advantage of including death or disease progression when calculating time to HRQL deterioration is that attrition (hence missing data), which is understandably common in this patient population, should not result in bias, given that all patients are taken into consideration in the time-to-event analysis and that death or deterioration with inability to complete HRQL assessment is appropriately characterized as deterioration in HRQL. This requires the assumption that patients with missing questionnaires were unlikely to be experiencing symptomatic or HRQL benefit at the time of the missing questionnaire, an assumption which medically is entirely appropriate. We acknowledge that, ideally, time to HRQL or clinical deterioration would be measured such that independent of radiological progressive disease, if a patient continues to derive clinical and HRQL benefit or stability while on a treatment, this could be measured and documented. However, as in most oncology clinical trials, HRQL data were not collected after date of progression, and therefore cannot be reported for the CABARET trial.

Given that there are no clear standard second-line anti-cancer agents that can provide anything more than modest survival benefits in this setting, any drug or regimen selected should not result in detriment to HRQL. Ours was an important study in comparing a doublet therapy with bevacizumab monotherapy, our concern being that having added carboplatin chemotherapy to bevacizumab might have adversely affected HRQL outcomes, while not providing additional survival benefit. However, we found no evidence of any difference in HRQL outcomes between treatments. Both arms had similar proportions of improvements and deteriorations in HRQL parameters, and there was no clear additional burden of toxicity indicated by the HRQL outcome measures. This could represent the disease itself and its subclinical progression exerting the dominant effect on HRQL; that the measures used were not sensitive to carboplatin-related effects on HRQL; or that HRQL was assessed in the wrong time frame for identifying chemotherapy toxicities (given that the questionnaire recall period was ‘during the last week’ and questionnaires were administered before day 1 of each 4-week treatment cycle, we effectively assessed HRQL in the last week of each cycle). Nevertheless, based on our HRQL data, we did not find any clear benefit for bevacizumab monotherapy over combination treatment, or vice versa. This study was designed in
2009 and carboplatin would no longer be a chemotherapy agent of choice in the recurrent setting; with lomustine being far more likely to be chosen as the control arm.

The issue of whether or not bevacizumab may benefit or worsen HRQL is an important one in light of the more modest effects of bevacizumab on progression-free survival reported in recent studies, and the uncertainty in the recurrent disease setting as to the overall survival benefits of the drug [17]. As such, any beneficial or detrimental effect of bevacizumab on HRQL becomes a critical aspect of determining the merit of treatment in this setting. The decline in HRQL noted for the majority of patients during radiological progression-free time may reflect disease status and subclinical progression rather than effects of therapy itself. This is supported by HRQL data from the BELOB randomized phase 2 study comparing lomustine with or without bevacizumab in a similar patient population, which reported no negative effects of bevacizumab on HRQL [12]. Similarly, in Part 2 of CABARET, in which 48 of the original 122 patients were randomized to either continuing or ceasing bevacizumab after progression on Part 1, there were no clinically or statistically significant differences between the randomized arms in time to deterioration in overall HRQL. Although we were limited by a small sample size with low statistical power, we did not find benefits or detriments in relation to HRQL when comparing patients who continued or ceased bevacizumab in this small randomized cohort.

Although many patients had some decline in HRQL preceding disease progression, a substantial proportion had some improvements in HRQL domains while on study. Post hoc analysis of patients who (based on baseline scores) had the potential for HRQL domain improvement showed that in domains relevant to symptoms from progressive glioblastoma, close to 50% reported clinically relevant improvements in at least one of these domains while receiving treatment. We postulate that these may represent those patients deriving meaningful clinical benefit and symptomatic improvement as a result of therapy.

There are some limitations to this study. The overall sample size is small, being a phase 2 study. A substantial percentage of patients missed assessment at the end of treatment, the high attrition rate at this time generally because patients were too unwell to complete questionnaires, which is to be expected in patients with glioblastoma. In anticipation of this clinical scenario, we planned to analyze time to HRQL deterioration, allowing us to include all patients, including those who did not complete questionnaires because of progression or death. This method is appropriate in this context as it avoids bias due to attrition in questionnaire completion at the end of treatment and was particularly relevant in Part 2 of the study, in which most patients’ HRQL deterioration was attributed to being not able to complete serial questionnaires because of clinical deterioration, disease progression or death. An additional strength of the CABARET trial was that HRQL assessment was mandatory, and therefore overall, most patients who were still on the study at each time point completed questionnaires, minimizing the risk of bias from noncompletion and avoiding loss of power.

In summary, the results from Part 1 of the CABARET study do not show any evidence of a difference in HRQL for patients with recurrent glioblastoma receiving bevacizumab monotherapy or bevacizumab plus carboplatin chemotherapy. However, improvements in HRQL domains reflecting disease burden were seen in almost 50% of patients, potentially reflecting symptom control from treatment received. It is feasible to complete a study with high HRQL completion rates in patients with recurrent glioblastoma if it is a mandatory aspect of the trial, the protocol provides relevant detail about HRQL administration, and staff receive good training. We found using time to HRQL deterioration a robust and useful statistical endpoint in this patient group, and suggest that this is an appropriate clinical trial endpoint in scenarios where attrition in questionnaire completion is likely and anticipated. These results should help inform future studies, and we encourage similar HRQL assessment methods in future clinical trial settings.

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Compliance with ethical standards

Conflict of interest KMF was funded through the University of Melbourne Stella Mary Langford Scholarship and the Royal Melbourne Hospital Research Medal and Watt-Geyer Memorial Research Fund. She has received travel grants from Roche to attend conferences. EJH has had consulting or advisory roles for Bayer, Janssen Oncology, Pfizer, and Roche, and has received travel grants from GlaxoSmithKline and Sanofi. MAR has been on a Roche Advisory Board. LC has received honoraria from and has had consulting or advisory roles for Roche Pharma AG, and has received institutional research funding from Celldex, Lilly, Merck, and Roche. AKN has had consulting or advisory roles for Boehringer Ingelheim and Roche and has received research funding from Boehringer Ingelheim. JS and KS have received institutional research funding from Roche through the Clinical Trials Centre. DE, EB and HW declare no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of
the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent**  Informed consent was obtained from all individual participants included in the study.

**Research involving animal participants**  This article does not contain any studies with animals performed by any of the authors.

**References**


**Supplementary Table 1:** Baseline characteristics by treatment (for all randomized patients who completed health-related quality of life questionnaires at baseline)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bevacizumab (n=60)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 (25–74)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>27 (45%)</td>
</tr>
<tr>
<td>Male</td>
<td>33 (55%)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>1</td>
<td>33 (55%)</td>
</tr>
<tr>
<td>2</td>
<td>16 (27%)</td>
</tr>
<tr>
<td>Prior diagnosis of grade I–III glioma</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>50 (83%)</td>
</tr>
<tr>
<td>Yes</td>
<td>10 (17%)</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>39 (65%)</td>
</tr>
<tr>
<td>Second or more</td>
<td>19 (32%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Corticosteroid use at baseline</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>16 (27%)</td>
</tr>
<tr>
<td>Yes</td>
<td>44 (73%)</td>
</tr>
<tr>
<td>Months from last radiotherapy to randomization</td>
<td>9 (3–101)</td>
</tr>
<tr>
<td>Months from initial glioblastoma surgery to randomization</td>
<td>11 (1–43)</td>
</tr>
</tbody>
</table>
**Supplementary Table 2:** Reasons for noncompletion of health-related quality of life forms at end of treatment (n=50)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient too unwell</td>
<td>23 (46%)</td>
</tr>
<tr>
<td>Patient did not attend</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Death before documented progression (NE)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Patient too upset</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Patient refused</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Site error</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Withdrew before any treatment (NE)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Still receiving treatment on study (NE)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (6%)</td>
</tr>
</tbody>
</table>

NE: not eligible (Did not have the opportunity to complete an end of treatment visit)
Supplementary Table 3: Baseline health-related quality of life scores by allocated treatment, including mean and proportions scoring ≤10 and ≥90

a) C30 scale

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab (n=62)</th>
<th>Bevacizumab + carboplatin (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>≥90</td>
</tr>
<tr>
<td>Quality of life</td>
<td>60</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>60</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>60</td>
<td>46 (74)</td>
</tr>
<tr>
<td>Pain</td>
<td>60</td>
<td>32 (52)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>60</td>
<td>42 (68)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>59</td>
<td>34 (55)</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>59</td>
<td>45 (73)</td>
</tr>
<tr>
<td>Constipation</td>
<td>60</td>
<td>44 (71)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>59</td>
<td>53 (85)</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>59</td>
<td>30 (48)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>60</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Role function</td>
<td>60</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>60</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>60</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>60</td>
<td>8 (13)</td>
</tr>
</tbody>
</table>
### BN20 scale

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab (n=62)</th>
<th>Bevacizumab + carboplatin (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>≤10</td>
</tr>
<tr>
<td>Bladder control</td>
<td>59</td>
<td>44 (71)</td>
</tr>
<tr>
<td>Communication deficit</td>
<td>59</td>
<td>23 (37)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>58</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Future uncertainty</td>
<td>60</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Headaches</td>
<td>60</td>
<td>23 (37)</td>
</tr>
<tr>
<td>Hair loss</td>
<td>59</td>
<td>52 (84)</td>
</tr>
<tr>
<td>Itchy skin</td>
<td>58</td>
<td>48 (77)</td>
</tr>
<tr>
<td>Motor dysfunction</td>
<td>59</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Seizures</td>
<td>60</td>
<td>53 (85)</td>
</tr>
<tr>
<td>Visual disorder</td>
<td>60</td>
<td>33 (53)</td>
</tr>
<tr>
<td>Weakness of legs</td>
<td>59</td>
<td>39 (63)</td>
</tr>
</tbody>
</table>
Supplementary Table 4: Average change scores on Part 1 treatment descriptive statistics

**a) C30 change scores by treatment**

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab monotherapy</th>
<th>Bevacizumab + carboplatin</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N: Mean(SD)</td>
<td>Median(IQR)</td>
<td>N: Mean(SD)</td>
</tr>
<tr>
<td>QoL</td>
<td>57: -5.14 (22.13)</td>
<td>-5.56 (-16.67-10.00)</td>
<td>52: 1.59 (18.67)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>57: 3.02 (22.11)</td>
<td>2.22 (-7.41-14.81)</td>
<td>52: 2.04 (21.25)</td>
</tr>
<tr>
<td>Nausea &amp; Vomiting</td>
<td>57: -2.39 (20.26)</td>
<td>0.00 (0.00-2.78)</td>
<td>52: 0.92 (11.18)</td>
</tr>
<tr>
<td>Pain</td>
<td>57: 4.33 (16.67)</td>
<td>3.33 (0.00-12.50)</td>
<td>52: -2.22 (27.11)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>57: 3.43 (20.97)</td>
<td>0.00 (0.00-16.67)</td>
<td>51: 0.51 (29.08)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>56: 2.84 (22.03)</td>
<td>0.00 (-0.51-7.41)</td>
<td>51: -3.22 (23.30)</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>56: 2.51 (25.21)</td>
<td>0.00 (0.00-15.00)</td>
<td>52: 0.35 (20.54)</td>
</tr>
<tr>
<td>Constipation</td>
<td>57: -3.47 (26.33)</td>
<td>0.00 (0.00-8.33)</td>
<td>52: -3.54 (24.62)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>57: 3.97 (15.45)</td>
<td>0.00 (0.00-11.11)</td>
<td>52: 3.75 (14.06)</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>57: -4.24 (28.19)</td>
<td>0.00 (0.00-3.45)</td>
<td>50: 0.15 (25.22)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>57: -8.86 (18.18)</td>
<td>-8.89 (-17.50-0.00)</td>
<td>52: -10.64 (19.94)</td>
</tr>
<tr>
<td>Role function</td>
<td>57: -7.19 (32.79)</td>
<td>-11.11 (-22.92-2.08)</td>
<td>52: -4.71 (30.25)</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>57: -0.57 (17.60)</td>
<td>0.00 (-10.65-8.33)</td>
<td>52: 2.81 (19.78)</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>57: -2.18 (20.90)</td>
<td>0.00 (-16.67-10.00)</td>
<td>52: 1.58 (22.37)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>57: -3.98 (25.12)</td>
<td>0.00 (-16.67-14.58)</td>
<td>52: -1.20 (24.00)</td>
</tr>
</tbody>
</table>

Note: P-value* testing for a difference in means
### BN20 change scores by treatment

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab monotherapy</th>
<th>Bevacizumab plus carboplatin</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>Median(IQR)</td>
</tr>
<tr>
<td>Bladder control</td>
<td>55</td>
<td>0.42</td>
<td>(19.40)</td>
</tr>
<tr>
<td>Communication deficit</td>
<td>55</td>
<td>-0.59</td>
<td>(18.69)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>53</td>
<td>2.29</td>
<td>(27.36)</td>
</tr>
<tr>
<td>Future uncertainty</td>
<td>56</td>
<td>-9.88</td>
<td>(25.12)</td>
</tr>
<tr>
<td>Headaches</td>
<td>56</td>
<td>-5.13</td>
<td>(22.06)</td>
</tr>
<tr>
<td>Hair loss</td>
<td>55</td>
<td>-1.27</td>
<td>(18.34)</td>
</tr>
<tr>
<td>Itchy skin</td>
<td>54</td>
<td>-3.67</td>
<td>(16.64)</td>
</tr>
<tr>
<td>Motor dysfunction</td>
<td>55</td>
<td>2.19</td>
<td>(19.56)</td>
</tr>
<tr>
<td>Seizures</td>
<td>55</td>
<td>-1.01</td>
<td>(15.55)</td>
</tr>
<tr>
<td>Visual disorder</td>
<td>56</td>
<td>0.95</td>
<td>(19.73)</td>
</tr>
<tr>
<td>Weakness of legs</td>
<td>55</td>
<td>1.49</td>
<td>(29.28)</td>
</tr>
</tbody>
</table>

Note: P-value* testing for a difference in means
**Supplementary figure 1:** Number of domains showing improvement versus number with potential to improve
Chapter 6: The role of early (4 week) MRI in disease assessment
The Role of Early Magnetic Resonance Imaging in Predicting Survival on Bevacizumab for Recurrent Glioblastoma: Results From a Prospective Clinical Trial (CABARET)

Kathryn M. Field, MBBS(Hons), FRACP, DMedSc, MPH 1,2; Pramit M. Phal, MBBS, FRANZCR 3; Greg Fitt, MBBS, FRANZCR 3; Christine Goh, MBBS, FRANZCR 3; Anna K. Nowak, MBBS, FRACP, PhD 4,5; Mark A. Rosenthal, MBBS, FRACP, PhD 1,2; John Simes, BSc(Med), MBBS, SM, MD, FRACP 6; Elizabeth J. Hovey, MBBS, FRACP 1,2; and Helen Wheeler, MBBS, FRACP 8

BACKGROUND: Bevacizumab has been associated with prolonged progression-free survival for patients with recurrent glioblastoma; however, not all derive a benefit. An early indicator of efficacy or futility may allow early discontinuation for nonresponders. This study prospectively assessed the role of early magnetic resonance imaging (eMRI) and its correlation with subsequent routine magnetic resonance imaging (MRI) results and survival. METHODS: Patients were part of a randomized phase 2 clinical trial (CABARET) comparing bevacizumab with bevacizumab plus carboplatin for recurrent glioblastoma. eMRI was conducted after 4 weeks in the trial (after 2 treatments with bevacizumab [10 mg/kg every 2 weeks]). The results were compared with the results of the subsequent 8-week MRI standard. RESULTS: For 119 of 122 patients, eMRI was available, and 111 had subsequent MRI for comparison. Thirty-six (30%) had an early radiological response, and 17 (14%) had progressive disease. The concordance between eMRI and 8-week MRI was moderate (k = 0.56), with most providing the same result (n = 79 [71%]). There was strong evidence that progression-free survival and overall survival were predicted by the eMRI response (both P values < .001). The median survival was 8.6 months for an eMRI response, 6.6 months for stable disease, and 3.7 months for progressive disease; the hazard ratio (progressive disease vs stable disease) was 3.4 (95% confidence interval, 1.9-6.0). Landmark analyses showed that eMRI progression was a strong predictor of mortality independent of other potential baseline predictors. CONCLUSIONS: In this study, early progression on MRI appears to be a robust marker of a poor prognosis for patients on bevacizumab. Cancer 2017;000:000-000. © 2017 American Cancer Society.

KEYWORDS: bevacizumab, clinical trial, glioblastoma, magnetic resonance imaging (MRI), prognosis, radiology.

INTRODUCTION

Glioblastoma is an aggressive malignant central nervous system cancer. Management options for recurrent disease, which have been limited, are now changing with the advent of targeted therapies. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), is now a common option for recurrent disease in some countries. VEGF causes peritumoral angiogenesis with an abnormal vascular network, which is hyperpermeable and results in peritumoral edema. 1 VEGF inhibition can result in the rapid normalization of glioma-associated blood vessels, a reduction in vascular permeability, and an improvement in patients’ symptoms.

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1Royal Melbourne Hospital, Melbourne, Victoria, Australia; 2University of Melbourne, Parkville, Victoria, Australia; 3Austin Hospital, Melbourne, Victoria, Australia; 4School of Medicine and Pharmacology, University of Western Australia, Crawley, Western Australia, Australia; 5Department of Medical Oncology, Sir Charles Gardiner Hospital, Nedlands, Perth, Western Australia; 6National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney, New South Wales, Australia; 7Prince of Wales Hospital, Sydney, New South Wales, Australia; 8Royal North Shore Hospital, St Leonards, Sydney, New South Wales, Australia.

This trial was conducted under the auspices of the Cooperative Trials Group for Neuro-Oncology, was coordinated at the National Health and Medical Research Council Clinical Trials Centre (University of Sydney), and was supported by Roche Products Pty Limited (Australia). Kathryn M. Field (chair), John Simes, Elizabeth J. Hovey, Anna K. Nowak, Lawrence M. Cher, Helen Wheeler, C. Brown, Elizabeth H. Barnes, Kate Sawkins, Anne Livingstone, and Mark A. Rosenthal composed the trial management committee; Pramit M. Phal, Greg Fitt, and Christine Goh composed the independent central radiological review committee; and Martin Tattersall (chair), P. Kelly, and A. Hayden composed the independent data safety monitoring committee. Kate Sawkins, Chris Brown, Elizabeth H. Barnes, Ann Livingstone, Diana Winter, Bernadette Tomes, Rhana Pike, and John Simes work at the Clinical Trials Centre, and Brad Moffat and Simon Salinas work at the Brain Imaging Laboratory of the Royal Melbourne Hospital.

This trial was performed after approval by the relevant ethics committee at each participating site. All principles outlined in the Declaration of Helsinki have been followed. Informed consent was obtained from each participant.

CABARET was prospectively registered with the Australian New Zealand Clinical Trials Registry (registration number ACTRN12610000915055).

Additional supporting information may be found in the online version of this article.

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Whether early radiological changes associated with bevacizumab use truly reflect a disease response remains debated in the literature because, on the whole, improvements in progression-free survival (PFS) have not translated into overall survival (OS) in most de novo and recurrent glioblastoma clinical trials involving bevacizumab.\(^2\) Targeted therapies in cancer medicine are not without significant cost and potentially serious toxicities. Bevacizumab is expensive, is not readily available in some countries because of its cost and/or uncertainty about the benefit of PFS without a corresponding OS benefit, and may be associated with rare but potentially serious toxicities.\(^5,6\)

It would be ideal if an early indicator of bevacizumab efficacy or futility in an individual patient could help guide management. If such an indicator reliably predicted a response or progression, prolonged and expensive use of the drug, with ongoing exposure to the risk of toxicity, could potentially be avoided for those individuals for whom it is unlikely to result in a durable benefit. In addition, an early switch to an alternative form of therapy might be appropriate, especially because of the increasing availability of clinical trials of other therapies for this patient population.

Our prospective study aimed to determine whether early magnetic resonance imaging (eMRI; ie, after 4 weeks or 2 bevacizumab treatments) was a reliable predictor of prognosis during bevacizumab treatment, with usual-care 8-week magnetic resonance imaging (MRI) used as the reference. We also documented whether changes on eMRI were associated with differential survival outcomes and/or changes in the clinical status or steroid dose. We used scans and data from patients enrolled in the CABA-RET trial, a randomized phase 2 study comparing bevacizumab monotherapy with bevacizumab plus carboplatin.

Examining the role of eMRI was a preplanned exploratory endpoint for this trial.

**MATERIALS AND METHODS**

**Study Population**

The CABARET trial included 122 adult patients with recurrent glioblastoma from 18 Australian sites who had previously received both radiotherapy and temozolomide but no other chemotherapy for glioblastoma. Details of the inclusion and exclusion criteria have been published.\(^7\) All patients received bevacizumab (10 mg/kg intravenously every 2 weeks); those randomized to doublet therapy also received carboplatin (area under the curve 5 every 4 weeks). Treatment was continued until disease progression or the withdrawal of treatment for other reasons (eg, toxicity). The Response Assessment in Neuro-Oncology (RANO) criteria, including the clinical status and steroid dose, were used for disease assessment for the trial’s primary endpoint: PFS as determined by central radiological review.\(^8\) There was no evidence of differences in survival outcomes between the 2 randomized treatment arms, so they were combined for this analysis.

**eMRI and Protocol**

In addition to standard MRI at the baseline and every 8 weeks, each participant also underwent eMRI at approximately 4 weeks as part of a prospectively designed exploratory endpoint to determine the role of eMRI in disease assessment. The results from eMRI were compared with the baseline MRI results, but they were not used in determining the overall disease response or progression and were not acted upon by treating sites with the exception of any potential safety concerns (eg, central nervous system hemorrhage). Both the eMRI results and the 8-week MRI results for this substudy were based on the trial’s central radiology review, which was not conducted in real time and did not take eMRI into consideration when it was determining the disease response on subsequent MRI. An individual trial participant’s series of scans was reviewed and reported by the same central radiologist. eMRI, as an exploratory substudy, was reviewed by the central radiologists only after the trial’s primary endpoint (a PFS date based on standard-timing imaging or the cessation of treatment for any other reason) had been established for that patient. Radiologists were blinded to the study treatment, steroid dosing, and clinical and neurological findings, and these were not included in this substudy comparison, which compares only radiographic findings without the clinical/steroid dosing component of the RANO criteria.

Each site was asked to conduct MRI in accordance with the acquisition protocol provided for the trial to ensure that, whenever possible, the quality of MRI was standardized. The scan series included precontrast and post-contrast T1-weighted imaging (volumetric acquisition) and T2/fluid-attenuated inversion recovery (FLAIR) sequences (maximum slice thickness of 5 mm with no interslice gap).

**Data Analysis and Statistical Methods**

Radiological findings from eMRI were compared with the findings of 8-week MRI, the first standard scan on the trial, to determine the level of correlation between the two. This comparison did not include the clinical status or steroid dosing, as described in the RANO criteria, but rather was based on T1 and T2/FLAIR changes alone. A \(\kappa\) statistic was calculated to determine the concordance between results from eMRI and results from 8-week MRI.
A preplanned exploratory objective of the trial was to correlate the eMRI response at 4 weeks with PFS and OS. PFS and OS dates were calculated from the date of eMRI, and they were described with the Kaplan-Meier method and were compared with proportional hazards regression models. In additional landmark analyses,9 OS was modeled from eMRI as a function of baseline risk factors (including the age, Eastern Cooperative Oncology Group performance status, number of relapses, and extent of initial surgery) and eMRI findings (progression or no progression).

When eMRI showed progression, the type of radiological progression (a T1 contrast-enhancing measurable lesion, a nonmeasurable lesion, a T2/FLAIR increase, or a new lesion) was documented, and OS for patients with contrast-enhancing (T1C+) progression versus T2/FLAIR progression was calculated.

Using a chi-square test, we also compared the clinical status (improved, stable, or deteriorated) and steroid dose (none, reduced, stable, or increased), as formally documented by sites at the week 4 visit (both components of the RANO criteria), for patients with a response, stable disease, or progressive disease at the time of eMRI.

As part of the CABARET trial, an experimental grading scale for T2/FLAIR changes was developed by the neuroradiologists who participated in the central radiology review and was applied at the time of the central review (modified RANO criteria).7 This classified T2/FLAIR changes into 5 categories (Supporting Table 1 [see online supporting information]). As an exploratory approach for determining the potential utility of this grading system, PFS and OS were calculated for patients categorized by the amount/grade of the T2/FLAIR change on eMRI. We also compared patients with T1C+ progression versus T2/FLAIR progression at week 4.

RESULTS
In total, 122 patients were randomized, and 120 underwent at least 1 treatment. Data for eMRI were available for 119 of these patients: 2 patients who withdrew consent after randomization but before treatment and 1 who did not undergo eMRI were excluded. One hundred eleven of the 119 patients underwent both 4-week MRI and 8-week MRI; the remainder had no MRI after week 4 because of the cessation of treatment for clinical progression, for toxicities, or by choice.

Concordance
The concordance between eMRI and 8-week MRI results for the 111 patients is shown in Table 1. The $\kappa$ statistic indicated moderate concordance ($\kappa = 0.56$). For 71% ($n = 79$), eMRI and 8-week MRI resulted in the same disease status finding. The disease status on eMRI was the same or better than the status on 8-week MRI for 99 patients (89%), and this is relevant to the decision to cease futile treatment. For 16 of the 17 patients with progressive disease at week 4, radiological progression or death occurred a median of 27.5 days later (range, 0-61 days). The 1 remaining patient was recorded to have a decreased tumor volume but also a new lesion, which resulted in the attribution of progressive disease on eMRI, and then subsequently had a partial response at 8 weeks with a continued decrease in the tumor volume and no new lesion documented at this time point. No subsequent MRI was conducted for this patient, who had treatment 3 days after the 8-week MRI but no subsequent therapy, chose to leave the trial 6 weeks after the 8-week scan, and died 1 week later.

PFS and OS
There was strong evidence of differences in PFS and OS according to the eMRI status (Table 2). Patients with progressive disease on eMRI had shorter survival than patients with either stable disease or a response. Figure 1 shows the OS for all 3 groups. The hazard ratio, if disease progression was seen on eMRI, with respect to stable disease was 3.35 (95% confidence interval, 1.88-5.95).
Proportional hazards regression models were fitted to the time from eMRI to death from any cause to assess whether the eMRI result had any prognostic value beyond baseline risk factors (Table 3). For both univariate and multivariate models, patient age and progression on eMRI were the only predictors for which there was evidence of an association with OS. Of these, eMRI progression was the strongest predictor of mortality, and it was independent of other potential predictors (multivariate model hazard ratio, 3.85; 95% confidence interval, 2.2-6.9; \( P < .001 \)).

### Clinical Status and Steroid Dose

The clinical status, determined and formally documented by the site at the week 4 visit, was compared for patients with an eMRI response, stable disease, and progressive disease. Most patients (n = 88 [74%]) had a stable clinical status at this time, and there was no association between the eMRI result and the clinical status (\( P = .30 \)). At week 4, 65 patients (55%) had a stable steroid dosage or were not receiving steroids at the baseline and week 4; 45 (38%) were on a decreased dosage or had ceased steroids after the baseline. Only 9 patients (8%) had increased their steroid dosage. There was no association between eMRI results and steroid use (\( P = .89 \)).

### T2/FLAIR Changes

OS was shorter for patients with any increase in T2/FLAIR signal abnormality on eMRI (n = 5) versus any decrease (n = 49); however, statistical inference is limited by the small sample size. Table 4 shows a comparison of OS based on T2/FLAIR grading, and Figure 2 shows Kaplan-Meier curves comparing T2/FLAIR decrease, stability, and increase. When the T2/FLAIR signal change

---

**TABLE 2.** Progression-Free Survival and Overall Survival Based on the 4-Week MRI Response and Calculated From the Date of 4-Week MRI (n = 105)

<table>
<thead>
<tr>
<th>Week 4 MRI Result</th>
<th>No.</th>
<th>Survival, Median (95% CI), mo</th>
<th>HR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression-free survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete or partial response( ^a )</td>
<td>33</td>
<td>2.8 (2.6-4.6)</td>
<td>0.99 (0.63-1.55)</td>
<td>(&lt; .001)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>56</td>
<td>2.7 (2.5-2.8)</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>16</td>
<td>0.9 (0.7-1.0)</td>
<td>8.39 (4.21-17)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete or partial response( ^a )</td>
<td>36</td>
<td>8.6 (6.1-10.0)</td>
<td>0.81 (0.54-1.22)</td>
<td>(&lt; .001)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>66</td>
<td>6.6 (4.6-7.4)</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>17</td>
<td>3.7 (2.2-4.7)</td>
<td>3.35 (1.89-5.95)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; MRI, magnetic resonance imaging.

Fourteen patients whose disease had progressed, as measured by clinical deterioration at the week 4 visit, were excluded. Only 1 of these 14 patients had radiological progressive disease at this time point.

\( ^a \)Reported on this scan only and not necessarily confirmed on subsequent imaging.

**TABLE 3.** Univariate and Multivariate Proportional Hazards Regression Models Assessing the Prognostic Value of eMRI Beyond Baseline Risk Factors

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Value</th>
<th>HR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG</td>
<td>2 vs 0 or 1</td>
<td>1.26 (0.84-1.88)</td>
<td>.27</td>
</tr>
<tr>
<td>Initial glioblastoma surgery</td>
<td>Resection vs biopsy or debulking</td>
<td>0.98 (0.67-1.42)</td>
<td>.89</td>
</tr>
<tr>
<td>Age</td>
<td>( \geq 65 ) vs (&lt; 65 ) y</td>
<td>1.56 (1.00-2.44)</td>
<td>.06</td>
</tr>
<tr>
<td>Relapse</td>
<td>1 vs ( \geq 2 ) or unknown</td>
<td>1.14 (0.77-1.68)</td>
<td>.50</td>
</tr>
<tr>
<td>eMRI Progression</td>
<td>vs not</td>
<td>3.61 (2.06-6.31)</td>
<td>(&lt; .001)</td>
</tr>
<tr>
<td><strong>Multivariate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG</td>
<td>2 vs 0 or 1</td>
<td>1.32 (0.88-1.99)</td>
<td>.18</td>
</tr>
<tr>
<td>Initial glioblastoma surgery</td>
<td>Resection vs biopsy or debulking</td>
<td>0.93 (0.63-1.39)</td>
<td>.73</td>
</tr>
<tr>
<td>Age</td>
<td>( \geq 65 ) vs (&lt; 65 ) y</td>
<td>1.63 (1.02-2.63)</td>
<td>.04</td>
</tr>
<tr>
<td>Relapse</td>
<td>1 vs ( \geq 2 ) or unknown</td>
<td>1.09 (0.73-1.62)</td>
<td>.69</td>
</tr>
<tr>
<td>eMRI Progression</td>
<td>vs not</td>
<td>3.85 (2.16-6.88)</td>
<td>(&lt; .001)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; eMRI, early magnetic resonance imaging; HR, hazard ratio.
was assessed, regardless of any other radiological findings, the degree of the T2/FLAIR change, as documented with the 5-point modified RANO scale (Supporting Tables 1 and 2 [see online supporting information]), did not provide any additional information regarding OS beyond that obtained by the classification of T2/FLAIR changes as decreased, stable, or increased (the current RANO criteria classification).

Of the 17 patients who had eMRI disease progression, 6 had T1/contrast-enhancing progression alone, and 2 had a T2/FLAIR increase alone. OS differed according to the type of progression at week 4, although the small sample size limits formal statistical comparison. The median OS was 3.7 months for those with T1 progression and 1.8 months for those with T2/FLAIR progression (hazard ratio, 3.41; 95% confidence interval, 0.58-19.9).

**DISCUSSION**

This prospective study is one of the first in the setting of glioblastoma to show that eMRI during bevacizumab therapy may predict OS. The multivariate model showed disease progression on eMRI to be a strong predictor of mortality, even when it was adjusted for baseline risk factors. Knowing a patient’s likely prognosis during the early stages of a treatment is useful, especially because of the potential costs of therapy (both financial costs and toxicity risks) and because additional therapies, including clinical trial therapy, may be available to patients. Ceasing a treatment that is likely to be futile before the performance status deteriorates could facilitate easier access to alternative treatment options.

There is scant literature regarding the value of eMRI in this context. Kreisl et al,10 in their single-arm phase 2 trial of bevacizumab for recurrent glioblastoma, compared a 4-week partial response on MRI with stable disease (according to the MacDonald and Levin criteria), and reported that an early partial response was associated with improved PFS, although early disease progression was not evaluated. A retrospective study of eMRI as a prognostic marker for patients from the Radiation Therapy Oncology Group 0625 clinical trial of bevacizumab with irinotecan or temozolomide found that early progression shown by T 1 (but not FLAIR) on 8- and 16-week scans was prognostic for OS.11 However, with respect to timing, 8-week MRI is more conventional for tumor assessment than our 4-week MRI. Huang et al12 in 2013 published a retrospective study of 91 patients with recurrent glioblastoma who were receiving bevacizumab. They analyzed the value of early posttreatment imaging (at approximately 30 days, which was similar to our MRI time frame), and reported that a posttreatment enhancing tumor volume and FLAIR volume were associated with both PFS and OS, although the FLAIR change did not remain statistically significant in a multivariate analysis. They concluded that eMRI volumetric analysis could identify patients who were more likely to benefit from bevacizumab therapy. Our study seems to support this, although we have not reported formal volumetric measurements, which may be a more sensitive tool and may potentially have identified even more patients with early progressive disease at the 4-week time point.

**TABLE 4. Overall Survival From Week 4 by T2/FLAIR at Week 4**

<table>
<thead>
<tr>
<th>Week 4 T2/FLAIR</th>
<th>Overall Survival From Week 4 MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survival, Median (95% CI), mo</td>
</tr>
<tr>
<td>Any decrease (n = 49)</td>
<td>6.7 (4.7-8.1)</td>
</tr>
<tr>
<td>Stable (n = 62)</td>
<td>5.7 (4.3-7.1)</td>
</tr>
<tr>
<td>Any increase (n = 5)</td>
<td>2.3 (1.3-8.7)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; FLAIR, fluid-attenuated inversion recovery; HR, hazard ratio; MRI, magnetic resonance imaging.

Three patients with unknown T2/FLAIR results for week 4 MRI were excluded.
Sorensen et al\textsuperscript{13} in 2009 described a vascular normalization index incorporating advanced MRI imaging that measured vascular permeability, microvessel volume, and circulating collagen IV levels after a single dose of cediranib, a pan-VEGF receptor tyrosine kinase inhibitor. This was able to predict the response to the drug. Several studies have found that early positron emission tomography imaging is more predictive than MRI of an early treatment response or progression in patients with recurrent glioblastoma on bevacizumab\textsuperscript{14-16}; however, 3'-deoxy-3'-[\textsuperscript{18}F]fluorothymidine (FLT) positron emission tomography is not routine and currently has limited use outside clinical trials in Australia.

The sample size of this study limits our ability to determine an association between early T2/FLAIR progression (alone or mixed with other change) and poorer outcomes. Other retrospective studies have resulted in conflicting findings related to whether T2/FLAIR tumor progression is adversely associated with survival.\textsuperscript{17-19} Although several have not found an association, a retrospective analysis of data from patients who participated in the recurrent glioblastoma AVF3708g clinical trial found that a T2/FLAIR assessment was significantly associated with differences in PFS and response rates.\textsuperscript{20} Our study has not incorporated advanced MRI techniques such as diffusion restriction, spectroscopy, and cerebral blood volume assessments; it is acknowledged that because of the conflicting studies on the prognostic significance of T2/FLAIR signal changes, advanced MRI may enlighten investigators and clinicians in this context.\textsuperscript{21-24}

We did not find an association between the steroid dose and the eMRI results. Nevertheless, almost 40% of the patients in the trial had decreased or ceased steroids after 4 weeks in the study. This highlights the important point that bevacizumab may be associated with a clinical benefit independent of radiographic findings. If bevacizumab is able to result in a reduction in steroid dose, this can be argued to be an example of a clinical benefit. Bevacizumab has been associated with reduced steroid requirements in multiple studies.\textsuperscript{5,25-27} This underpins the importance, when one is assessing any patient on treatment, of considering both the radiological findings and the clinical status when determining the potential benefit of therapy.

It is also interesting to note that the median PFS was similar when patients with an eMRI response and patients with stable disease were compared (Table 2). Although the exploratory nature of this analysis precludes robust statistical inference, the lack of a statistically significant association between response and PFS was also noted in a landmark analysis of scans for patients who participated in the BRAIN study, although the response was correlated with OS in their analysis.\textsuperscript{28} However, as previously noted, Kreisl et al\textsuperscript{10} did find an association between an eMRI response and PFS, although the RANO criteria were not used for this study. In the CABARET study, eMRI progression was the finding most strongly associated with survival outcomes, rather than an eMRI response.

There are several limitations to our study. Although 2-dimensional quantitation of abnormal enhancement was performed, formal volumetric assessments and advanced MRI sequences were not included. Seventeen patients showed progressive disease on eMRI, but only 5 had any T2/FLAIR increase at the 4-week mark, and only 2 had a solitary T2/FLAIR signal increase at this time; this means that robust statistical comparisons of survival for this group are not feasible. Furthermore, our findings apply to MRI after two 2-week bevacizumab treatments, and it is unclear how they would apply to bevacizumab given at a 3-week interval: whether 4 weeks would be an appropriate time point, or whether 2 treatment cycles are required. Nevertheless, strengths include the prospective study design, the uniformity of the centralized radiological assessment, and the fact that the majority of the patients who participated in the CABARET study had both 4- and 8-week scans available for assessment.

In summary, we found that early (4-week) MRI after the commencement of 2-week bevacizumab therapy correlated at least moderately with subsequent 8-week imaging. Compared with stable disease at 4 weeks, progressive disease was a significant prognostic marker for poorer survival, but a partial response at this time point was not a significant prognostic marker for better survival in this patient cohort.

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CONFLICT OF INTEREST DISCLOSURES
Anna K. Nowak reports research support from Roche Pharmaceuticals outside the submitted work.

AUTHOR CONTRIBUTIONS
Kathryn M. Field: Editing, revision, and approval of the final version of the manuscript; accountability for all aspects of the work; original trial conception and design; patient recruitment; trial
management; and interpretation of the results. Pramit M. Phal: Editing, revision, and approval of the final version of the manuscript; central radiological review of magnetic resonance imaging scans; and analysis and interpretation of the results. Greg Fitt: Editing, revision, and approval of the final version of the manuscript; central radiological review of magnetic resonance imaging scans; and analysis and interpretation of the results. Christine Goh: Editing, revision, and approval of the final version of the manuscript; central radiological review of magnetic resonance imaging scans; and analysis and interpretation of the results. Anna K. Nowak: Editing, revision, and approval of the final version of the manuscript; original trial conception and design; patient recruitment; trial management; and interpretation of the results. Mark A. Rosenthal: Editing, revision, and approval of the final version of the manuscript; original trial conception and design; patient recruitment; trial management; and interpretation of the results. John Simes: Editing, revision, and approval of the final version of the manuscript; original trial conception and design; patient recruitment; trial management; and interpretation of the results. Elizabeth H. Barnes: Editing, revision, and approval of the final version of the manuscript; original trial conception and design; patient recruitment; trial management; and interpretation of the results. Helen Wheeler: Editing, revision, and approval of the final version of the manuscript; original trial conception and design; patient recruitment; trial management; and interpretation of the results.

REFERENCES

**Supplementary Table 1: 5-point scale for T2/FLAIR used in ‘modified’ RANO criteria**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>&gt;50% decrease in size of T2 / FLAIR abnormality</td>
</tr>
<tr>
<td>-1</td>
<td>25-50% decrease in size of T2 / FLAIR abnormality</td>
</tr>
<tr>
<td>0</td>
<td>Stable (+/- 25% from nadir T2/FLAIR appearance)</td>
</tr>
<tr>
<td>+1</td>
<td>25-50% increase in size of T2 / FLAIR abnormality</td>
</tr>
<tr>
<td>+2</td>
<td>&gt;50% increase in size of T2 / FLAIR abnormality</td>
</tr>
</tbody>
</table>
Chapter 7: Comparison between site and central radiological assessments

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Comparison between site and central radiological assessments for patients with recurrent glioblastoma on a clinical trial

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Abstract

Aim

Assessment of magnetic resonance imaging (MRI) in glioblastoma can be challenging. For patients with recurrent glioblastoma managed on the CABARET trial, we compared disease status assessed at hospitals and subsequent blinded central expert radiological review.

Methods

MRI results and clinical status at specified time points were used for site and central assessment of disease status. Clinical status was determined by the site. Response Assessment in Neuro-Oncology (RANO) criteria were used for both assessments. Site and central assessments of progression-free survival (PFS) and response rates were compared. Inter-rater variability for central review progression dates was assessed.

Results

Central review resulted in shorter PFS in 45% of 89 evaluable patients (n=40). Median PFS was 3.6 (central) versus 3.9 months (site) (hazard ratio 1.5, 95% CI 1.3–1.8, P<0.001). Responses were documented more frequently by sites (n=16, 18%) than centrally (n=11, 12%). Seven of 120 patients continued on trial without site-determined progression for more than 6 months beyond the central review determination of progression. Of scans reviewed by all three central reviewers, 33% were fully concordant for progression date.

Conclusion

While the difference between site and central PFS dates was statistically significant, the 0.3 month median difference is small. The variability within central review is consistent with previous studies, highlighting the challenges in MRI interpretation in this context. A small proportion of patients benefited from treatment well beyond the centrally determined progression date, reinforcing that clinical status together with radiology results are important determinants of whether a therapy is effective for an individual.

Key words

Bevacizumab, carboplatin, clinical trial, glioblastoma, magnetic resonance imaging
Introduction

Glioblastoma is a devastating primary central nervous system tumor, with near-universal mortality. Different patterns of progression and treatment-related effects are commonly seen on imaging, which makes radiological interpretation and formal measurement of disease challenging. Accurate assessment of disease status is critical for clinical trials, in which continuation or cessation of treatment depends on radiological findings in addition to the patient’s clinical status. Progression-free survival (PFS), a commonly used endpoint in glioblastoma clinical trials, is calculated using the date at which radiological or clinical progression (or death from any cause without radiologically documented progression) occurs. PFS is important as a surrogate endpoint for overall survival and as an endpoint unaffected by subsequent therapy. Prolonged PFS can indicate clinical benefit and tumor stabilization, even in the absence of objective response.

Clinical trials often include blinded, centralized review of radiological endpoints such as response and PFS, especially in open-label studies, where knowledge of the treatment arm may bias reporting by investigators. The Australian Cancer Network Clinical Practice Guidelines for Neuro-oncology recommend central radiological review owing to reported inter-observer variability in response assessment. However, centralized review does not generally occur in real time, and date discordance between site and central radiological reviews is common. Bias, for example, from awareness of treatment allocation, is not entirely removed with centralized review: if a site determines that progression has occurred and scans cease the central review necessarily censors the patient at this point. Therefore, the necessity of centralized radiology review in clinical trials has been called into question.

Magnetic resonance imaging (MRI) is the standard method for assessing glioblastoma radiologically. Over the last decade, with the advent of targeted therapies such as bevacizumab, interpretation of MRI findings in glioblastoma has become more complex. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), may reduce contrast enhancement on T1-weighted MRI. This may result in an appearance of tumor response (pseudoresponse) on post-treatment imaging through normalization of vasculature with restoration of blood-brain barrier integrity and a reduction in gadolinium enhancement. Hence, nonenhancing tumor progression has become a key component of tumor assessment, reinforced by recent Response Assessment in Neuro-Oncology (RANO) criteria which include assessment of T2/FLAIR MRI changes unlike the previous neuro-oncology assessment method, Macdonald criteria.
In this study, we compared site-based assessment with central radiology review in Part 1 of CABARET, a phase II trial in which patients with recurrent glioblastoma were randomized to bevacizumab monotherapy or bevacizumab plus carboplatin. At the time of trial design, RANO criteria had only just been published, and most clinical trials before this had relied on the Macdonald criteria in assessing disease. The CABARET trial provided a unique opportunity to compare central and site radiology reviews incorporating the new criteria. Our aims were to compare centralized radiology review with the site-determined date of progression and disease response assessment. We hypothesized that, given the specific neuroradiological expertise of the central panel of radiologists, central review might determine disease progression earlier and result in a lower proportion of patients with documented response than site reviews.

**Materials and methods**

*Patient eligibility*

Eligibility criteria for the CABARET study have been reported. Briefly, 120 consenting adult patients with recurrent glioblastoma from 18 sites across Australia were randomized and received at least one dose of treatment on trial. Inability to undergo contrast-enhanced MRI was an exclusion criterion. Measurable disease was defined according to RANO criteria: at least one site of bidimensionally measurable disease with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that were preferably at most 5 mm thick with 0 mm skip between the slices on the baseline MRI. At least 12 weeks had to have passed since completion of radiotherapy to avoid the period in which pseudoprogression is most commonly observed. Patients without measurable disease (after postsurgical resection for recurrent disease) were eligible to participate, but their best response could only be stable disease, in line with RANO criteria.

Patients were excluded from the central and site radiology analysis described here if they did not have any scans after the baseline scan; if death occurred before radiological progression was determined; or if clinical progression occurred without either site or central radiological progression. If the date of progression was not available for either site or central review for an individual, that patient was not included when the time difference between site and central review was calculated.
**MRI assessment timing**

MRI was completed at baseline and every two treatment cycles (approximately every 8 weeks). On-study MRI scans were performed, where possible, within 7 days prior to the patient’s scheduled treatment.

In follow-up, MRI was conducted every 2 months for patients without objective radiological disease progression according to the site (for example, patients who had withdrawn owing to toxicities). After disease progression, further MRIs were not required.

**MRI acquisition**

Each site was provided with an acquisition protocol, including details for scan standardization, to facilitate central radiology review (Supplementary materials). Standard imaging of the brain consisted of precontrast and postcontrast enhanced T1-weighted imaging (T1C+), T2, and T2 FLAIR. Consistency of consecutive MRIs for individual patients was also ensured wherever possible (for example, using the same 1.5T or 3T scanner).

**MRI interpretation**

RANO criteria were used for disease assessment, with T2/FLAIR changes specifically documented.11 For patients with measurable contrast-enhancing lesions at baseline, the sum of the products of the largest perpendicular diameters for the tumor in the axial plane was calculated and recorded. If there were multiple lesions, all lesions were measured, to a maximum of five. If the largest lesions could not be measured reproducibly, the next largest lesions that could be measured reproducibly were selected. For index lesions, the products of the diameters of the index lesions (maximum of five lesions) were added together to determine the sum of the products of the diameters (SPD). In cases of progressive disease based on the index-lesions evaluation, the SPD of the nadir was used to calculate the increase in size of the index lesions. In addition, on subsequent imaging, unequivocal new enhancing lesions of any size, not within the original tumor volume, were recorded as new lesions (representing progressive disease).

Worsening overall performance status and/or neurological decline considered to be attributable to underlying disease, without lack of radiographic evidence of progressive disease and/or an increasing dose of steroids, were incorporated into assessment of progression. Such patients were classified as having clinical progressive disease if they met the
RANO criteria for clinical progression. In the case of clinical progressive disease, MRI continued where feasible until the time of documented objective radiological progression.

Site review

The site reviews were also according to RANO criteria; ultimately the site investigator was responsible for documenting and interpreting MRI results although this assessment was facilitated by radiology reporting of the scans at the site. These occurred at the time of clinical review and were used to make decisions about disease response, patient care, and study treatment continuation. It was possible for a patient to continue on Part 1 of the study with site-assessed stable disease or response, even if subsequent central review determined that progression had occurred earlier.

Central review

Central review occurred later and was used to report the endpoints of response and PFS for the primary efficacy results of the trial. Scans were reviewed at the Brain Imaging Laboratory at Royal Melbourne Hospital by a panel of three experienced neuroradiologists (GF, PP, and CG) blinded to treatment allocation. All reviewers had been trained in the RANO criteria; test reviews were conducted on a subset of five patients by all radiologists, where results were compared between reviewers to determine consistency.

Scan data were anonymised and uploaded into a graphical user interface designed and implemented in Matlab (Mathworks MA, USA). Radiologists were trained in the use of this interface, which enabled measurement of enhancing disease and assessment of T2/FLAIR signal abnormality. The system subsequently calculated the SPD and allowed for categorization of the radiological response to the treatment.

Each patient was randomly allocated to a primary radiologist (Reviewer 1) by the trial statistician. Radiologists were required to interpret the full series of scans in sequence for each of their allocated patients. Ten percent of patients (n=12) were reviewed by all three radiologists, to determine inter-rater reliability. Within the series of scans assigned to each radiologist, 10% of the reviews (n=12) were duplicated to determine intrarater reliability. The duplicated scans were allocated a dummy patient ID to keep the reviewer blinded.

For all published analyses of study outcomes and for the comparison of site and central assessments described here, the primary review (Reviewer 1’s assessment of disease status)
has been used, even if there was discordance between the three reviewers for duplicated reviews. Scans were not re-reviewed if discordance was noted, as this analysis (inter-rater reliability) was conducted after the primary endpoint had been reported and as an exploratory trial objective.

Scan series were reviewed by the radiologists in time sequence, with the exception of a 4-week research-only MRI, which was reviewed last and is not reported here. All scans were reviewed with blinding to both treatment allocation and site assessment of response or progression. Scans were presented to the reviewer one at a time, so the reviewer was not aware how many scans in total the patient had undergone, in order to remain blinded to the site’s determination of progression date. The trial statistician combined the radiological assessment with the site-reported steroid dose and clinical status (both of which are components of the RANO criteria) to determine the overall disease response.

Statistics

Given that there was no significant difference between arms for the centrally determined primary endpoint, PFS,12 we used the entire cohort when comparing the site-determined PFS date with the central review-determined date. The Kaplan-Meier method was used to describe PFS times. Proportional-hazards regression was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) to compare rates of progression determined by the two sources, taking into account the paired nature of the data. Where the progression date differed between site and central assessments, the type of progression determined by central review (T1C+, T2/FLAIR, new lesion, clinical only, or combination) was recorded to determine whether a particular type of radiological change was detected discrepantly. To compare responses, the McNemar-Bowker test of symmetry was performed and a kappa concordance statistic calculated.16 All analyses used SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Between November 2010 and March 2012, 122 patients were enrolled. Two withdrew consent and did not receive any treatment after randomization. The trial closed in December 2014 with two patients remaining on Part 1 of the study, who continued to receive treatment with bevacizumab beyond the date of study closure.
Data for 89 of 120 patients who were randomized and received at least one treatment were available for analysis. Of the remaining patients, nine had no scans after the 4-week (research only) MRI, seven died without documented site or central radiological progression, and 15 had clinical progression only, without site or central radiological progression. Ten of the 89 patients were deemed by the site to have progressive disease, but not yet by central review when they were censored because other anticancer treatment had commenced; these are included when testing for concordance between site and central response and progression but not for time-sensitive analyses.

**Intra- and inter-rater variability**

For intra-rater duplicates, all scans reviewed twice were consistently given the same date of progression by the same radiologist. For inter-rater comparisons, all reviewers agreed that progression had occurred at the same date or had not occurred for four of 12 patients (33%). For another four patients (33%), all agreed that progression had occurred but the date of progression differed for one of the three reviewers: three with a difference <2 months (that is, one scan period) and one with a difference >6 months. For the other four patients, one (n=2 patients) or two (n=2 patients) of the three radiologists, but not all three, concluded that progression had occurred.

**Progression-free survival**

Differences in PFS date are shown in Table 1. Concordance in PFS date between site and central review was achieved for 37% of participants. The PFS date was earlier for 45% by central review and earlier for 18% by the site review. Where a discrepancy occurred, the median difference was 1.84 months, which is the approximate difference between the timing of MRI examinations (every 8 weeks). However, when central review determined earlier progression, the discrepancy was up to 24.6 months.

Where the date was available for both site and centrally determined progression and was discordant (n=46), the median PFS was (central versus site): 3.6 months vs 3.9 months, HR 1.52, 95% CI 1.28–1.81, \( P < 0.0001 \) (Figure 1).
The reasons for progression where centrally determined progression was earlier were heterogeneous and are shown in Table 2. The most common reasons were enhancing disease progression and T2/FLAIR progression. Less common reasons were a combination of T1C+ and T2/FLAIR changes and/or a new lesion.

Of the 33 patients whose central and site dates of progression were concordant, for 23 (70%) the type of radiological findings that determined progression were discordant. Of these, five were determined to have ‘clinical only’ progression by the site, but radiological progression was determined by the central review at the same MRI scan date.

Response

Comparison of the site and central best responses is shown in Table 3. Although we hypothesised that responses would be documented more frequently by site than central review, tests of symmetry showed no evidence that documented responses differed between site and central assessments ($P=0.8$). Overall, for 53 (60%) there was agreement for best response and for 36 (40%) disagreement (weighted kappa statistic 0.30, indicating fair agreement overall). For six patients (7%), the central review determined partial response and for one patient a complete response where sites documented stable disease as best response; and for twelve patients (13%) the sites determined either a complete or partial response where the central review documented stable ($n=10$) or progressive ($n=2$) disease as the best response.

Patients continuing treatment beyond date of central progression

Seven (6%) of the 120 patients continued to receive study treatment on the basis of the site determination of stability or response for more than 6 months beyond the progression date determined by central review. The median age of continuing patients was 56 years (range 47–65 years), similar to the median age of 55 for all study patients. Two of these patients continued on bevacizumab monotherapy with compassionate access to the drug beyond the date of study closure and data collection (December 2014); at the time of study closure the sites had not determined radiological or clinical progression in these two patients. The central reviewers’ progression determination was based on T2/FLAIR change alone for all seven patients. Figure 2 shows examples of patients whose date of progression at central review preceded the date of progression at the site by at least 6 months.
Discussion

In this comparison between site and central radiological review of MRI for patients who received bevacizumab on a clinical trial, we found that central review determined progression earlier than the sites for a substantial proportion (45%) of patients, but on average the sites determined progression at the time of the next trial scan (median 1.9 months). The proportion with discrepancies is similar to that previously reported.\(^8\) Although the rate of progression was approximately 50% higher when determined by central review (HR=1.52), the difference in median PFS of only 0.3 months is not clinically meaningful. This is also in keeping with available literature indicating that while centralized review may result in discrepancies at the patient level, it often does not substantially alter an overall PFS endpoint at trial level.\(^7,17,18\)

While intra-rater consistency was absolute for the small number of image sets reviewed twice, there was obvious inconsistency between all three radiologists on the date of progression. This finding is not unexpected: the pivotal BRAIN study of bevacizumab with or without irinotecan used an independent response facility for MRI assessment, requiring two radiologists to read all MRIs, and documented only approximately 50% concordance between reviewers. For discordant results, a third radiologist reviewed scans; further discordance with both earlier reviews was noted in 12%.\(^19\) The lack of consistency is also apparent when comparing the type of radiological progression documented between site and central reviewers for scans with concordant progression dates: most (70%) were different radiological reasons for progression despite the same date of progression being recorded. This exemplifies some of the challenges in MRI reporting, interpretation and application of the RANO criteria.

One of the most thought-provoking aspects of this study is that seven patients were deemed not to have progressed by sites and continued treatment for at least six months beyond the date at which the central review determined progression. All were determined to have progressed on T2/FLAIR changes alone. Clearly, these patients derived a durable survival benefit from therapy. If central review had been used to make decisions about continuing or ceasing therapy, these patients would have completed treatment much earlier. The authors of the RANO criteria themselves indicate that if there is uncertainty regarding progression on imaging, the patient may continue on treatment; if subsequent evaluations indicate progression, then the progression date is backdated to the time point at which the ambiguity occurred.\(^11\) Even in the setting of a clinical trial, there is some degree of flexibility with treatment continuation without compromising the final determination of progression date.
Based on our experience with CABARET, we concur that this is an appropriate strategy, in particular for T2/FLAIR signal changes alone without other evidence of progression on imaging, such as contrast-enhancing disease or new lesions, and without clinical progression.

The results of our study highlight some challenges in using the RANO criteria. For example, in analyzing the images, the first MRI study was used to determine the plane showing the largest tumor dimensions. This plane and location were used for subsequent measurements of the tumor, so there are limitations related to the slice position and image plane selected initially and the tumor growth pattern on subsequent imaging, given that analysis was based on the sum of the products of the perpendicular diameters. This was particularly relevant in the nonvolumetric-acquired sequences. Furthermore, this made it difficult to account for tumor enlargement in different planes on subsequent studies. Another difficulty related to measuring enhancing disease in cystic or necrotic tumors, in terms of confidence in the formal measurements of active tumor. At the time of the trial, RANO criteria were new to both radiologists and clinical investigators; this trial was one of the first to apply and use the criteria, so it is likely a learning curve existed for their application.

An additional challenge is differentiating between disease progression on FLAIR images and treatment-related FLAIR signal change. Typically, in treatment-related leukoencephalopathy the signal change develops gradually in white matter, is relatively ill defined, and has associated volume loss rather than expansion. FLAIR progression related to tumor tends to be more focal and expansile, and may include the overlying cortex. Over multiple scans the difference between the two generally becomes clear, but may be harder to see when comparing only two scans. Figure 2b exemplifies this challenge. Additionally, serial scans may show a clear focal region of expansile FLAIR progression that may nevertheless remain smaller than the larger area of treatment-related signal abnormality, and so could be missed by the measurement criteria. An additional pitfall relates to the slice position in nonvolumetric FLAIR acquisitions, which may not truly reflect the change in FLAIR status.

Should central radiology review be mandated for all clinical trials in glioblastoma? Centralized review does not eliminate inconsistencies in reporting, as exemplified by this trial, and is an additional expense and not in real time, bringing limitations in implementation. One proposed strategy is to use a blinded central audit of a proportion of scans to determine whether there is any evidence of evaluation bias. Ultimately, while there may be discrepancies at the patient level, it is at the population level that the efficacy (and effectiveness) of an intervention is determined. If minimal differences at this group level are established, then central review of every scan for every patient ultimately may not be necessary. On the other
hand, if very early evidence of response or progression is sought in clinical trials, then expert neuro-radiology review is ideal. As exemplified by this and other studies, however, even centralized review does not result in uniformity when determining radiological progression, given the complexities of MRI assessment of high grade glioma.

A limitation is that we did not re-analyse any scans where discordance was noted, whether between site and central dates, or between different central reviewers’ dates. This would not have changed the primary endpoint of the trial (where central reviewer 1’s assessment was always used, and analysis for discordance occurred later); and was beyond the trial scope for this exploratory endpoint.

Several other limitations are worth noting. The sample size and power calculations for the trial were not designed to formally address this research question, which was an exploratory endpoint. Only 89 of the 120-patient cohort were ultimately formally compared, the remainder not comparable for a variety of reasons. Differences in time to progression could only be compared in 79 owing to censoring before central determination of progression. However, all clinical trials in recurrent glioblastoma include patients who progress or die without radiological changes or who are censored for various reasons; therefore we do not believe these findings are likely to differ from those of other studies.

In summary, central radiology review of scans from patients on the CABARET clinical trial resulted in fewer complete or partial responses and a shorter duration of PFS, although ultimately the difference in median PFS of 0.3 months was small. Considerable heterogeneity exists among radiologists when determining the type of radiological progression, even when there is concordance in progression date. In a minority of patients, treatment continued as a result of site reviews for more than 6 months, with durable clinical benefit, reinforcing the conclusion that clinical as well as radiological assessment of therapeutic benefit is relevant in the setting of recurrent glioblastoma.
References


### Table 1: Progression-free survival date differences between site and central assessments

<table>
<thead>
<tr>
<th>Progression-free survival date</th>
<th>n (%)†</th>
<th>Median difference (mo)‡</th>
<th>Lower/upper quartile (mo)‡</th>
<th>Minimum/maximum (mo)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site first</td>
<td>16 (18)</td>
<td>1.8</td>
<td>1.6–2.1</td>
<td>0.8–3.7</td>
</tr>
<tr>
<td>Concordant</td>
<td>33 (37)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Central first</td>
<td>40 (45)</td>
<td>1.9</td>
<td>1.6–4.2</td>
<td>0.7–24.6</td>
</tr>
</tbody>
</table>

† Total n=89 includes:
- n=75 where date available for both site and central progression
- n=4 where date available for central progression, but patient had not progressed on site review at the time of study closure
- n=10 where date available for site progression, but patient was subsequently censored at time of commencing other anticancer therapy before any central progression was documented

‡ Calculated for patients with date available for both site and central progression at time of study closure (December 2014)
Table 2: Type of centrally determined progression when it was earlier than site-determined progression (n=40)

<table>
<thead>
<tr>
<th>Type of progression</th>
<th>Number</th>
<th>%</th>
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<tbody>
<tr>
<td>T1C+ only†</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>T2/FLAIR only</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>T1C+ and new lesion</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>T1C+ and T2/FLAIR</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>New lesion</td>
<td>4</td>
<td>10</td>
</tr>
</tbody>
</table>

†C+ = contrast enhancing
Table 3: Assessed best response (n=89)†

<table>
<thead>
<tr>
<th>Central review assessment</th>
<th>Complete response</th>
<th>Partial response</th>
<th>Stable disease</th>
<th>Progressive disease</th>
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</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0†</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Partial response</td>
<td>0</td>
<td>4†</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>2</td>
<td>8</td>
<td>37†</td>
<td>7</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>12†</td>
</tr>
</tbody>
</table>

† n=89 where data available for both site and central best response

‡ Concordant

Response assessed as per RANO criteria, inclusive of T1C+, T2/FLAIR, clinical status and steroid dose
Figure 1: Kaplan-Meier curve comparing site review (dotted line) and central review (solid line) for progression-free survival.
**Figure 2:** T1C+ (contrast enhancing) and T2/FLAIR MRI images for two patients whose centrally determined date of progression was >6 months before the site-determined date.

2a) At month 11, axial FLAIR, and axial and coronal contrast-enhanced T1-weighted sequences show almost complete response to treatment of the enhancing disease present on baseline imaging. Between months 11 and 15, increasing expansile FLAIR hyperintensity in the corpus callosum (open arrows) and subcortical white matter (arrowhead) was deemed FLAIR progression at central review. By month 17, when disease progression was called by the site, FLAIR hyperintense expansion within the corpus callosum had also extended to the right frontal cortex (*), and there was also increased enhancement inferior to the cavity plus new punctate foci of enhancement in the corpus callosum (closed arrows).
2b) Increased FLAIR hyperintensity about the resection cavity at month 2 (arrowheads) was called as progression by central review. However, this regressed on subsequent scans. FLAIR signal change throughout bilateral supratentorial white matter (*) slowly increased over subsequent months, but due to its ill-defined nature and lack of positive mass effect this was felt to represent treatment effect rather than progression. There was no recurrence of enhancing disease throughout the study period.
Chapter 8: Discussion and Summary

Introduction

My research and PhD work encompassed the development, implementation and outcomes of the CABARET (Carboplatin And Bevacizumab in REcurrent glioblastoma) clinical trial, an Australian multi-centre, stratified randomized phase II study for which I was the Principal Investigator and Study Chair.

This trial compared bevacizumab monotherapy with bevacizumab + carboplatin chemotherapy in 122 adult Australians with recurrent GBM. The primary endpoint was progression-free survival (PFS); several other endpoints have also been the subject of investigation.

The CABARET trial represents a substantial achievement in Australian medical research. This is the largest investigator-initiated brain tumour clinical trial in Australia to date. It was conceptualized, developed and conducted entirely within Australia and provided 122 Australian patients access to a drug that is otherwise too expensive for many. The trial went from concept stage to actual commencement in less than 12 months; and accrual to the trial was rapid.

Throughout this work, I have been assisted by staff from the Co-operative Group for Neuro-Oncology (COGNO) and the Trial Management Committee, consisting of Australian neuro-oncologists. This has been a collaborative effort and the most significant prospective clinical trial in Australian brain tumour research to date, which attracted significant interest at an international level.

Summary of findings

Survival outcomes

The primary objective of CABARET was to determine the effect of bevacizumab plus carboplatin versus bevacizumab monotherapy on PFS in patients with recurrent GBM. The study documented that the addition of carboplatin to bevacizumab did not increase PFS but did result in more toxicity. In addition, there were no significant differences in response rate or overall survival.
Continuation of bevacizumab beyond disease progression

CABARET was the first prospective study worldwide to test the use of bevacizumab beyond progression in GBM. After initial progression on trial, patients considered suitable for further therapy underwent a second randomization to either continue or cease bevacizumab. In this study, continuation of bevacizumab beyond disease progression did not result in a PFS or OS benefit when compared to patients who had bevacizumab ceased at disease progression. This is the only prospective data analysing the continuation of the drug beyond progression. In addition, there was no evidence of rapid rebound progression in those patients randomized to cease bevacizumab. This had been reported in previous retrospective studies.

Health-related quality of life (HRQL)

In incurable disease, quality of life is a key endpoint in clinical trials, aiming to ensure that palliative-intent treatment is not increasing morbidity. HRQL testing, using two validated instruments (EORTC QLQ-C30 and BN20), occurred at baseline and regularly throughout the trial, including at progression. We found HRQL testing feasible in this patient population with participation rates >90% at most time points. We found neither detrimental nor beneficial effects on HRQL with combination therapy compared with bevacizumab monotherapy. In both arms, close to 50% of patients experienced improvement in selected HRQL symptom domains, indicating potential therapeutic benefit.

Radiology endpoints

Not all patients derive benefit from bevacizumab, and an early and reliable indicator of efficacy or futility may allow early discontinuation in non-responders. We prospectively assessed the role of early MRI (eMRI) four weeks after commencement of bevacizumab. We found strong evidence that both PFS and OS differed by eMRI response – with median overall survival 8.6 months (eMRI response) versus 3.7 months (eMRI progression). Early radiological progression on MRI for patients on bevacizumab appears to be a robust marker for poor prognosis in our study. This is of significant relevance in the Australian context where patients pay up to $20,000 for the first 3 months of treatment; ceasing a futile drug could be associated with substantial cost savings for these individuals.
We compared central and site radiology reviews incorporating the new ‘Response Assessment in Neuro-Oncology’ (RANO) criteria of MRI reporting. While central radiological review resulted in an earlier date of progression in close to 50% of patients on trial, the difference in date of progression for the entire cohort – while statistically significant - was small (0.3 month difference in median PFS). Mandating centralized review for all neuro-oncology clinical trials, which is expensive and time consuming, may thus be questioned. A small proportion of patients remained alive and well on treatment months after the central review had determined progression, reinforcing the importance of clinical determination of benefit from therapy. Additionally, inter-rater variability between central radiologists when reporting the same scans was high – not inconsistent with prior reports from centralized review of brain tumour trials. This represents the challenges in interpreting MRI findings in this context, and perhaps the learning curve associated with the introduction of the new RANO criteria for MRI reporting.

Limitations to the study

Choice of Progression-free survival (PFS) as a primary endpoint:

(This section has been adapted from my own (co-first author) published review paper ‘Bevacizumab and GBM: Scientific review, newly reported updates, and ongoing controversies’ (Cancer April 2015) – See Appendix 2)

Progression-free survival (PFS) was selected as the primary endpoint for the CABARET study to enable meaningful comparison with contemporary trials of bevacizumab in recurrent GBM, which also reported PFS as the primary endpoint. PFS has been considered a surrogate endpoint in clinical trials – that is, on its own it is not a meaningful endpoint unless ultimately it translates ultimately to a valid clinical endpoint such as overall survival (OS) benefit. Herein lies one of the key difficulties with the two large first-line bevacizumab studies: although both showed improved PFS for bevacizumab, only one (AVAglio) showed a statistically significant PFS advantage, and neither translated to an OS benefit.\textsuperscript{1,2} Similarly at the time of trial design, in recurrent GBM although single-arm studies reported better OS outcomes than historical control data, there were no randomized data comparing bevacizumab with chemotherapy and
reporting OS. Our trial, including bevacizumab in both arms, was not designed to answer this question.

PFS can be argued to be a valid endpoint of its own, and it was justified to use this as the primary endpoint for CABARET. An enlargement of a central nervous system tumour is not uncommonly accompanied by deterioration in clinical symptoms. Many would argue that for malignant glioma, time without tumour progression – provided that this time is of good quality and not at the expense of intolerable or dangerous side effects from a drug – is meaningful. Keeping an individual without progression from symptoms related to their brain tumour could be argued to be an example of meaningful clinical benefit.

PFS had previously been shown to be a valid clinical endpoint that was predictive of overall survival benefit in studies prior to the advent of targeted therapies in neuro-oncology. However, in the setting of anti-angiogenic therapy, it cannot be concluded from available evidence that PFS results in either downstream OS benefit, or is objectively associated with improved/stable QOL or symptom control for a longer duration, given the conflicting results in the two large first-line phase III studies. In fact, some argue that the effect of bevacizumab on PFS could simply be a reflection of the drug masking radiological progression or altering the recurrence pattern without having substantial impact on the disease process itself; although this is contentious.

Choice of therapies

Initially the CABARET study was designed as a three-arm study: Bevacizumab monotherapy, carboplatin monotherapy, or bevacizumab/carboplatin combination therapy. This study design intended to address the question of whether combination therapy improved outcomes compared with either drug used as monotherapy. At the time, no other prospective trial had compared bevacizumab with chemotherapy and this was an unanswered question; the original trial design would have resulted in substantial world-wide interest. Ultimately the carboplatin monotherapy arm was not included in the final trial design; and that particular research question has been answered by the subsequent BELOB and EORTC 26101 studies. As a phase II trial, the limitation of sample size means it is still possible for a difference between arms to have been missed; however there are no plans to expand this trial to the phase III setting.
**Bevacizumab beyond progression: The second randomization**

Some have argued that our study does not eliminate the possibility of bevacizumab continuation providing benefit. With a limited sample size of 48 patients, the study was exploratory and not powered to detect small differences in outcome. The intended sample size was 60 patients (half of the original 120 patient cohort) and failure to meet the original sample size does not negate the study findings, as we were clear from the beginning that any results were exploratory rather than definitive. Many patients did not undergo further MRIs after clinical deterioration so radiological confirmation of disease status was also limited; however this is in keeping with the decisions that would be made in a clinical setting (there is no ‘point’ in doing an MRI if a patient has substantially clinically deteriorated due to disease).

**Quality of life**

Because patients received bevacizumab in both arms of CABARET, we were not able to make comparison of HRQL between those receiving and not receiving bevacizumab. This is of key interest given conflicting findings in the two first-line GBM studies using bevacizumab. The AVAGlio study reported longer time to HRQL deterioration in bevacizumab-treated patients, using a method similar to ours. HRQL was maintained over the progression-free period in patients receiving bevacizumab. Conversely, the RTOG 0825 trial (in which HRQL completion was optional, and for which MacDonald rather than RANO criteria were utilised to document progression) reported that bevacizumab-treated patients had worse HRQL. The RTOG 0825 statistical analysis used data only from patients without progression at specified time points, with substantial attrition in questionnaire completion over time, more so in the placebo arm. We cannot provide insight into these conflicting outcomes; however it is apparent that any analysis of HRQL must be methodologically robust, especially given the (expected) attrition rate over time. This is important to account for when planning statistical analysis.

**Radiology sub-studies**

The central radiologists reported challenges in incorporating and interpreting the new RANO criteria. There was substantial heterogeneity between central reviewers when determining date of progression or even when progression had occurred. Within the trial there was no
budget to subsequently reassess those cases until concordance was reached. A decision was made and remained the same throughout the conduct of the trial, to use the ‘primary reviewer’s assessment as the one to determine disease status. Because this was consistent throughout the trial, and because the comparison between central and site radiology reporting was not the primary endpoint, we did not feel it was necessary to re-analyse these data. Heterogeneity between central reviewers is commonly reported in international trials.

Advanced MRI techniques for determining disease status were not part of this analysis. A small sub-study of patients on CABARET using advanced MRI techniques (perfusion-weighted MRI imaging) has been published.8 (Bennett, Field et al, *Journal Neuro-Oncology* January 2017, see appendix 4). Ideally future trials would incorporate the capacity for advanced MRI technique analysis as there is substantial promise in the use of MRI findings as radiological ‘biomarkers’ for targeted therapies.

In Part 1 of CABARET, several patients remained clinically well and derived obvious clinical benefit from continuing bevacizumab for many months after the central review determined their disease to have progressed radiologically (the central review was not conducted in real-time and so site reviews for these patients had reported ongoing disease control). This highlights the important point of assessing a patient based on clinical status rather than making any ‘blanket’ decisions based on radiological findings alone.
Bevacizumab in recurrent GBM: Developments since the CABARET trial

Table 1 summarizes the key prospective clinical trials in recurrent GBM that had not been completed or reported at the time that CABARET was designed and conducted. The CABARET trial is also included in the table for comparison. These trials reflect more recent interpretation of the role of bevacizumab in recurrent GBM, in light of the new RANO criteria and a better understanding of the significance of T2/FLAIR progression. None of the more contemporary trials have reported results as impressive as the earlier trials that resulted in registration of the drug.

The Dutch BELOB study was a randomized phase II three-arm study comparing bevacizumab monotherapy, lomustine monotherapy or the combination, in 153 patients with first recurrence. Patients in the combination arm had better outcomes than either monotherapy arm, with the primary endpoint of 9-month OS being met (59% versus 38% bevacizumab and 43% lomustine), median OS 11 months versus 8 months (monotherapy arms), and an impressive improvement in 6-month PFS (41% versus 18% and 11%). This was an important study in the context of many single arm phase II trials having been conducted investigating bevacizumab, as well as the prior large-scale randomized studies in the recurrent setting not including a control arm without bevacizumab.

Of note, the study design originally compared bevacizumab monotherapy with bevacizumab plus lomustine; the third arm of lomustine monotherapy was added only after the European Medicines Agency (EMA) ruled against approval of bevacizumab due to lack of a control arm in prior studies. The authors concluded that a phase III follow-up study was warranted based on these findings; the EORTC 26101 study which followed, is described below. It is notable that the 6-month PFS for bevacizumab monotherapy of only 18% was substantially lower than the 43% that was seen in the BRAIN study. This does bring into some question the value of bevacizumab monotherapy; although OS outcomes for the monotherapy arm were similar to contemporary literature. The PFS discrepancy may have been partly related to the BELOB study using RANO criteria for assessment of disease progression, which may be more sensitive.
than MacDonald criteria, especially for the non-enhancing component of the tumour; or the fact that this was a community-based study with possibly more unwell patients being enrolled.

The Phase III study EORTC 26101, as a follow-on study from BELOB, has been presented in 2016 but not yet published.\textsuperscript{11} This large study randomized 437 patients to either lomustine + bevacizumab or lomustine monotherapy. Overall survival was not superior for combination therapy (median OS 9.1 vs 8.6 months, HR 0.95, 95% CI 0.74-1.21, p=0.650), although PFS was improved (4.2 versus 1.5 months, HR 0.49, 95% CI 0.39-0.61, p<0.05). Over a third of patients not randomized to receive bevacizumab did cross over to receive it on progression, which may have diluted any potential OS benefit; but nevertheless there were no compelling trends towards overall survival.

At this point the role of bevacizumab in recurrent GBM is somewhat uncertain given the lack of overall survival benefit in this trial. Work continues try to identify biomarkers that may predict which patients are most likely to benefit from the drug; and with the lack of effective alternative agents, bevacizumab continues to be used commonly (depending on the region of the world) in the recurrent disease setting.
### Table 1: Contemporary trials of bevacizumab (B) in recurrent GBM

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Trial design</th>
<th>Drugs used</th>
<th>N</th>
<th>Outcomes</th>
<th>6PFS</th>
<th>Median OS</th>
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<tr>
<td>Reardon</td>
<td>2012</td>
<td>Phase II</td>
<td>B + carboplatin + irinotecan</td>
<td>40</td>
<td></td>
<td>47%</td>
<td>8.3m</td>
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<tr>
<td>Taal (BELOB)</td>
<td>2014</td>
<td>Randomized Phase II</td>
<td>B + lomustine vs B vs lomustine</td>
<td>153</td>
<td></td>
<td>41%</td>
<td>11m</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>11%</td>
<td></td>
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<tr>
<td>Field (CABARET)</td>
<td>2015</td>
<td>Randomized Phase II</td>
<td>B + carboplatin vs B</td>
<td>122</td>
<td></td>
<td>26%</td>
<td>6.9m</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
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<td>24%</td>
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<tr>
<td>Sepulveda</td>
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<td>Phase II</td>
<td>B + temozolomide</td>
<td>32</td>
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<td>22%</td>
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<td>Brandes</td>
<td>2016</td>
<td>Non-comparative</td>
<td>B or fotemustine</td>
<td>91</td>
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<td>62%</td>
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<td>Weathers</td>
<td>2016</td>
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<td>B vs low-dose B + lomustine</td>
<td>71</td>
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<td>24%</td>
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**Systematic reviews**

An earlier 2011 systematic review and meta-analysis of bevacizumab in recurrent GBM included 15 studies and a total of 548 patients, and reported median OS of 9.3m, 6m PFS of 45% and a 6.1 month time to tumour progression. Overall 6% of patients were reported to have complete response and 49% partial response.\(^{18}\) This compares with findings from more recent prospective phase II/III trials as shown in Table 1.

A more contemporary systematic analysis of bevacizumab in newly diagnosed and recurrent GBM was published in July 2017.\(^{19}\) In the recurrent setting, improvements in PFS and OS compared to historical controls were described; however overall the body of literature is limited by the fact that only one trial (EORTC 26101) has compared bevacizumab with chemotherapy.

A 2014 Cochrane review of anti-angiogenic therapy in glioblastoma (both newly diagnosed and recurrent), included only trials that had anti-angiogenic versus no anti-angiogenic randomization and so within the recurrent disease setting, only the BELOB trial was included (the EORTC trial had not yet been reported).\(^{20}\) Overall when pooling results from both the newly diagnosed and recurrent disease setting, and including several tested anti-angiogenic agents including bevacizumab, improvement in PFS was noted (HR 0.74, 95%CI 0.68-0.81, P<0.00001). However, despite this, no improvements in overall survival were found (pooled hazard ratio 0.94, 95% CI 0.86-1.02, p=0.16).

**Use of bevacizumab in Australia since CABARET**

Bevacizumab is currently approved as monotherapy for recurrent GBM through the Therapeutic Goods Administration (TGA), but is not currently Pharmaceutical Benefits Scheme (PBS) approved. This means that giving the drug comes at considerable cost to the patient. While Roche provides an access program for bevacizumab, the out-of-pocket cost for the first three months of therapy is, on average, $20,000 per patient. If a patient remains progression-free and is felt to be deriving clinical benefit at that time point, the remainder of therapy is provided by Roche at no cost to the patient for the drug. This may result in considerable ethical dilemmas for the clinician – whereby access to a medication is limited by affordability to an individual patient. In the world of oncology this is becoming increasingly common.
Access to high cost drugs is arguably more easy in private oncology, bringing with it the risk of disparate treatments between private and public patients. With access to the internet, patients may become aware of novel therapies still in clinical trial development that show early promise and want to access these; next generation sequencing can potentially identify ‘druggable’ mutations – which may be acted upon by patients and clinicians even if there is a paucity of evidence to support this. Access to drugs in this way is somewhat unregulated and not supported by robust evidence; furthermore, ‘cherry picking’ drugs for an individual in this way – without prospectively recording results and outcomes – makes it difficult for any knowledge to be gained from such a strategy.

**Scientific impact**

This work has been presented at several National and International meetings, including several Society for Neuro Oncology annual meetings (USA). I was awarded an American Society of Clinical Oncology Conquer Cancer Foundation of the American Society of Clinical Oncology Merit Award for this work in 2013 where the research was presented.

This has been a significant contribution to the management of GBM in Australia as our research suggests we do not need to add carboplatin chemotherapy to bevacizumab, and thus can avoid unnecessary toxicities from chemotherapy. In fact, since CABARET was designed and conducted, the use of carboplatin as a second line agent for recurrent GBM is now rare in Australia; lomustine is now more commonly used if bevacizumab is not available or appropriate.

Part 2 of the CABARET trial has significantly added to international literature on this topic. At the time of protocol writing, bevacizumab was commonly continued even after disease progression, based on data from other tumour types where bevacizumab beyond progression has been associated with survival advantages; and retrospective studies in GBM with concerns of a possible rapid ‘rebound’ effect when stopping bevacizumab. This secondary endpoint of the CABARET trial remains the only randomized study world-wide to have addressed this
research question. These data were presented as an oral presentation at the American Society of Clinical Oncology Annual Meeting in 2015, and at several Australian neuro-oncology meetings. The results have been met with intense interest and speculation amongst the international neuro-oncology community.

For the HRQL sub-study, the methodology of HRQL testing and analysis was found to be robust and will help inform future clinical trials. Specifically, we tested time to HRQL deterioration, allowing inclusion of all patients including those who did not complete questionnaires because of progression or death. This method is appropriate as it avoids bias due to attrition in questionnaire completion. We found using time to HRQL deterioration a robust and useful statistical endpoint in this patient group.

The research paper describing the early MRI findings has been published in the international journal *Cancer*. Using RANO criteria and extending the capability of centralized review to include more advanced MRI techniques is now being incorporated into newer trial designs, such as the NUTMEG study (another COGNO investigator initiated study, where MRI scans will be reviewed by collaborators in the USA and advanced MRI imaging and reporting techniques will be a key aspect of this trial. The experience from CABARET has helped to inform this design.

**Final Conclusions**

The work on CABARET has shown that conducting an investigator-initiated study in Australia in patients with recurrent GBM is feasible and achievable. The study results have significantly improved knowledge regarding the use of bevacizumab in the setting of recurrent GBM. This will have an impact on managing patients with this disease as we have further insight into anticipated effects and survival in the Australian context. The methodology of HRQL testing in our study will help inform future clinical trial development, and we have a better understanding of the benefits and limitations of the use of RANO criteria and centralized radiological review in clinical trial populations. Figure 1 shows graphically a current decision tree for bevacizumab use in GBM; the CABARET trial has helped to inform these decisions.
To know if bevacizumab truly helps patients with GBM, ideally we should be able to objectively answer whether it benefits particular patient subgroups; its optimal dosing and timing; whether it should be used as monotherapy or in combination; and finally, whether it maintains - if not improves - clinical functioning for an extended duration. Some, but not all of these questions have been addressed by the CABARET and other contemporary trials. We know from other contemporary studies and systematic reviews that bevacizumab improves PFS but does not improve OS in either the newly diagnosed or recurrent disease settings.\(^1,2,11\) The results from CABARET have challenged previous dogma regarding the use of bevacizumab in recurrent GBM, and have significantly added to international understanding by showing that:

- The addition of chemotherapy (carboplatin) to bevacizumab resulted in no additional clinical benefit and indeed, caused a significant increase in toxicity.
- Continuation of bevacizumab beyond progression resulted in no apparent clinical benefit.
- Treatment may improve some quality of life measures for up to 50% of patients; and quality of life deterioration often precedes clinical or radiological disease progression.
- While centralized review of radiology is often recommended, it does not eliminate discordance between reviewers, and may not ultimately substantially alter the trial’s outcome reporting.

**The future**

The traditional method of ‘proving’ a cancer drug is beneficial relies on phase I, II and III clinical trials to demonstrate efficacy in a population of cancer patients; and the Australian Pharmaceutical Benefits Scheme (PBS) needs to be assured of clinical and cost-effectiveness for government subsidies to occur. However, we are starting to move away from this traditional clinical trial design. In particular for GBM, an exciting clinical research initiative underway is the AGILE study, an adaptive clinical trial using Bayesian statistics to obtain real-time data from each patient and use this information for subsequent patients.\(^21,22\) The trial will test therapies on individual participants based on their own tumour’s molecular biomarker profile and will be adapted in real time as more knowledge is gained during the conduct of the study.

Improved methods of obtaining an unbiased assessment of whether a patient is clearly improved, stable or worsened during therapy are clearly paramount. The RANO criteria are one step forward towards this goal, in today’s era of complexity; however interpretation of
MRI scans remains difficult, and additional radiological techniques are in development, which are likely to aid in radiological assessment in the era of anti-angiogenics and other targeted agents.

Quality of life and neurocognitive function are increasingly recognized clinical endpoints of significance. The North American Food and Drug Administration (FDA) acknowledges that improvement in neurocognitive function or delay in neurocognitive progression are acceptable endpoints in clinical trials. What does need to be elucidated is whether there are, in fact, clinical consequences of VEGF inhibition itself. With the exception of reversible posterior leucoencephalopathy syndrome, this has not been reported for other tumour types such as colorectal cancer where bevacizumab has been in common use for several years; however formal testing for this has not occurred for other tumour types. As trials in GBM continue, the most appropriate methodology for assessing and analysing neurocognitive outcomes must be robust. While there are several validated forms of neurocognitive function testing, ideally the testing battery should be relatively quick and without undue stress for participants. Ideally similar tests could be used across trials allowing for comparison. Our study of the CogState testing methodology is underway, and will help to inform this issue.

There are clearly some patients who do appear to benefit greatly from bevacizumab therapy. Identifying those patients who may fall into this category is a continuing issue and the search for predictive biomarkers is ongoing – not only for GBM but all tumour types where the drug is used. The ability to select those patients who are most likely to benefit, while sparing others unnecessary toxicities, would be ideal and this pursuit is ongoing. For now, we anticipate the ongoing use of bevacizumab in the setting of recurrent GBM, but without the magnitude of progression-free survival benefit that had been anticipated following the sentinel clinical trials. Bevacizumab does remain arguably the most significant anti-cancer agent since temozolomide to become available for the management of recurrent GBM. While it may not be the panacea we hoped for all patients, its beneficial effects have been unsurpassed by many other agents that have been tested in this setting. The search for other, newer agents that may help to combat GBM; and the application of novel trial designs that can provide more rapid answers to research questions, is an ongoing and collaborative process.
**Figure 1:** Decision tree for bevacizumab use in GBM; assuming fit healthy patient with no clear contraindications

- Newly diagnosed: Chemoradiation, then temozolomide
- First recurrence: Bevacizumab monotherapy*
- Second recurrence: Consider bevaxizumab if not previously used

*Approved by TGA only as monotherapy in Australia

^CABARET Part 2 found no survival benefits when continuing beyond progression

- There are no current predictive biomarkers for bevacizumab use; hence, all patients can be considered.
- All patients should be considered for clinical trials where available and eligible.
- Consider surgery where feasible at recurrence.
- Consider repeat radiation in recurrent disease if substantial time since prior radiotherapy (>5 years) or in different location from previously irradiated field. Stereotactic radiosurgery may be appropriate.
- Available decisions differ based on bevacizumab approval indication in regional location (e.g., USA versus Europe versus Australia).
References

Chapter 1


30. Mustafa Khasraw, Kerrie Leanne McDonald, Mark Rosenthal, al e. VERTU: Veliparib, radiotherapy (RT) and temozolomide (TMZ) trial in unmethylated MGMT glioblastoma (GBM). *J Clin Oncol.* 34, 2016 (suppl; abstr TPS2081).


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Chapter 2


**Chapters 3-7 (see individual reference list at end of each chapter)**

**Chapter 8**


Appendices

Appendix 1: CABARET protocol
A randomised phase II study of Carboplatin and Bevacizumab in Recurrent Glioblastoma Multiforme (CABARET study)

**COGNO Protocol number COGNO0902**
**Roche Protocol number ML25442**

**Version 1.3, dated 12th August 2011**

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**Collaborative Group:**
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NHMRC Clinical Trials Centre  
University of Sydney  
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Representative name and signature

Date

This is an independent investigator-sponsored study conducted under the auspices of the Co-operative Trials Group for Neuro-Oncology (COGNO), coordinated at the NHMRC Clinical Trials Centre, University of Sydney as a multi-centre study.

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Statistician: Val Gebski

CONFIDENTIAL
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TITLE
A randomised phase II study of Carboplatin and Bevacizumab in Recurrent Glioblastoma Multiforme (CABARET study)

SPONSOR
University of Sydney (Investigator initiated)

INDICATION
Recurrent Glioblastoma Multiforme (World Health Organization (WHO) IV astrocytoma)

OBJECTIVES
Primary objective:
To determine the effect of the combination of bevacizumab plus carboplatin versus bevacizumab alone on progression-free survival (PFS) (using modified Response Assessment in Neuro-Oncology (RANO) criteria) in patients with recurrent grade IV glioma (glioblastoma multiforme).

Secondary objectives:

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<td>To determine the effect of bevacizumab in combination with carboplatin versus bevacizumab alone on:</td>
<td>To determine the effect of continuing or stopping bevacizumab after disease progression on:</td>
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- Objective radiological response rate (according to modified RANO criteria)
- Objective radiological response rate (according to modified Macdonald criteria)
- Cognitive function (CogState and Mini-Mental State Examination (MMSE))
- Health-related quality of life (HRQL) (European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires QLQ-C30, BN20 and the EuroQol Group EQ-5D)
- Corticosteroid dose
- Toxicity (National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0)
- Overall survival (OS)
- Time to treatment failure
- Subsequent progression-free survival (PFS) (modified Macdonald and modified RANO criteria) (for part 2 only)

Exploratory objectives:
- Correlation of MRI response at 4 weeks with clinical outcome (PFS and OS)
- Correlation between steroid usage and dose and clinical outcome (PFS and OS)
- Comparison between modified Macdonald criteria and modified RANO criteria for assessment of disease response/progression
- To document the location and type of radiological progression on and after discontinuation of bevacizumab
- Correlation between blood and tissue biomarkers and clinical outcome (including PFS, OS, response rate)

TRIAL DESIGN
Sequential stratified randomised phase II. In part 1 of the study patients will be stratified by centre, age, gender and performance status. In part 2 additional stratification by allocation in part 1.

NUMBER OF PATIENTS
Total 120 patients

TARGET POPULATION
Consenting male and female patients aged ≥ 18 years with recurrent grade IV glioma (glioblastoma multiforme) who have had prior treatment with both radiotherapy and temozolomide chemotherapy (concurrently and/or sequentially), and have had no prior chemotherapy other than temozolomide for the treatment of glioma.
TREATMENTS:  
Part 1  
Arm A: Bevacizumab 10mg/kg given intravenously (IV) every 2 weeks until disease progression  
Arm B: Bevacizumab 10mg/kg given intravenously (IV) every 2 weeks + carboplatin AUC 5 given IV every 4 weeks until disease progression  

Part 2  
Following disease progression patients who are able to continue treatment will be further randomised to cease bevacizumab or continue bevacizumab 10mg/kg every 2 weeks. In addition to this:  
Arm A: Patients in Arm A in Part 1 will commence carboplatin AUC 5 IV every 4 weeks or best supportive care (BSC).  
Arm B: Patients in Arm B in Part 1 will cease carboplatin and commence clinician’s choice of additional chemotherapy agent (see appendix 3) or best supportive care.  

Patients can be randomised and continue on Part 2 of the study if they receive best supportive care rather than carboplatin (Arm A) or clinicians’ choice of chemotherapy (Arm B). The decision as to whether further chemotherapy will be administered and which chemotherapy (for clinician’s choice), must be specified PRIOR to the second randomisation.  

ENDPOINTS  
Primary endpoint: Progression-free survival (modified RANO criteria)  
Secondary endpoints:  
The following will be evaluated separately for Part 1 and Part 2 of the trial:  
- Objective radiological response rate (according to modified RANO criteria)  
- Objective radiological response rate (according to modified Macdonald criteria)  
- Cognitive function (CogState and MMSE)  
- HRQL (EORTC QLQ-C30, BN20 and EuroQol EQ-5D)  
- Corticosteroid dose  
- Toxicity (NCI CTCAE Version 4.0)  
- Overall survival (OS)  
- Time to treatment failure  
- Subsequent progression-free survival (modified Macdonald and modified RANO criteria) (for part 2 only)  

STATISTICAL ANALYSES  
120 patients are sufficient to evaluate progression-free survival rates of the two arms in Part 1 with reasonable accuracy (95% confidence of ±12% based on Kaplan-Meier estimate). Each of the 4 arms in Part 2 of the study is expected to have between 15-20 patients which will be sufficient to broadly estimate treatment outcomes to inform further studies.
1 BACKGROUND INFORMATION

1.1.1 Glioblastoma multiforme

High grade gliomas are the most common malignant brain tumour, accounting for around 80% of all malignant brain and central nervous system (CNS) tumours. Glioblastoma Multiforme (GBM) is the most aggressive malignant glial tumour, accounting for 60-70% of malignant gliomas\(^1\). Despite a low incidence, it carries a high mortality burden, a high social burden to both the cancer sufferer and carer, and high costs for the healthcare system. There are over 1000 diagnoses of GBM projected for Australia in 2010, and currently 2 and 5-year overall survival despite best management is 27.2% and 9.8% respectively\(^2\).

1.1.2 Treatment

The optimal management of these patients is complex and multidisciplinary. Primary treatment for GBM usually involves maximal surgical resection where both the site of the tumour and the condition of the patient make this approach safe. However, the infiltrative nature of this disease makes a complete resection difficult, leading to virtually all patients relapsing and most commonly within 2-3cm of the original tumour\(^3\).

Best-practice treatment after surgery is combined chemoradiotherapy with 60 Gray in 30 fractions radiotherapy concurrently with low dose temozolomide\(^4\). Chemoradiotherapy is followed by 6 cycles of chemotherapy with oral temozolomide for 5 days of every 28 days. This is based on data from the large EORTC/National Cancer Institute of Canada (NCIC) phase III clinical trial\(^4\) which set a new standard for the management of patients with GBM. This is the standard of care in Australia.

Despite this aggressive multimodality approach, relapse is almost inevitable for patients with GBM. In Australia, there is no accepted standard management for patients following disease progression. Surgery or stereotactic radiosurgery is considered and performed if feasible, however management decisions must be made on a case-by-case basis and the site of original and recurrent tumour and size of recurrence are important factors. Treatment with chemotherapy at relapse aims to prolong PFS and OS, reduce morbidity, and restore or preserve neurological function. Commonly used chemotherapy agents include low-dose temozolomide, single-agent carboplatin, and nitrosoureas (CCNU/BCNU). Phase II data provides some support for each of these approaches\(^5\).

Recent phase II studies have examined the role of novel agents targeting specific elements of the tumour cell molecular machinery. These agents have included: epidermal growth factor receptor (EGFR) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, integrin inhibitors and vascular endothelial growth factor (VEGF)/Vascular Endothelial Growth Factor Receptor (VEGFR) inhibitors among many. Phase II data provides some support for each of these approaches. The Therapeutic Goods Administration (TGA) as well as the Food and Drug Administration (FDA), amongst others, recently approved the use of bevacizumab in recurrent GBM on the basis of studies that documented partial responses in up to 26% and a six month PFS of 36%\(^6\). This compares with a review by Wong et al 1999, suggesting the six month PFS was in the order of 15% for non-temozolomide chemotherapy\(^7\).

Due to the paucity of active treatment options, and the clear need for improvement in current standard of care, recurrent GBM is an ideal setting for the development of new drug treatment strategies.

1.1.3 Prognostic factors

Age and performance status are known prognostic factors for GBM. There are several other potential prognostic factors which are not yet routinely used in deciding upon treatment strategies in
routine care for patients with GBM but may become more significant as further treatment strategies emerge.

A recursive partitioning analysis (RPA) classification has been performed using data from several clinical trials in malignant glioma and has been able to correlate several clinical and treatment features with survival allowing the distinction of subsets of patients with different prognosis\(^8,9\). The class description takes into account age, World Health Organization (WHO) performance status, extent of surgery and MMSE test.

It would be ideal to identify other biomarkers for GBM that could act as either prognostic or predictive factors to help in treatment selection decisions for patients at the time of their diagnosis.

### 1.1.4 Health-related quality of life

Health-related quality of life (HRQL) is an important consideration for patients with high grade gliomas because of the neurological impairment that the tumour frequently causes, and to interpret results in the context of the patient’s experience. The effectiveness of a treatment in high grade glioma would be therefore based on both a significant improvement in PFS and OS, together with an acceptable effect on HRQL. See section 1.2.5 for more information regarding the tools to be used.

### 1.1.5 Neurocognitive function (NCF)

Clearly because of their location, brain tumours frequently affect patients’ cognitive function and this is an important consideration when assessing quality of life. The US FDA has stated that “improvement in neurocognitive function or delay in neurocognitive progression are acceptable endpoints”\(^10\). Neurocognitive assessment is complex, and there is no consensus on the best tools for measurement. However, it is clear that simple tools such as Folstein’s MMSE, whilst appealing in their simplicity, were developed as a screening tool for dementia and show poor sensitivity in detecting cognitive impairment in the setting of intracerebral tumours\(^11\). The ideal tools should be brief, simple, sensitive, cheap, and if administered repeatedly, should have alternative versions to reduce the effects of learning\(^12\). Another method of rapid cognitive assessment is CogState ClinicalTrials\(^13\) which is a range of computerised cognitive tasks able to measure baseline and change in all cognitive domains. The CogState testing method has been validated in peer-reviewed journals\(^14\) and has been used extensively in phase I to phase IV trials with both healthy volunteers and patient groups, including dementia studies and studies of drug effects. It has not been used in brain tumours but is sensitive to changes over time and is reproducible.

### 1.1.6 Vascular endothelial growth factor (VEGF)

Members of the VEGF family include VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placental growth factors (PIGF) 1 and 2. VEGF-A is a multifunctional cytokine, which is a central regulator of physiological and pathological angiogenesis\(^15,16\). The human VEGF gene is localized in chromosome 6p21.3 and is organised in eight exons, separated by seven introns. Human VEGF has 6 isoforms that derive from alternative exon splicing of one single gene. Due to its bioactivity and biological potency, VEGF-165 is the predominant isoform. Native VEGF is a basic, heparin binding, homodimeric glycoprotein\(^17,18\). Tumour cells secrete VEGF in response to many stimuli including hypoxia, tissue acidosis or cellular stress, which are prevalent in many solid tumours. VEGF exerts its biologic effect through interaction with three variants of type III receptor tyrosine kinase, VEGFR-1 (Flt-1), VEGFR-2 (Flk-1) and VEGFR-3 (Flt-4). VEGF receptors are expressed on the cell surface of many bone marrow derived cells such as hematopoietic cells\(^19\), macrophages and endothelial cells\(^20\) and vascular smooth muscle cells\(^21\). Signalling specificity of VEGF receptors is further modulated upon recruitment of co-receptors such as neuropilins, heparin sulphate, integrins or cadherins. VEGFR-2 appears to be the main receptor responsible for mediating the pro-angiogenic effects of VEGF\(^22-24\). The pro-survival effects of VEGF/VEGFR-2 are mediated by the phosphoinositol 3 kinase-Akt pathway\(^25\).
Each VEGF isoform binds to a particular subset of these receptors. Binding activates discrete signalling pathways that promote many functions including the mobilisation of endothelial progenitor cells from the bone marrow that likely play a significant role in tumour neovascularisation. It also serves as a potent mitogen for vascular endothelial cells, which proliferate and migrate to the area of tumour growth to begin formation of new blood vessels. Once new vessels are formed, VEGF functions as a survival factor and inhibits apoptosis of the poorly formed vasculature. Through this mechanism, tumour cells are able to sustain growth by securing continued blood flow and nutrition. VEGF is a potent angiogenic mediator, and angiogenesis has important effects on tumour growth and metastasis. Thus, expression of VEGF may be an indicator of the angiogenic potential and aggressiveness of a tumour. In the normal state, endothelial cells divide approximately every 7 years, but in the malignant state this growth rate is accelerated and endothelial cells can divide as rapidly as every 7-10 days. This ‘angiogenic switch’ is necessary for tumours to obtain the necessary nutrients and oxygen to grow beyond a diameter of 1 mm.

1.1.7 Bevacizumab

Bevacizumab is a recombinant humanised monoclonal antibody to VEGF that blocks the binding of human VEGF to its receptors. Bevacizumab has been tested in Phase I to IV studies in a variety of solid tumours in combination with chemotherapy. It is approved for the treatment of metastatic colorectal cancer, metastatic breast cancer, metastatic lung cancer, metastatic renal cancer and grade IV glioma after relapse or disease progression in Australia and many other countries.

1.1.8 Clinical activity of bevacizumab in high grade gliomas

Most of the trials reporting the clinical effect of bevacizumab in GBM have been performed in the relapsed setting, upon tumour progression following the 1st line treatment with chemoradiation and maintenance with temozolomide. Vredenburgh et al. were the first to report a phase II trial showing a clinical improvement in relapsed glioblastoma with the use of a combination of bevacizumab (10 mg/kg, 2 weekly or 15 mg/kg, 3 weekly) and irinotecan. In their cohort of 35 patients, the 6-month PFS was 46%, and at least a partial response was observed in 57% of the patients, with moderate toxicity. Compared to historical controls, the improvement was striking. Additional phase II data from Kreisl et al, in a study of 48 heavily pretreated patients with GBM, treated patients initially with single agent bevacizumab and then on disease progression added irinotecan to bevacizumab. The 6 month PFS was 29%, and 35% of patients achieved radiographic response (Macdonald criteria). Early MRI response was predictive of longer PFS. The addition of irinotecan after initial progression did not result in clinical benefit.

A large phase II trial (AVF3708g, sponsored by Genentech) was designed to further evaluate the anti-tumour activity of the combination of bevacizumab plus irinotecan or bevacizumab alone in patients with recurrent, treatment-refractory GBM. A total number of 167 patients previously treated with temozolomide and radiation were randomised, and the results have recently been published. Bevacizumab, given at a dose of 10 mg/kg every 2 weeks as a single agent or in combination with irinotecan, was well tolerated. Radiological response was determined using a blinded independent radiology facility and was according to WHO Response Evaluation Criteria, taking steroid dose into account. Any new area of non-enhancing T2 signal was considered progressive disease. No new safety signals were observed according to the toxicity profile of bevacizumab and irinotecan. The incidence of all grades of intracerebral haemorrhage in the bevacizumab and bevacizumab + irinotecan arms was 2.4% and 3.8%, respectively. Wound healing complications related to craniotomy sites occurred in 3/85 (3.6%) subjects in the bevacizumab arm and 1/82 (1.3%) subjects in the combination arm.

In terms of efficacy, the use of bevacizumab as a single agent or in combination with irinotecan in patients in first or second relapsed GBM resulted in the following:

- A prolonged objective response exceeding the response rate for patients receiving salvage therapy or irinotecan alone as reported in the literature.


• 24 out of 85 patients treated with bevacizumab alone had either a partial or a complete response; the objective response rate was 28.2% with a median duration of response of 5.6 months.²⁹
• 31 out of 82 patients treated with bevacizumab/irinotecan had either a partial or a complete response; the objective response rate was 37.8% with a median duration of response of 4.3 months.²⁹
• The six-month PFS observed in the bevacizumab (42.6%) and bevacizumab/irinotecan (50.3%) arms exceeded the historical rate (15%) reported by Wong et al.⁷
• The duration of overall survival in the bevacizumab and bevacizumab/irinotecan arms was 9.2 months and 8.7 months, respectively²⁹.

The AVF3708g results are consistent with previous trials evaluating bevacizumab in combination with irinotecan in this setting, supporting the conclusion that bevacizumab provides a consistent clinical benefit in the treatment of relapsed GBM, both in terms of delayed progression and increased median overall survival over historical controls. This trial demonstrates anti-tumour activity of single agent bevacizumab and bevacizumab in combination with irinotecan in pre-treated, relapsed patients with glioblastoma²⁹.

There are significant outstanding questions in the therapy of gliomas and the use of bevacizumab. While it is clear that based on standard imaging criteria the response rate is robust, the overall benefit is unclear. Objective assessments of cognitive function require further validation in patients with brain tumours. One study retrospectively compared patients treated with bevacizumab and chemotherapy with an earlier cohort and suggested that in the bevacizumab arm, functional status was more likely to be maintained or improved³⁰.

There is a potential for anti-angiogenic agents to perturb the relationship between contrast enhancement seen on gadolinium-enhanced MRI (Gd-MRI), and actual presence of tumour. In other words, bevacizumab may demonstrate an appearance of tumour response on post-treatment imaging through normalisation of vasculature with restoration of the blood brain barrier. This effect is sometimes referred to as a “pseudo-response”.

As to date there has been no overall survival benefit demonstrated for the use of bevacizumab in recurrent GBM, it will be important to assess QOL, functional status and dexamethasone use carefully as markers of therapeutic benefit. The AVF3708G study noted a trend for patients who were taking corticosteroids at baseline to take stable or decreasing doses over time²⁷,³⁰. It has become clear that patients may progress in a conventional manner with increasing regions of gadolinium enhancement on MRI, but also may progress with non-enhancing infiltrating tumour progression that is harder to gauge. A non-enhancing pattern of tumour progression was correlated with worse survival in a recently published retrospective study of 37 patients³¹.

The role of bevacizumab beyond progression of disease remains unanswered in any prospective study; expert opinion has suggested that progression may accelerate on withdrawal of bevacizumab³² however one study has suggested that continuing bevacizumab with another chemotherapy agent is not beneficial³³. Given the results from breast cancer studies using trastuzumab, another monoclonal antibody targeted therapy, suggesting that continuation beyond disease progression may provide some clinical benefit³⁴ it is of clinical interest to explore this phenomenon in other tumour types and for other targeted therapies.

1.2 Rationale

1.2.1 Rationale for the use of anti-VEGF therapy in malignant glioma
One of the hallmarks of GBM is its high degree of vascularisation. According to the WHO 2007 classification, one of the criteria that helps distinguish GBM from other astrocytic tumours is the
presence of microvascular proliferation. The microvascular hyperplasia found in GBM highlights the importance of angiogenesis in this tumour. It is thought that VEGF plays a major angiogenic role in glioblastoma. Indeed, VEGF mRNA and protein are highly expressed by GBM, and VEGF is one of the best markers to distinguish GBM from gliomas of lower grade. Consistent with the knowledge that VEGF expression is hypoxia-driven, VEGF localisation within GBM lesions is strongly associated with areas of viable tumour immediately bordering necrotic regions.

Several other mechanisms of action of anti-VEGF therapy could also explain its efficacy in GBM. For instance, GBM is an astrocytic tumour and VEGF is an important mitogenic factor and plays a significant role in growth of astrocytes in the central nervous system (CNS). It has also been shown that in the context of glial tumour, anti-angiogenic therapy may have an effect by selectively targeting brain tumour stem-like cells and reversing their stem cell phenotype. Moreover, it has been shown that exposure to radiation increases VEGF in glioblastoma cells. Blocking VEGF with bevacizumab may decrease a potential angiogenic response triggered by radiation. A number of reports have shown a benefit of targeting VEGF or its receptors in animal models of glioma. In fact, the first paper to describe in vivo activity of an anti-VEGF antibody reported antitumour activity in a subcutaneous glioma xenograft. Since this initial study, benefit has been demonstrated with systemic administration of anti-VEGF antibodies in both subcutaneous and orthotopic models of GBM, and anti-VEGF antibodies have been shown to augment the antitumour activity of both radiation and chemotherapy.

1.2.2 Rationale for the choice of agents and dose selection

Carboplatin has been studied in the phase II setting for recurrent GBM. Response rates in this setting are around 14%. It is generally well tolerated and is a very reasonable second line chemotherapy choice for patients with GBM whose disease is refractory to temozolomide. In addition, in responders the response can be prolonged up to 12 to 18 months in some patients, unlike nitrosoureas that are limited by progressive bone marrow toxicity. Many Australian oncologists routinely use carboplatin in this second-line setting.

Bevacizumab is known to have activity in patients with GBM and has efficacy both as a single agent and in combination with chemotherapy. It has been approved as a single agent for the use in grade IV glioma after relapse or disease progression by the TGA. As patients with recurrent high grade glioma may deteriorate clinically relatively quickly, this provides the rationale to introduce an active agent such as bevacizumab early in the disease. Given the results of the Vredenburgh trial of bevacizumab +/- irinotecan, and the Kreisl phase II study of single agent bevacizumab with irinotecan at progression demonstrating efficacy of bevacizumab as a single agent, it is acceptable to randomise patients to receive bevacizumab as a single agent in recurrent temozolomide-refractory malignant glioma. The combination of bevacizumab with carboplatin may add a clinical benefit and improve the treatment of malignant glioma. Recent animal model research has demonstrated that the combination of carboplatin and bevacizumab was superior for survival and asymptomatic tumour volume over bevacizumab or carboplatin monotherapy.

Bevacizumab at a dose of 10 mg/kg every 2 weeks has been chosen for development in malignant gliomas, because:

- This is the approved dose according to the Australian Product Information;
- Clinical studies in the setting of relapsed GBM have been performed with a dose of 10 mg/kg, 2 weekly of bevacizumab and demonstrated clinical activity and acceptable safety;
- The 2 weekly schedule is convenient considering that carboplatin is dosed every 4 weeks for patients who are randomised to receive the combination.
1.2.3 Rationale for the use of PFS as the primary endpoint

The primary goal of therapy for recurrent astrocytic tumours is to prolong PFS and OS, while reducing morbidity, restoring or preserving neurologic function and the capacity to perform daily activities\textsuperscript{54}. Overall survival, unlike PFS, may be affected by crossover and sequential therapy. The reliance on OS as the sole primary endpoint in the setting of widely available and active salvage therapy may result in an observed survival effect that underestimates the true clinical benefit afforded to these patients. The most notable impact on patients is rapid neurologic deterioration, affecting the ability to perform everyday functions. As tumour invades brain tissue, it can also distort aspects of personality and identity, such as mood, memory, emotion and intelligence. Therefore tumour stabilisation is expected to translate to clinical benefit\textsuperscript{55}. PFS can serve as an indicator for tumour stabilisation. Based upon Kaplan-Meier and Cox proportional hazard analyses of data from 596 subjects from the North American Brain Tumor Coalition (NABTC) Phase II protocols from February 1998 and December 2002, Lamborn et al. concluded that PFS “is a strong predictor of survival, and is a valid end point for trials of therapy for recurrent malignant glioma”\textsuperscript{55}.

The use of PFS as a primary end point and OS as a secondary endpoint provides the best opportunity to demonstrate evidence of clinical benefit in this population.

1.2.4 Rationale for neurocognitive functional assessment

Brain tumours and therapeutic interventions against the tumour including surgery, radiation, and chemotherapy may affect brain functions. Therefore, survival, PFS, and objective response rate (ORR) in a clinical trial may not fully describe the outcome of an intervention. Additional information regarding NCF and HRQL should also be considered as therapeutic outcomes across the disease course in order to describe objectively the natural history of recurrent disease for these outcomes. These outcomes can be correlated to progression and will enable an assessment of the effect of bevacizumab on patient-related outcomes. Serial assessment during both the early treatment phase when the majority of patients may demonstrate an initial treatment effect, and during the later stage of the study where subjects may experience longer term impact on their NCF and HRQL is needed to fully characterise the net clinical benefit of therapy for patients.

The MMSE and subjective measures of HRQL (EORTC QLQ-C30 and BN20) included in this study have been validated in the brain tumour population as additional indicators of treatment benefit. CogState has not to date been validated in a brain tumour population and thus this study will be the first to assess and validate this method of NCF assessment. NCF has been demonstrated to predict tumour progression\textsuperscript{11} and to independently predict survival for patients with central nervous system tumours\textsuperscript{12,57,58}. Neurocognitive dysfunction in patients with brain tumours, and neurodegenerative diseases, is associated with diminished independence in instrumental activities of daily living\textsuperscript{56,57}. NCF has long been recognised as a critical determinant of quality of life (QOL) and associations between NCF and QOL have been demonstrated in patients with malignant glioma\textsuperscript{56,57}. Neurocognitive dysfunction in patients with brain tumours, and neurodegenerative diseases, is associated with diminished independence in instrumental activities of daily living\textsuperscript{56,57}. In patients with metastatic brain tumours, NCF was predictive of QOL with neurocognitive decline occurring in advance of decrease in QOL\textsuperscript{56}. Further, patient caregivers and spouses have reported greater burden and distress associated with neurocognitive and neurobehavioural changes than physical difficulties\textsuperscript{58}. In a recent presentation of data from the BRAIN study (randomised phase II trial of bevacizumab +/- irinotecan), most patients with an objective response or PFS greater than 6 months had improved or stable NCF compared to baseline\textsuperscript{30}. The importance of these measures was denoted by the FDA indicating that ‘improvement in NCF or delay in neurocognitive progression are acceptable endpoints’ in clinical trials. The proposed assessment of NCF by the CogState system will provide unique information about NCF that frequently is not captured by self-reported measures\textsuperscript{59}.

1.2.5 Rationale for health-related quality of life (HRQL) assessment

HRQL is an important consideration for patients with high grade gliomas. A new and effective treatment prolonging survival would be less appealing if it impaired HRQL. The EORTC QLQ-C30 was developed for a general cancer patient population, whilst the EORTC BN20 module is specific to patients with brain tumours; both are validated instruments with extensive experience in their use.
The QLQ-C30 is a 30-item self-report questionnaire that has patients rate the items on a 4-point scale, with 1 “not at all” to 4 “very much”. The instrument measures several domains, including physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, pain, nausea and vomiting, and several single items (dyspnoea, insomnia, anorexia, constipation, diarrhoea, and financial impact). 

The BN20 consists of 4 scales comprised of multiple items (future uncertainty, visual disorder, motor dysfunction, communication deficit) and 7 single items (headache, seizures, drowsiness, hair loss, itching, difficulty with bladder control, and weakness of both legs) of specific relevance to neurological tumours. The combined instrument takes an average of 8 minutes to complete by patients with primary brain tumours. The evaluation of NCF and HRQL will support the determination of clinical benefit of one treatment approach relative to the other.

The EQ-5D is a standardized instrument for use as a measure of health outcome, and provides a simple descriptive profile and a single index value for health status. It is cognitively simple and takes only a few minutes to complete, and is available in a range of different languages. It has been used in numerous studies of patients with cancer, in particular breast, prostate and gastrointestinal cancers, but to date has not been well studied in patients with malignant gliomas and other brain tumours.

1.2.6 Rationale for the use of RANO criteria for disease evaluation

Modified Macdonald criteria
For the last two decades, Macdonald criteria have been a standard method of assessing brain tumours radiologically. Using these criteria, response categorisation is determined on the basis of changes in the cross-sectional area of a tumour on neuroimaging, coupled with clinical assessment of neurological status and corticosteroid utilisation. However, since the time these criteria were first described, imaging technology, therapeutic approaches, and clinical trials requirements have advanced substantially. In addition, the use of anti-angiogenic agents that block VEGF will reduce the degree of enhancement given that gadolinium enhancement is related to increased permeability of blood vessels due to angiogenesis. This has made the use of standard methods such as Response Evaluation Criteria in Solid Tumors (RECIST) limited. With this evolution, limitations of the Macdonald criteria as well as ambiguity in key features appeared (appropriate threshold for lesion size and actual methods for applying the stated criteria in real practice). In order to avoid these limitations, modified Macdonald criteria will be used, in which the non-imaging component of the disease evaluation will be re-emphasized and clarified (see Appendix 8). This approach has been used in many contemporary clinical trials for patients with malignant brain tumours.

Response assessment in neuro-oncology (RANO) criteria
A new proposal for an updated response assessment for high-grade gliomas has recently been developed. The RANO criteria aim to address challenges in evaluating malignant gliomas by introducing several new features not previously incorporated into assessment strategies. These include definitions of measurable disease addressing sub-centimetre lesions, cysts, and surgical cavities. Non-measurable lesions also are defined, i.e. completely resected tumours that would not be considered for response-based trials. Multiple lesions are defined as a minimum of 2 and a maximum of 5, wherein response is assessed by the sum of the products of the perpendicular diameters. Response requires a minimum decrease by 50% in the summed products. Conversely, disease progression requires an increase by 25% of these summed tumour areas. Definitions of response are expanded to include non-enhancing tumour (tumour enlargement based on T2W or FLAIR assessment) which is important in assessing response to angiogenesis inhibitors such as bevacizumab. A suggestion is made to define clinical deterioration as a decrease in Karnofsky performance status by 20% or deterioration to 50% or less from baseline. Non-enhancing tumour volume enlargement was felt at present not to be readily quantifiable, and currently remains a subjective determination in the current RANO criteria. The ‘modified’ RANO criteria in this study will
include a FLAIR grading scale (Appendix 9) to assess its utility in quantifying non-enhancing (T2/FLAIR) change.

Validating the new RANO criteria is essential, and this trial provides an opportunity to prospectively compare modified Macdonald criteria with modified RANO criteria as part of the central radiology review for disease assessments in patients who are receiving an angiogenesis inhibitor for recurrent malignant glioma. To date such a prospective comparison in a large randomised study has not occurred.

2 TRIAL OBJECTIVES

2.1 Primary objective:
To determine the effect of the combination of bevacizumab plus carboplatin versus bevacizumab alone on progression-free survival (using modified RANO criteria) in patients with recurrent grade IV glioma (glioblastoma multiforme).

2.2 Secondary objectives:

<table>
<thead>
<tr>
<th>Part 1</th>
<th>Part 2</th>
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<tbody>
<tr>
<td>To determine the effect of bevacizumab in combination with carboplatin versus bevacizumab alone on:</td>
<td>To determine the effect of continuing or stopping bevacizumab after disease progression on:</td>
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- Objective radiological response rate (according to modified RANO criteria)
- Objective radiological response rate (according to modified Macdonald criteria)
- Cognitive function (CogState and MMSE)
- HRQL (EORTC QLQ-C30, BN20 and EuroQol EQ-5D)
- Corticosteroid dose
- Toxicity (NCI CTCAE Version 4.0)
- Overall survival (OS)
- Time to treatment failure
- Subsequent progression-free survival (modified Macdonald and modified RANO criteria) (for part 2 only)

2.3 Exploratory objectives:

- To correlate the MRI response at 4 weeks with clinical outcome (PFS/OS)
- To assess for correlation between steroid usage and dose and clinical outcome (PFS/OS)
- To compare modified Macdonald criteria with modified RANO criteria for assessment of disease response or progression
- To document the location and type of radiological progression on and after discontinuation of bevacizumab
- Correlation between blood and tissue biomarkers and clinical outcome (including PFS, OS, response rate)
3 TRIAL DESIGN

3.1 Design

3.1.1 Overview
This is a randomised two part, 2-arm, non-blinded non-placebo-controlled multicentre phase II study.

Part 1

Part 2
Arm A
There are two randomisation phases to this study: Parts 1 and 2.

**Part 1** - consists of subjects being randomised 1:1 to receive either:

- **Arm A**: Bevacizumab 10mg/kg given intravenously (IV) every 2 weeks until disease progression

- **Arm B**: Bevacizumab 10mg/kg given intravenously (IV) every 2 weeks + carboplatin AUC 5 given IV every 4 weeks until disease progression

**Part 2**
Following disease progression patients who are able to continue treatment will be further randomised to cease bevacizumab (Arm C and E) or continue bevacizumab 10mg/kg every 2 weeks (Arm D and F). In addition to this:

- **Arm A**: Patients in Arm A in Part 1 will commence carboplatin AUC 5 IV every 4 weeks or best supportive care (BSC).

- **Arm B**: Patients in Arm B in Part 1 will cease carboplatin and commence clinician’s choice of additional chemotherapy agent (temozolomide or etoposide) (see appendix 3) or BSC.

Patients can be randomised and continue on Part 2 of the study if they receive BSC rather than carboplatin (Arm C and D) or clinicians’ choice of chemotherapy (Arm E and F). The decision as to whether further chemotherapy will be administered and which chemotherapy (for clinician’s choice), must be specified PRIOR to the second randomisation.

Best supportive care includes any concomitant medications or treatments: antibiotics, analgesics, corticosteroids, transfusions, palliative surgery, or any other symptomatic therapy necessary to provide best supportive care, except other investigational anti-tumour agents or anti-neoplastic chemo/hormonal/immunotherapy.
3.1.2 Definition of a treatment cycle
A treatment cycle is defined as 28 days (4 weeks). The first dose of study treatment in Part 1 and Part 2 defines day 1 of the cycle and the last day of a complete cycle is day 28. This means each cycle duration is 28 days and includes two administrations of bevacizumab (with the exception of patients randomised to cease bevacizumab in Part 2).

Dose delays and dose reductions, and management of allergic and hypersensitivity reactions are described in Section 5.

3.1.3 Expected study duration
This study will accrue over approximately 18-24 months followed by a follow-up phase (which includes Part 1 and Part 2 of the study) in which all patients are followed until death, loss to follow up or withdrawal of consent. It is anticipated that the total study duration will be approximately 30 – 36 months.

Patients who, in the Investigators’ opinion, are benefiting from study medication may continue with treatment until disease progression, death or withdrawal from the study.

Safety data will be collected for all patients at least until 30 days after last study drug dose. Following cessation of study treatment, all patients will be followed-up at monthly assessments until death, loss to follow-up or withdrawal of consent.

3.1.4 Treatment for patients still receiving study treatment at end of study
If the study is terminated for any reason other than safety, patients who have not yet progressed at this time and are still receiving bevacizumab will have the opportunity to continue to receive treatment with bevacizumab upon enrolment into an extended access program. Prior to entry to the extension program, patients will require further evaluation by their Investigator, who will decide if there is any evidence of disease progression (at which point the patient should withdraw from bevacizumab treatment) and if the patient is otherwise still eligible to receive bevacizumab. Safety data will be collected from these patients at least until 30 days after the last study drug dose.

3.1.5 Randomisation process
On completion of the randomisation form, the site Investigator or designee will randomise the patient using an online electronic randomisation system. Randomisation by contacting the COGNO Coordinating Centre at the CTC will be available as an alternative method of randomisation when required. Further details regarding the randomisation process will be provided in the Investigator Site File.

It is the responsibility of the Investigator to ensure that the patient meets all eligibility criteria. This must be documented in the patient’s medical record. The patient’s study number, allocated treatment and date of randomisation will be provided to the Investigator or designee by the electronic randomisation system at the time of randomisation.

3.1.6 Randomisation
Patients will be randomised in a 1:1 fashion as discussed in section 3.1.1. Patients will be stratified by centre, age, gender and performance status in Part 1.

Patients who fulfil the following criteria will be randomised to Part 2 of the study:
- PD on initial treatment
- Not having withdrawn from bevacizumab during Part 1
Considered suitable for carboplatin/clinician’s choice of further chemotherapy specified or
best supportive care if the clinician decides not to give further chemotherapy
Considered suitable to continue further potential bevacizumab

Randomisation in Part 2 will be additionally stratified by treatment allocation in Part 1.

3.2 Endpoints

3.2.1 Primary endpoint

Primary endpoint: Progression-free survival (modified RANO criteria)

3.2.2 Secondary endpoints

The following will be evaluated separately for Part 1 and Part 2 of the trial:

- Objective radiological response rate (according to modified RANO criteria)
- Objective radiological response rate (according to modified Macdonald criteria)
- Cognitive function (CogState and MMSE)
- HRQL (EORTC QLQ-C30, BN20 and EuroQol EQ-5D)
- Corticosteroid dose
- Toxicity (NCI CTCAE Version 4.0)
- Overall survival (OS)
- Time to treatment failure
- Subsequent progression-free survival (modified Macdonald and modified RANO criteria) (for part 2 only)

4 SUBJECT POPULATION

4.1 Subject Population

Consenting male and female patients aged ≥ 18 years with recurrent grade IV glioma (glioblastoma multiforme) who have had prior treatment with both radiotherapy and temozolomide chemotherapy (concurrently and/or sequentially), and have had no prior chemotherapy other than temozolomide for the treatment of glioma.
4.2 Inclusion criteria

For inclusion in this study, all of the following inclusion criteria must be fulfilled:

1. Patients with glioblastoma multiforme (GBM) with a tissue diagnosis that has been established following either a surgical resection or biopsy, and who have had prior treatment with both radiotherapy and temozolomide (concurrently and/or sequentially)

2. Recurrent/progressive disease confirmed by surgical resection or MRI (measurable disease according to RANO criteria). Measurable disease will be characterised by all of the following:
   - at least one site of bi-dimensionally measurable disease
   - two perpendicular diameters of at least 10mm, visible on 2 or more axial slices that are preferably, at most, 5mm thick with 0-mm skip (or at least two times the slice thickness if the MRI is performed with thicker slices)
   - must be measured using contrast enhanced MRI
   - MRI showing progression must be performed within 14 days before randomisation and at least 12 weeks post cessation of radiotherapy or stereotactic radiosurgery. The MRI must be compared with a prior MRI performed post-radiotherapy

3. Craniotomy or intracranial biopsy site must be adequately healed; free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of randomisation. Study treatment should be initiated 28 days following the last surgical procedure (including biopsy, surgical resection, wound revision, or any other major surgery involving entry into a body cavity)

4. WHO/Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

5. At least 12 weeks must have elapsed since the cessation of radiotherapy or stereotactic radiosurgery

6. Adequate renal function (within 2 weeks prior to randomisation):
   - Creatinine ≤ 1.25x ULN or creatinine clearance rate ≥ 60ml/min AND
   - Urine dipstick for proteinuria <2+ OR urine protein/creatinine ratio (UPC) ≤1.0. Patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis at screening should undergo a urine protein/creatinine ratio (or 24 hour urine collection if preferred) and must demonstrate ≤ 1.0g of protein in 24 hours.

7. Laboratory values (within 2 weeks prior to randomisation):
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   - Leucocyte count > 3.0 x 10^9/L
   - Platelets ≥ 100 x 10^9/L
   - Haemoglobin ≥ 100 g/L
   - Total bilirubin ≤ 1.5 x ULN
   - AST, ALT and ALP ≤ 2.5 x ULN (≤ 5 x ULN when attributable to anticonvulsants)

8. International normalized ratio (INR) or prothrombin time (PT) (secs) and activated partial thromboplastin time (aPTT)
   - ≤ 1.5 x ULN (except for subjects receiving anticoagulation therapy at the time of screening) in the absence of therapeutic intent to anticoagulate the subject, OR
   - within therapeutic limits (according to the medical standard in the institution) in the presence of therapeutic intent to anticoagulate the subject at the time of screening.

NOTE: As per American Society of Clinical Oncology (ASCO) guidelines, low molecular weight heparin (LMWH) is the preferred approach.

9. Signed informed consent
4.3 Exclusion criteria

Patients are not eligible for this study if they fulfil one or more of the following exclusion criteria:

1. Prior therapy with bevacizumab or any other VEGF/VEGFR inhibitor or EGFR inhibitor
2. Prior chemotherapy (other than temozolomide) or investigational agent for the treatment of glioma
3. Investigational agent (for reason other than treatment of GBM) within 28 days prior to randomisation or at any time during the study
4. Chemotherapy (i.e. temozolomide) within 21 days prior to randomisation (with the exception of dose dense/continuous low dose ‘metronomic’ temozolomide in which chemotherapy must cease ≥ 7 days prior to randomisation)
5. Treatment with biologic agent/s within 28 days prior to randomisation
6. Known hypersensitivity to any excipients of bevacizumab formulation or to carboplatin
7. Hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanised antibody
8. Have had any surgery, open biopsy, intracranial biopsy, ventriculoperitoneal shunt or significant traumatic injury within 4 weeks prior to start of treatment on this study or who have not recovered from side effects of such therapy
9. Core biopsy (excluding intracranial biopsy) within 7 days prior to randomisation, or other minor surgical procedure including placement of a central venous access device (CVAD) within 2 days prior to bevacizumab administration
10. Pregnancy or lactation
11. Patient (male or female) is not willing to use highly effective methods of contraception (e.g. double barrier method) during treatment and for 6 months (male or female) after the end of treatment
12. Evidence of recent haemorrhage on MRI of the brain. However patients with clinically asymptomatic presence of haemosiderin, resolving haemorrhagic changes related to surgery, and presence of punctate haemorrhage in the tumour are permitted entry into the study
13. Calculated creatinine clearance (Cockroft-Gault) <60ml/min
14. Inability to undergo MRI (e.g. has a pacemaker)
15. Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule, including alcohol dependence or drug abuse
16. Any of the following conditions:
   a) Inadequately controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mm Hg); or prior history of hypertensive crisis or hypertensive encephalopathy
   b) New York Heart Association (NYHA) Grade II or greater congestive heart failure
   c) History of myocardial infarction, unstable angina, stroke or transient ischaemic attack (TIA), or significant vascular disease (e.g. aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to randomisation
   d) History of ≥ grade 2 haemoptysis according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 criteria within 1 month prior to randomisation
   e) History of abdominal fistula, gastrointestinal perforation, or intracranial abscess within 6 months prior to randomisation
   f) History of coagulation disorder associated with bleeding or recurrent thrombotic events
   g) Prior or co-existent malignancy except non-melanomatous skin cancer, or malignancy treated and disease free for >5 years
   h) Concurrent illness, including serious non-healing wound, active ulcer or untreated bone fracture, that may jeopardize the ability of the patient to receive the procedures outlined in this protocol with reasonable safety
4.4 Withdrawal criteria

Patients are free to discontinue participation in the study or withdraw their consent at any time without providing a reason for withdrawal. Efforts should be made to obtain follow-up for PFS and OS outcomes, and safety information, even after premature treatment or study discontinuation, unless the patient also withdraws consent to collect further disease-related data. The outcome of such discussions should be documented in both the medical record and the case report form (CRF).

In the event that patients withdraw from carboplatin in part 1 due to toxicity or intolerance they should still continue on bevacizumab until progressive disease is documented. In the event of all treatment being withdrawn, patients should still be followed until progressive disease (on imaging) if possible.

Patient participation in the trial (or continuation of treatment) may be stopped at any time at the discretion of the Investigator or at the request of the Sponsor for any of the following reasons:

1. Withdrawal of the patient’s consent or the patient refuses to continue study drug administration. Reasons should be documented in the medical records
2. Toxicity occurrence of an adverse event requiring permanent treatment discontinuation according to the criteria specified in section 5; or unacceptable toxicity as determined by the patient or site Investigator
3. Violation of the protocol. If a patient has failed to attend scheduled assessments in the study, the Investigator must determine the reasons and document the circumstances as completely and accurately as possible in the medical records
4. The Investigator has the opinion that continuation of treatment is not in the patient’s best interest
5. Occurrence of an exclusion criterion that is clinically relevant and affects the patient’s safety, e.g. occurrence of pregnancy
6. Intake of prohibited concomitant medication/treatment, as defined in section 5.4, in cases where the predefined consequence is study withdrawal
7. Progressive disease (PD): patient is to discontinue Part 1 study treatment at the time PD is documented and progress to Part 2 (if eligible). Patient is to discontinue Part 2 study treatment at the time PD is documented. However, a patient with documented PD on Part 2 may remain in the study and continue study treatment if the Investigator believes they are still obtaining clinical benefit from treatment; i.e. if the patient has maintained adequate performance status and is fit enough for further treatment. Non tumour-related causes of clinical or radiologic worsening (i.e. pseudo progression) are not to be considered as PD.
8. Intercurrent illness

If a patient fails to attend scheduled visits or other contacts with the site, the Investigator will undertake every effort to obtain further information about the patient. The reason why a patient has not contacted the site should be determined and documented. In particular the Investigator should determine whether the patient has experienced any AEs since the last contact with site.

5 TREATMENT OF SUBJECTS

5.1 Study Drug Administration & Preparation

Pre-medication for bevacizumab or carboplatin
Specific pre-medication is not required for bevacizumab. For carboplatin, a patient is routinely given anti-emetics which should include a serotonin (5HT3) antagonist and dexamethasone.
If during or after any infusion a reaction occurs, pre-medication (e.g. paracetamol and/or an antihistamine (H1 or H2 blocker) may be used for subsequent infusions (the specific pre-medication is at site discretion and should be recorded on the concomitant medications list).
Preparation of bevacizumab and carboplatin
Preparation of bevacizumab and carboplatin will be performed using aseptic techniques. Detailed instructions for the reconstitution of bevacizumab are contained in the Pharmacy Manual for the study. Carboplatin should be prepared as per usual site practices.

Dose of bevacizumab and carboplatin
During Part 1 of the study patients will be randomised to receive bevacizumab 10mg/kg every 2 weeks alone or bevacizumab 10mg/kg every 2 weeks plus carboplatin AUC 5 every 4 weeks, each given intravenously until disease progression. Those patients who do not receive carboplatin in Part 1 will have the option to receive carboplatin in Part 2 of the study.

The initial doses of bevacizumab and carboplatin will be calculated based upon the patient’s actual body weight at baseline. The dose will not be recalculated unless the actual body weight changes at least ±10% from the baseline weight. If the calculated bevacizumab dose falls within 10% over a vial size then the dose should be rounded down to the vial size. Otherwise the calculated dose should be administered. For patients with a glomerular filtration rate (GFR) >125mL/min it is suggested that the dose of carboplatin be capped at the Investigator’s discretion.

Interruption of bevacizumab and carboplatin infusions
Patients who experience any serious infusion reaction (e.g. dyspnoea, chest tightness, fever, rigors or hypotension) during administration of either drug must have the infusion stopped.

Continuation of dosing will be based on the severity and resolution of the event and will be at the discretion of the Investigator. Treatment for an infusion reaction will be per Investigator discretion and may include hydrocortisone 100mg IV (or equivalent), ranitidine 50mg IV bolus (or equivalent), and/or diphenhydramine 50mg IV bolus (or equivalent). Suspected infusion reactions will be reported as an adverse event. All patients who experience such an event will be followed for safety. If a patient is not able to recommence treatment within 8 weeks (bevacizumab or carboplatin) due to an infusion reaction, the patient must be permanently discontinued from study treatment.

5.2 Management of allergic/hypersensitivity reactions during or post infusion

Table 1

<table>
<thead>
<tr>
<th>CTC Grade Allergic/hypersensitivity reaction</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 Mild transient reaction</td>
<td>Decrease infusion rate by 50% and monitor closely for any worsening.</td>
</tr>
<tr>
<td>Grade 2 Urticaria, drug fever ≥ 38°C and/or asymptomatic bronchospasm. Intervention indicated; responds promptly to symptomatic treatment</td>
<td>Stop infusion. Administer bronchodilators, oxygen etc as medically indicated. Resume infusion at 50% or previous rate once allergic/hypersensitivity reaction has resolved or decreased to grade 1 in severity, and monitor closely for any worsening.</td>
</tr>
</tbody>
</table>
### CTC Grade Allergic/hypersensitivity reaction

<table>
<thead>
<tr>
<th>Grade 3 or 4</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 3:</strong> symptomatic bronchospasms requiring parenteral medication with or without urticaria; hypersensitivity related oedema, angioedema. Prolonged (not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence following initial improvement; hospitalisation indicated for clinical sequelae</td>
<td>Stop infusion immediately and disconnect tubing from patient. Administer adrenaline, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc as medically indicated. Patients should be followed up until resolution of the event. If patients are receiving two drugs (e.g. carboplatin and bevacizumab) and one drug is felt by the Investigator to be the cause of the reaction, the other drug can be subsequently continued if the toxicity resolves, and is thought to be related to the delayed/discontinued drug and not the other. This is at the discretion of the Investigator. The causative agent must be discontinued for any grade 3 or 4 reaction.</td>
</tr>
<tr>
<td><strong>Grade 4:</strong> anaphylaxis (life-threatening consequences; urgent intervention indicated)</td>
<td>Stop infusion immediately and disconnect tubing from patient. Administer adrenaline, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc as medically indicated. Patients should be followed up until resolution of the event.</td>
</tr>
</tbody>
</table>

- Appropriate therapeutic interventions may be initiated at any time.
- Patients experiencing grade 1 or 2 reactions will not be prohibited from receiving subsequent infusions.
- For allergic reactions with a severity of ≥ grade 3, the causative agent must be discontinued

### 5.3 Dose Modification

If one or more drug related toxicities are present with the following severity:

#### Table 2

<table>
<thead>
<tr>
<th>Adverse drug reaction</th>
<th>Value</th>
<th>CTCAE grading version 4.0</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological/biochemical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count (ANC)</td>
<td>&lt;1.5 - ≥ 1.0 x 10^9/L</td>
<td>2</td>
<td>Stop carboplatin until ANC ≥ 1.5 x 10^9/L then resume at initial dose. Bevacizumab may be continued</td>
</tr>
<tr>
<td>Absolute neutrophil count (ANC)</td>
<td>&lt;1.0 - ≥ 0.5 x 10^9/L</td>
<td>3</td>
<td>Stop bevacizumab and carboplatin until ANC ≥ 1.5 x 10^9/L then resume at carboplatin AUC 4. If ≥ Grade 3 neutropenia occurs again, reduce carboplatin dose to AUC 3. Bevacizumab does not require a dose reduction for this toxicity.</td>
</tr>
<tr>
<td>Absolute neutrophil count (ANC)</td>
<td>&lt;0.5 x 10^9/L</td>
<td>4</td>
<td>Stop carboplatin until platelets ≥ 100 x 10^9/L then resume at initial dose. Bevacizumab may be continued.</td>
</tr>
<tr>
<td>Platelets</td>
<td>&lt;75 - ≥ 50 x 10^9/L</td>
<td>2</td>
<td>Stop carboplatin until platelets ≥ 100 x 10^9/L then resume at initial dose. Bevacizumab may be continued.</td>
</tr>
<tr>
<td>Platelets</td>
<td>&lt;50 - ≥ 25 x 10^9/L</td>
<td>3</td>
<td>Stop carboplatin until platelets ≥ 100 x 10^9/L then resume at carboplatin AUC 4. Stop bevacizumab until platelets ≥ 75 x 10^9/L then resume at same dose.</td>
</tr>
</tbody>
</table>
If ≥ Grade 3 thrombocytopenia occurs again, reduce carboplatin dose to AUC 3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>&lt; 25 x 10^9/L</td>
<td>4</td>
<td>Permanently discontinue carboplatin, can continue bevacizumab at same dose once platelets ≥ 75 x 10^9/L</td>
</tr>
<tr>
<td>ALT</td>
<td>&gt;3-5 x ULN</td>
<td>2</td>
<td>Stop carboplatin until Grade ≤ 1 then resume at initial dose. Bevacizumab may continue.</td>
</tr>
<tr>
<td>ALT*</td>
<td>&gt;5-20 x ULN</td>
<td>3</td>
<td>Stop bevacizumab and carboplatin until Grade ≤ 2 (bevacizumab) or Grade ≤ 1 (carboplatin) then resume at carboplatin AUC 4; If ≥ Grade 3 toxicity occurs again, reduce carboplatin dose to AUC 3. Bevacizumab does not require a dose reduction for this toxicity.</td>
</tr>
<tr>
<td>ALT</td>
<td>&gt;20 x ULN</td>
<td>4</td>
<td>Permanently discontinue carboplatin and bevacizumab.</td>
</tr>
<tr>
<td>AST</td>
<td>&gt;3-5 x ULN</td>
<td>2</td>
<td>Stop carboplatin until Grade ≤ 1 then resume at initial dose. Bevacizumab may continue.</td>
</tr>
<tr>
<td>AST*</td>
<td>&gt;5-20 x ULN</td>
<td>3</td>
<td>Stop bevacizumab and carboplatin until Grade ≤ 2 (bevacizumab) or Grade ≤ 1 (carboplatin) then resume at carboplatin AUC 4; If ≥ Grade 3 toxicity occurs again, reduce carboplatin dose to AUC 3. Bevacizumab does not require a dose reduction for this toxicity.</td>
</tr>
<tr>
<td>AST</td>
<td>&gt;20 x ULN</td>
<td>4</td>
<td>Permanently discontinue bevacizumab and carboplatin.</td>
</tr>
</tbody>
</table>

Recommendations for other toxicities (except for conditions listed in tables 3 and 4; alopecia; nausea and vomiting, unless on maximum antiemetic; and asymptomatic laboratory abnormalities/toxicities which are not deemed clinically significant by the Investigator)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Stop bevacizumab and carboplatin until Grade ≤ 1 then resume at initial dose.</td>
</tr>
<tr>
<td>3</td>
<td>Stop bevacizumab and carboplatin until toxicity has resolved to grade 1 or less then resume at carboplatin AUC 4; If ≥ Grade 3 toxicity occurs again, reduce carboplatin dose to AUC 3. Bevacizumab does not require a dose reduction for this toxicity.</td>
</tr>
<tr>
<td>4</td>
<td>Permanently discontinue bevacizumab and carboplatin.</td>
</tr>
</tbody>
</table>

* For any concomitant conditions already present at baseline, the dose modifications will apply according to the corresponding shift from baseline in the toxicity grade, if the Investigator feels it is appropriate. For example, if a patient has grade 1 asthenia at baseline which increases to grade 2 during treatment, this will be considered as a shift of one grade and treated as grade 1 toxicity for dose modification purposes.
### 5.3.1 Dose modification for specific bevacizumab related toxicities

#### Table 3

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Severity (intensity) CTCAE grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>No bevacizumab dose modifications.</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>Start anti-hypertensive therapy. Bevacizumab may be continued when BP is ( \leq 150/100 \text{ mmHg} ). If BP &gt;150/100 mmHg, bevacizumab should be delayed until ( \leq 150/100 \text{ mmHg} ) and then can be restarted.</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>Delay bevacizumab and start anti-hypertensive therapy. Bevacizumab may restart when BP is ( \leq 150/100 \text{ mmHg} ). If BP is not controlled to ( \leq 150/100 \text{ mmHg} ) with medication, discontinue bevacizumab.</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue bevacizumab</td>
<td></td>
</tr>
<tr>
<td><strong>Haemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade CNS</td>
<td>Discontinue bevacizumab (with the exception of patients with clinically asymptomatic presence of haemosiderin and punctate haemorrhage who are permitted to continue in the study at the discretion of the Investigator)</td>
<td></td>
</tr>
<tr>
<td>Grade 1 or 2 non-pulmonary or non-CNS</td>
<td>No bevacizumab dose modifications</td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4 non-pulmonary or non-CNS</td>
<td>Discontinue bevacizumab</td>
<td></td>
</tr>
<tr>
<td>Grade 1 pulmonary</td>
<td>Delay bevacizumab until resolved</td>
<td></td>
</tr>
<tr>
<td>Grade 2, 3 or 4 pulmonary</td>
<td>Discontinue bevacizumab</td>
<td></td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 (&gt; 3.5g/24h)</td>
<td>Delay bevacizumab until proteinuria improved to Grade ( \leq 2 ), either measured by urine dipstick ( \leq 2+ ), UPC ratio ( \leq 3.5 ) or 24 hour urine collection ( \leq 3.5g )</td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Permanently discontinue bevacizumab</td>
<td></td>
</tr>
<tr>
<td><strong>Venous thrombosis/embolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 or 2</td>
<td>No bevacizumab dose modifications</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Criteria</td>
<td>Action</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Grade 3 or 4 Delay</td>
<td>Bevacizumab until resolution or full-dose anticoagulation is established. Bevacizumab may be restarted during anticoagulation if: • INR or aPTT are within therapeutic limits (if applicable) • Anticoagulation treatment is stable for ≥ 7 days • Patient has not had a grade 3 or 4 haemorrhagic event during anticoagulation therapy. Note LMWH is the recommended and preferred anticoagulation.</td>
<td></td>
</tr>
<tr>
<td>Wound Dehiscence</td>
<td>Any grade requiring medical or surgical therapy</td>
<td>Delay bevacizumab until fully healed.</td>
</tr>
<tr>
<td>Bowel obstruction</td>
<td>Grade 2</td>
<td>Delay bevacizumab for partial obstruction requiring medical intervention, restart upon complete resolution</td>
</tr>
<tr>
<td></td>
<td>Grade 3-4</td>
<td>Delay bevacizumab for complete obstruction, may restart after surgery (if required) once fully recovered and at Investigator’s discretion</td>
</tr>
<tr>
<td>Congestive Heart Failure/ Left Ventricular Systolic Dysfunction</td>
<td>Grade 3</td>
<td>Delay bevacizumab until resolution to ≤ grade 1</td>
</tr>
<tr>
<td>Other non-specified bevacizumab-related event</td>
<td>First occurrence of grade 3 or grade 4</td>
<td>Delay bevacizumab until resolution to baseline or at least improved to ≤ grade 1</td>
</tr>
</tbody>
</table>

5.3.2 Dose modification for bevacizumab toxicity

General notes
The dose of bevacizumab will not be reduced or modified. Criteria for treatment modification and guidelines for the management of toxicities are summarised in Table 2 and 3. If adverse events occur that necessitate delaying bevacizumab, the dose will remain unchanged once treatment resumes. Continuation/resumption of bevacizumab treatment after a delay of more than 8 weeks (56 days) must be discussed with the study Principal Investigator or her/his designee and would only be acceptable in extenuating circumstances. Any toxicity associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Discontinuation of bevacizumab will have no immediate therapeutic effect. Bevacizumab has an estimated terminal half-life of approximately 21 days; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab. Patients should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity due to bevacizumab occurs at any time during the study, treatment with bevacizumab should be discontinued. Patients who discontinue treatment with bevacizumab because of toxicity will be followed for survival, as will all other patients.

First occurrence of a grade 3 or 4 bevacizumab related event:
• Delay bevacizumab until toxicity has resolved to baseline or at least improved to CTCAE...
grade ≤ 1 (with exception of the special cases outlined below and in tables). Note that in the event of febrile grade 4 neutropenia and/or grade 4 thrombocytopenia, the treatment with bevacizumab should be withheld until resolution or at least improved to CTCAE grade ≤ 1 since such conditions are predisposing factors for an increased bleeding tendency.

**Second occurrence upon re-introduction:**
- In the event of a second episode of grade 3 toxicity related to the use of bevacizumab, the Investigator should consider the individual benefit versus the risk of continuing the bevacizumab therapy. If bevacizumab has been re-introduced for a second time and the event recurred, bevacizumab treatment should be discontinued permanently.
- In the event of a second episode of grade 4 toxicity, permanently discontinue treatment.

**Wound Healing Complications**

In a previous study in the glioblastoma relapsed setting, wound healing complications were observed with bevacizumab (craniotomy site wound dehiscence and cerebro-spinal fluid leak), but no new safety concerns were raised\(^3\). However, special attention should be paid to any post-surgery complications before initiating study treatment. In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed, is free of drainage or cellulitis, and the underlying cranioplasty appears intact. Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. The above applies to all body wounds and not just those related to neurosurgery. Bevacizumab therapy should be withheld for an interval of at least two half lives (approximately six weeks) before conducting major elective surgery. Emergency surgery should be performed as appropriate without delay after a careful risk benefit assessment. Any suspicion of impending craniotomy or intracranial biopsy site wound healing complication should be aggressively managed with appropriate local wound care and antibiotics, as required. Early consultation with a neurosurgeon should be considered.

**Bowel Obstruction**

Patients who experience a partial obstruction not requiring medical intervention do not require any bevacizumab interruption. Bevacizumab should be held if the partial obstruction requires medical intervention and restarted upon complete resolution. In the case of grade 3 or 4 bowel obstruction, bevacizumab should be held. If surgery is necessary, the patient may restart bevacizumab after full recovery from surgery, and at the discretion of the Investigator.

### 5.3.3 Guideline for bevacizumab treatment discontinuation

**Table 4**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Severity (intensity) CTCAE grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal perforation</td>
<td>Any grade</td>
</tr>
<tr>
<td>Fistula</td>
<td></td>
</tr>
<tr>
<td>• tracheo-oesophageal fistula (TOF)</td>
<td>Any grade</td>
</tr>
<tr>
<td>• Any non-TOF</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Grade 4 or medically significant HT not controlled with medication</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Venous thrombosis/embolism</td>
<td>Recurrent grade 3 or grade 4</td>
</tr>
<tr>
<td>Arterial thrombosis/embolism</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td></td>
<td>Any grade recurrence or</td>
</tr>
</tbody>
</table>
Any grade if elderly or at risk of thromboembolism

<table>
<thead>
<tr>
<th>Haemorrhage</th>
<th>Any grade if elderly or at risk of thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-CNS or non-pulmonary</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>CNS</td>
<td>Any grade (with the exception of patients with clinically asymptomatic presence of haemosiderin and punctate haemorrhage who are permitted to continue in the study at the discretion of the Investigator)</td>
</tr>
<tr>
<td>pulmonary</td>
<td>Grade 2, 3 or 4</td>
</tr>
</tbody>
</table>

| CHF (left ventricular systolic dysfunction) | Grade 4 |
| RPLS (reversible posterior leucoencephalopathy syndrome) | Any grade |

In case of haematological toxicity, a full blood count should be performed at least weekly until the toxicity has recovered to grade 0-1 prior to recommencement of treatment.

In case of non-haematological toxicity, the subject should be assessed at least weekly with relevant laboratory test(s) until the toxicity has recovered to grade 0-1 prior to recommencement of treatment.

**Note:**

- If one drug is delayed or discontinued then the other drug can be continued if the toxicity is felt to be related to the delayed/discontinued drug and not the other. For patients on two agents in Part 1 or of the study if one drug is delayed, it should be restarted 2 weeks later in order to maintain the 2-weekly scheduling of medication administration. If both drugs are delayed (or the single drug if on monotherapy) on Day 1 of a cycle, they can be restarted once the reason for the delay has resolved (as per tables above)
- Delays of administration beyond 8 weeks (for bevacizumab and carboplatin) from the previous dose are not allowed and patients will cease therapy of that drug
- If the dose was reduced or delayed for toxicity at any point, there will be no dose re-escalation. The reason(s) for dose reduction and/or delay must be documented in the CRF
- For any concomitant conditions already present at baseline, the dose modifications will apply according to the corresponding shift from baseline in the toxicity grade, if the Investigator feels it is appropriate. For example, if a patient has grade 1 asthenia at baseline which increases to grade 2 during treatment, this will be considered as a shift of one grade and treated as grade 1 toxicity for dose modification purposes

For toxicities which are considered by the Investigator unlikely to develop into serious or life-threatening events, study treatment can be continued at the same dose without reduction or interruption. In addition, no dose reductions or interruptions will be required for anaemia (non-haemolytic) as it can be satisfactorily managed by transfusions.

Patients who discontinue treatment because of toxicity will be followed up for survival information unless the patient requests to be withdrawn from survival follow-up. This request must be documented in the source documents and signed by the Investigator.

### 5.4 Concomitant Medications/Treatments

All concomitant medications at study entry will be documented in the medical record. All changes to all concomitant medications or therapy during the study must be recorded in the medical record, noting generic drug name, dose, duration, and indication. If, during the study, the administration of a prohibited concomitant medication or therapy becomes necessary (e.g. because of an AE), the patient must permanently discontinue study treatment. Prior chemotherapy use 3 months prior to randomisation should be documented in the medical record. Patients may take any concomitant medications (including low molecular weight heparin), with the exception of those listed below.
Prohibited Prior and/or Concomitant Medication and Therapies

1. Prior therapy with bevacizumab or any other VEGF/VEGFR inhibitor or EGFR inhibitor
2. Prior chemotherapy (other than temozolomide) or investigational agent at any time for the treatment of glioma
3. Investigational agent (for reason other than treatment of GBM) within 28 days prior to randomisation or at any time during the study
4. Chemotherapy (i.e. temozolomide) within 21 days prior to randomisation (with the exception of dose dense/continuous low dose ‘metronomic’ temozolomide in which chemotherapy must cease ≥ 7 days prior to randomisation)
5. Biologic agents within 28 days prior to randomisation

Permitted Concomitant Medication and Therapy:
The following medications are permitted with the indicated dosing requirements

1. Anticonvulsants: Enzyme-inducing anticonvulsants are permitted. The doses of anticonvulsants may be adjusted as the Investigator deems appropriate. The only exception to this is if patients receive oral etoposide in the ‘clinician’s choice’ chemotherapy in Part 2, in which anticonvulsants (if received) would need to be changed to a non-enzyme-inducing anticonvulsant (e.g. levetiracetam)
2. Corticosteroids: These are allowed. During the study the dose should be adjusted as the Investigator deems appropriate.
3. Anticoagulation: LMWH (enoxaparin) is allowed. Patients who are on warfarin are permitted on study, but as per American Society of Clinical Oncology (ASCO) guidelines, low molecular weight heparin (LMWH) is the preferred approach.

Permitted concomitant treatment or procedure with caution
As a precautionary measure, it is recommended that bevacizumab administration is delayed for 7 days following placement of a central venous access device (CVAD). If it is not feasible to respect this recommended 7-day interval patients will be permitted to start bevacizumab no less than 2 days after placement of the central line: the status of the wound must be satisfactory before bevacizumab administration. If a peripherally inserted central catheter (PICC) line is used, the 2 day interval does not need to be respected.

Patients who have undergone minor surgical procedures should wait at least 2 days before bevacizumab administration. In all cases, caution should be exercised and study treatments withheld for longer if the nature of a minor procedure places the patient at a high risk of bleeding and impaired wound healing in the opinion of the Investigator. For such patients, a discussion with the sponsor is recommended before starting treatment. Patients who experience wound healing complications during bevacizumab treatment should have bevacizumab withheld.

Supportive care guidelines
The corticosteroid treatment for disease control will be explored in this study. Steroids should be used in the lowest dose to control symptoms of cerebral oedema and mass effect, and discontinued if possible. Steroid use should be routinely monitored. See appendix 13 for the relative potencies of commonly used steroids. The dose of steroid at each visit should be documented in the medical record and on the concomitant medication CRF.
Prophylaxis against *Pneumocystis jirovecii* is not required, but is allowed at the discretion of the Investigator and must be recorded as a concomitant medication. Supportive care therapy e.g. anti-emetic, antidiarrhoeal, hydration, is permitted according to local practice. The use of colony-stimulating factors (e.g. G-CSF, CM-CSF, erythropoietin) is discouraged as this does not reflect routine clinical practice in Australia.

Blood and platelet transfusions where required are permitted at Investigator discretion and must be recorded in the CRF and medical record.

### 6 Efficacy and Safety

#### 6.1 Assessment of Safety

##### 6.1.1 Definitions

An **Adverse Event** (AE) is any untoward medical occurrence in a patient or clinical investigational patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product. An adverse event is any adverse change (developing or worsening) from the patient’s pre-treatment condition, including intercurrent illness.

A **Serious Adverse Event** (SAE) is any untoward medical occurrence that at any dose:
- results in death,
- is life-threatening (i.e. the patient is at risk of death at the time of the event),
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect.

**NOTE:** The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Important medical events which may not be immediately life-threatening or result in death or hospitalisation but which may jeopardise the patient or may require intervention to prevent one of the listed outcomes in the definition above should also be considered serious.

For the purposes of this study disease progression is not classified as an SAE. The following conditions are also excluded from SAE reporting:
- Hospitalisations or death related to disease progression
- Any planned hospitalisation
- Elective hospitalisation for treatment of the underlying disease
- Elective hospitalisation allowing a simplification of study treatment/study procedure

A **Suspected Unexpected Serious Adverse Reaction** SUSAR is a serious adverse (drug) reaction, the nature or severity of which is not consistent with the applicable product information.

##### 6.1.2 Definition of Adverse Events of Special Interest

All AEs will be recorded and collected in the medical record and CRF; in particular the potential bevacizumab-related AEs (of special interest) are listed below:
- Hypertension
- Proteinuria
• Gastrointestinal perforation
• Wound healing complications
  o Craniotomy wound healing complications (including wound dehiscence, CSF leak, pneumocephalus, and cranial wound infections)
• Any non-craniotomy wound healing complication
• Thromboembolic events
• Bleeding
  o Mucocutaneous bleeding
  o Cerebral haemorrhage
  o Other haemorrhages (gastrointestinal or pulmonary haemorrhage, etc)
• Congestive heart failure
• Abscesses and Fistulae
• Reversible posterior leukoencephalopathy syndrome (RPLS)

Adverse events of special interest may or may not be serious adverse events, and they may or may not be considered related to study treatment.

### 6.1.3 Collection of Adverse Events

The NCI CTCAE version 4.0 will be used to classify and grade the intensity of adverse events and their relationship to study drug administration.

Adverse events will be assessed on day 1 prior to treatment, every 2 weeks during treatment, and ≥ 30 days after the last study treatment dose (at the first follow-up visit). Adverse event information and intercurrent illness information will be documented in the patient medical record. Adverse events will be collected and recorded from consent through to ≥ 30 days after the last study drug dose.

The following information will be recorded for each AE: event and primary diagnosis (if different), severity, assessment of relatedness to bevacizumab and/or carboplatin and action/s taken.

### 6.1.4 Reporting of Serious Adverse Events

The Investigator is responsible for reporting all Serious Adverse Events occurring during the study regardless of the treatment arm to the NHMRC Clinical Trials Centre within 24 hours of their knowledge of the event using the SAE form. SAEs/SUSARS should be reported for a minimum of 30 days from the end of study drug administration, or until resolution.

SAE reports should be faxed to (02) 9562 5026.

Sites should ensure that the latest investigator's brochure is used as the source document for determining the expectedness of an SAE.

The site Investigator must notify the local Human Research Ethics Committee (HREC), if appropriate, in accordance with international and local laws and regulations and is responsible for filing copies of all related correspondence in the Investigator site file (ISF), and providing any additional information as requested by the CTC or HREC.

The CTC shall ensure that all reporting requirements according to respective regulatory guidelines are followed, and ensure that reporting to Roche and the regulatory authorities as documented in the Study Agreement takes place.

### 6.1.5 Pregnancy

In the event of a pregnancy occurring during the course of a study, the subject must be withdrawn from study drug immediately. Pregnancies occurring up to 6 months after the completion of the
study drug must also be reported to the Investigator. The Investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

The NHMRC Clinical Trials Centre must be notified within 24 hours using the SAE form and the subject followed during the entire course of the pregnancy and postpartum period. Parental and neonatal outcomes must be recorded even if they are completely normal.

Pregnancy occurring in the partner of a patient participating in the study and up to 90 days after the completion of the test drug should also be reported to the Investigator and the NHMRC Clinical Trials Centre. The partner should be counselled and followed as described above.

Any pregnancy occurring during this study will be reported to Roche as documented in the Study Agreement.
6.2 Schedule of Assessments

The study schedule for this study consists of the following phases:

1. **Screening**: Time from date of signing of informed consent for participation in the study until day of randomisation.

2. **Randomisation (part 1)**: patients will be randomised to treatment and begin allocated treatment within 3 days. Where circumstances prevent commencement of treatment within 3 days (for example public holidays) treatment must begin within 5 days of randomisation.

3. **Treatment phase (part 1)**: day 1 until discontinuation of study treatment for any reason. Patients will be required to return for 2 weekly visits during treatment.

4. **End of treatment (part 1)**: an end of treatment visit is performed at the next scheduled visit following the decision to discontinue part 1 study treatment for any reason.

5. **Randomisation (part 2)** when progressive disease is documented in Part 1 eligible patients will be randomly allocated to receive one of 4 treatment options, 2 per study arm.

6. **Treatment phase (part 2)**: day 1 until discontinuation of study treatment for any reason. Patients will be required to return for 2 weekly visits during treatment, with the exception of patients receiving best supportive care only, who will receive follow up phone calls on Day 15 of each cycle. Patients on each arm will be seen by an Investigator every 4 weeks (day 1 of each cycle). Part 2 treatment must start ≥ 2 weeks after the last dose of study drug in Part 1.

7. **End of treatment (part 2)**: an end of treatment visit is performed at the next scheduled visit following the decision to discontinue part 2 study treatment for any reason.

8. **Follow up phase**: All patients will be followed at monthly intervals until death, loss to follow up or withdrawal of consent. Follow-up assessments will occur monthly from the date of the last End of treatment visit (End of treatment visit for Part 1 if patients do not continue onto Part 2). Where clinical visits are impractical, follow-up information may be obtained via telephone call to the patient or their general practitioner, or by reviewing the patient’s medical record.

All laboratory tests will be performed at local site laboratories.

All laboratory assessment tests must be performed no more than 3 days before study drug is administered.

All MRI scans scheduled during treatment (Part 1 and Part 2) should be performed within 7 days prior to the patient’s scheduled treatment. Where this is not possible the MRI scan should be performed as soon as possible following the scheduled treatment. In the absence of the MRI results, planned treatment can continue at the clinician’s discretion based on the patient’s clinical status. Where there are significant concerns regarding the patient’s clinical status, treatment should be withheld until the results of the MRI are available.

Study treatment may be administered within +/- 3 days of the scheduled treatment.

The assessments and procedures described represent the minimum required for the purpose of the trial.
### 6.2.1 Visit Schedule

<table>
<thead>
<tr>
<th>Visit timing (D = day)</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>Cycle 5</th>
<th>Cycle 6</th>
<th>Cycle 7 onwards</th>
<th>End of Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>-14 days from randomisation</td>
<td>D 1</td>
<td>D 15</td>
<td>D 1</td>
<td>D 15</td>
<td>D 1</td>
<td>D 15</td>
<td>D 1</td>
<td>D 15</td>
<td>D 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screenings</th>
<th>Treatment (Part 1 and 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>X</td>
</tr>
<tr>
<td>Histopathological confirmation</td>
<td>X</td>
</tr>
<tr>
<td>Tissue for research</td>
<td>X</td>
</tr>
<tr>
<td>History</td>
<td>X</td>
</tr>
<tr>
<td>Physical examination</td>
<td>X</td>
</tr>
<tr>
<td>Neuro Examination</td>
<td>X</td>
</tr>
<tr>
<td>ECOG/Karnofsky Performance Status</td>
<td>X</td>
</tr>
<tr>
<td>Mini-Mental State Examination (MMSE)</td>
<td>X</td>
</tr>
<tr>
<td>HRQL</td>
<td>X</td>
</tr>
<tr>
<td>CogState</td>
<td>X</td>
</tr>
<tr>
<td>Vital signs</td>
<td>X</td>
</tr>
<tr>
<td>Adverse events</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant medications (inc steroids)</td>
<td>X</td>
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<tr>
<td>Pregnancy test</td>
<td>X</td>
</tr>
<tr>
<td>Biochemistry</td>
<td>X</td>
</tr>
<tr>
<td>FBC</td>
<td>X</td>
</tr>
<tr>
<td>Blood for research (plasma)</td>
<td>X</td>
</tr>
<tr>
<td>Blood for research (DNA)</td>
<td>X</td>
</tr>
<tr>
<td>Coagulation parameters</td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>X</td>
</tr>
<tr>
<td>Gd-MRI scan</td>
<td>X</td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
</tr>
<tr>
<td>Treatment</td>
<td>X</td>
</tr>
<tr>
<td>Survival status</td>
<td>X</td>
</tr>
<tr>
<td>Non-protocol treatment</td>
<td>X</td>
</tr>
<tr>
<td>Steroid dose</td>
<td>X</td>
</tr>
</tbody>
</table>
1 An adverse event assessment must be performed at the first follow-up visit (i.e. ≥ 30 days after last study drug dose)
2 Unless objective radiological disease progression has previously been documented
3 Gd-MRI scans every 2 months during follow up completed only on patients who have not previously demonstrated objective radiological disease progression (e.g. patients who have withdrawn due to toxicities)
4 Gd-MRI scans are to be completed every 8 weeks during treatment until disease progression, i.e. cycle 3 day 1, cycle 5 day 1 etc; within 7 days prior to treatment where possible
5 MRI to be completed at 4 weeks after commencing Part 1 treatment
6 Laboratory tests do not have to be repeated at cycle 1 day 1 if completed within 7 days prior
7 Laboratory tests must be performed no more than 3 days prior to commencement of treatment (with the exception of cycle 1 day 1 as per footnote 6)
8 Serum pregnancy test will only be performed for women of childbearing potential
9 Urinalysis during treatment phase only required for patients receiving bevacizumab
10 Only for patients receiving bevacizumab
11 Patients receiving best supportive care only in Part 2 will not receive any study treatment
12 Not required for patients receiving best supportive care only in Part 2
13 Obtained via telephone call for patients receiving best supportive care only in Part 2
14 Blood for research (plasma) will be recovered for biomarker research at first disease progression (not at ‘end of treatment’).
15 Blood for DNA (Deoxyribonucleic acid) analysis is taken at one time point only (at baseline where possible; or at next visit for patients already on study).
16 Optional biomarker substudy is an exploratory objective. Tissue and blood (plasma and DNA) will only be collected if additional consent is provided. Refer to the CABARET Biological Sampling Manual for specific collection and processing details.
17 Tissue (FFPE) for research will be obtained when the patient consents to the optional biomarker substudy. This may not be during screening for patients who have already commenced study treatment when consent is obtained.
18 Additional tumour samples taken from the patient during their participation in the study (e.g. surgical resection of recurrence) may be obtained for the optional biomarker substudy.

6.2.2 Screening (within 14 days prior to randomisation)
All patients must provide written informed consent before any study specific procedures are performed. The following should be recorded before randomisation.
- Histological confirmation of disease
- Tissue (Formalin Fixed Paraffin-Embedded (FFPE)) sent for biomarker substudy (only if additional consent is provided)
- Laboratory parameters including biochemistry and haematology
- Coagulation parameters, urinalysis and serum pregnancy test (for women of childbearing potential)
- Vital signs, BP, pulse, temperature, height, weight and ECOG and Karnofksy performance status assessment
- Patient history, which includes:
  o Previous and current diseases
  o History of prior grade I-III glioma, location of disease, details of surgery performed
  o All medication and surgeries over the last 3 months prior to inclusion into the study (includes over the counter and herbal remedies)
- Physical examination, including brief neurological examination (and completion of the Mini Mental State Examination)
- Concomitant medications, including corticosteroid use
- Adverse events
- CogState assessment (practice followed by formal assessment)
- HRQL
- Gd-MRI scan (to be used as baseline radiological assessment)
- ECG
6.2.3 Day 1 of every cycle of study treatment (Part 1 and Part 2)
- Laboratory parameters including biochemistry and haematology (not required for patients receiving best supportive care only in Part 2)
- Vital signs, including BP, pulse, temperature, weight and ECOG and Karnofsky performance status assessment
- Urinalysis (only for patients receiving bevacizumab)
- Adverse events
- Concomitant medications including corticosteroid dose
- Physical examination, including brief neurological examination
- CogState assessment and MMSE (MMSE not repeated C1D1 as will have been done during screening)
- HRQL (not repeated C1D1 as will have been done during screening)

Additionally at day 1 of cycle 1 (or during screening period prior), day 1 cycle 2 and day 1 cycle 3
- Blood for biomarker research (if additional consent is obtained)

Additionally at day 1 of cycle 2 (Part 1 only), day 1 of cycle 3 (Part 1 and 2) then 8 weekly at day 1 of alternate cycles (e.g. 5, 7, 9) during treatment (Part 1 and 2)
- Gd-MRI scan (within 7 days prior to treatment wherever possible)

6.2.4 Day 15 of every cycle of study treatment (Part 1 and Part 2)
- Laboratory parameters including biochemistry and haematology (not required for patients receiving best supportive care only in Part 2)
- Vital signs, including BP, pulse, temperature (not required for patients receiving best supportive care only in Part 2)
- Urinalysis (only for patients receiving bevacizumab)
- Adverse events (obtained via telephone call for patients receiving best supportive care only in Part 2)
- Concomitant medications including corticosteroid dose (obtained via telephone call for patients receiving best supportive care only in Part 2)

Additionally at cycle 1 the following must also be collected
- Weight and ECOG and Karnofsky performance status assessment
- Physical examination, including brief neurological examination

6.2.5 Day 1 of cycles 2 (Part 1 only) and 3 (Part 1 and 2) and then 8 weekly at day 1 of alternate cycles 5, 7, 9, 11, 13, 15 etc during treatment (Part 1 and Part 2)
- Gd-MRI scan (The first MRI to be performed 4 weeks after commencing study treatment for Part 1 is intended for central radiology review and should not be used by the clinicians to make treatment decisions (with the exception of safety-related decisions). See 6.3.1)

6.2.6 At baseline (during screening or on day 1 of cycle 1, prior to treatment), week 4 (day 1 of cycle 2), week 8 (day 1 of cycle 3) and at first disease progression
- Blood for biomarker research (if additional consent is obtained)
6.2.7 End of treatment visit (complete for end of Part 1 and end of Part 2)

- Laboratory parameters including biochemistry and haematology (not required for patients receiving best supportive care only in part 2)
- Vital signs, BP, pulse, temperature, weight and ECOG and Karnofsky performance status assessment
- Physical examination, including brief neurological examination (and completion of the MMSE)
- CogState assessment
- HRQL
- Adverse events
- Concomitant medications including corticosteroid dose
- Gd-MRI scan (unless objective radiological disease progression has previously been documented during Part 1 (for Part 1 visit) or Part 2 (for Part 2 visit))

6.2.8 Monthly during follow up*

- Survival status
- Non-protocol treatment including any chemotherapy, surgery or radiotherapy
- Steroid dose
- Adverse events (at first monthly follow up only)
- Additional tumour samples taken from the patient during their participation in the study (e.g. surgical resection of recurrence) may be obtained for the optional biomarker substudy.

* Information may be obtained via telephone call to the patient or their general practitioner, or by reviewing the patient’s medical record if it is impractical for the patient to attend a clinic.

6.2.9 Every 2 months during follow up

- Gd-MRI scan (only) performed on patients who have not previously demonstrated objective radiological disease progression (e.g. patients who have withdrawn due to toxicities).

6.2.10 Assessments and procedures after discontinuation of study treatment

All patients who discontinue from study treatment will be followed for survival information unless the patient requests to be withdrawn from survival follow-up; this request must be documented in the source documents and signed by the Investigator. Survival follow-up information will be collected via telephone calls and/or clinic visits every month (± 1 week) until death, loss to follow-up, or study termination by the Sponsor. If a patient decides to stop the study treatment their health status will be periodically reviewed via continued study visits or phone contact or from their general practitioner or medical records.

For patients who withdraw from study treatment as a result of progressive disease: all further anti-neoplastic treatment (including regimen and duration) will be recorded, survival information will be obtained every month until death or the end of the study, whichever occurs first as long as the patient does not withdraw consent to follow up. The first follow-up assessment should be scheduled 1 month from the date of the last End of treatment visit (End of treatment visit for part 1 if the patient does not continue onto part 2). A blood sample (plasma) for biomarker research is taken at first disease progression if the patient has consented to the optional biomarkers substudy.

For patients who prematurely withdraw from study treatment without documented disease progression: disease assessments will be performed until disease progression is observed (a blood sample (plasma) is taken for biomarker research at first disease progression if the patient has
consented to the optional substudy), all further anti-neoplastic treatment (including regimen and duration) will be recorded, survival follow-up information will be collected every month until death or the end of the study, whichever occurs first as long as the patient does not withdraw consent to follow up.

Upon disease progression (post Part 2), patients will be treated at the Investigator’s discretion. It should be noted that no data on treatment with carmustine-containing wafers (Gliadel®) following bevacizumab therapy is available at the time of protocol writing.

After disease progression (post Part 2), further MRI scans are not required as part of this study if objective radiological progression has been documented while on study; but should be recorded if they are carried out at the Investigator’s discretion (e.g. if a new therapy is commenced).

6.3 Assessment of Efficacy

The primary criterion for assessment of efficacy will be progression-free survival. Further clinical activity by means of PFS and response will be assessed by Gd-MRI, clinical/neurological examination, and steroid use.

The primary endpoint of PFS will be derived from disease progression according to modified RANO criteria. The decision on disease progression for the patient and the further therapy will be made by the Investigator based on:

1. Clinical history and physical examination prior to study entry and 4-weekly while on study

2. RANO criteria, although the MRI results (both modified RANO and modified Macdonald criteria) will also be centrally reviewed. RANO criteria will be used to assess cerebral MRI including T1, T2, Gadolinium-enhanced and FLAIR sequences at baseline, then visits at weeks 4 (part 1 only), then 8-weekly or as clinically indicated during study treatment until disease progression. Assessment for the presence of non-enhancing T2 hyperintensity must be made.

6.3.1 MRI scans

In this study, radiological assessment will be performed using MRI scans. The acquisition protocol for MRI (provided as a separate document) will provide further details for scan standardisation. All efforts should be made to perform MRI acquisition according to the corresponding specification in order to ensure that quality of MRI will be standardised among all sites. This will facilitate a central radiographic review. Consistency of consecutive MRIs should be ensured during all assessments for each patient, with the same technique being used for evaluating lesions throughout the treatment period. The use of IV contrast etc. should, as long as it is clinically possible, be kept consistent. Tumour measurements should be made by the same Investigator/radiologist for each patient during the study to the extent that this is feasible. If more than one scanning method is used, select the most accurate method when recording data.

Standard imaging will consist of pre- and post-contrast enhanced MRI of the brain (T2 weighted, FLAIR, T1 weighted without contrast and T1 weighted with contrast) according to the study plan. All tumour measurements will be made on the T1 weighted contrast enhanced MRI and the other scans may be used to aid interpretation of tumour versus non tumour for tumour measurements on the T1 weighted contrast enhanced MRI. For patients with measurable contrast enhancing lesions (bi-dimensionally contrast enhancing lesions with clearly defined margins by MRI scan, with two perpendicular diameters of at least 10mm, visible on 2 or more axial slices that are preferably, at most, 5mm thick with 0mm skip (or at least two times the slice thickness if the MRI is performed with
thicker slices) at baseline, the sum of the products of the largest perpendicular diameters for the tumour in the axial plane will be measured and recorded. If there are multiple lesions, all lesions will be measured up to a maximum of five. If the largest lesions are not able to be measured reproducibly, the next largest lesions that can be measured reproducibly should be selected. In addition, unequivocal new enhancing lesions of any size, not within the original tumour volume will be recorded as new lesions.

The first MRI to be performed 4 weeks after commencing study treatment (Part 1 only) is obtained for the purposes of central review; however, will be made available to the Investigator. Treatment decisions should not be made by the Investigator based on the 4 week MRI, with the exception of safety-related decisions. Similarly, the 8 week MRI when being reported should be compared with the baseline rather than the 4 week MRI for assessment of response. All other results of MRI tests will be made available to the Investigator and decisions regarding disease response (and thus continuation on trial) will be made by the Investigator and the centre at which the patient is being treated. All MRI scans will be subject to central review for formal assessment of disease response.

6.3.2 Objective response rate

Objective tumour response is defined as the proportion of patients exhibiting complete or partial response (CR or PR) as defined by the modified Macdonald criteria and modified RANO criteria (see Appendices 8 and 10).

The RANO criteria for disease assessment in neuro-oncology have been developed based on the understanding that contrast enhancement is non-specific and that changes in this parameter may not be a surrogate for tumour response; and additionally the recognition that the non-enhancing component of the tumour (depicted on T2/FLAIR images), which has not conventionally been documented as a marker of disease response or progression, is important in the era of targeted therapies and angiogenesis inhibition. The RANO criteria have been developed with the aim to incorporate standardised assessment criteria into clinical trial design of agents for recurrent malignant gliomas. In particular the Macdonald criteria do not account for the non-enhancing component of the tumour, which is an integral component of tumour assessment in patients receiving anti-angiogenic agents. Although the RANO criteria are not finalised, this study provides an important opportunity to compare the current criteria prospectively against the modified Macdonald criteria in assessment of patients receiving bevacizumab.

A proposed addition to the currently available RANO criteria incorporates a scoring/grading system for the degree of T2/FLAIR abnormality seen on MRI imaging. This proposed grading system has been developed by an expert panel of neuro-radiologists but has not been to date prospectively validated. This grades the appearance of T2/FLAIR change on a 5-point scale as shown in Appendix 9. This is the means by which the RANO criteria are ‘modified’ in this study. The grading system will be applied at the time of central radiology review and sites are not required to apply the grading system. Sites will document radiological disease status using RANO criteria and not the ‘modified’ RANO criteria. Further details of the RANO criteria and the proposed grading system for FLAIR abnormalities are in Appendices 10 and 9.

Patients with non-tumour-related causes of clinical or radiologic worsening (i.e. pseudo-progression) are not to be considered as PD. Pseudo-progression is defined as an increase in the size of contrast-enhancing lesion, or new areas with contrast enhancement, which is due to treatment effects, as assessed by the site Investigator.

Worsening overall performance and/or neurological decline felt to be attributable to underlying disease despite lack of radiographic evidence of PD and/or increasing dose of steroids may be taken into account for assessment of progression. Such patients may be classified as clinical PD upon discussion between the site Investigator and the patient’s primary neuro-oncologist, if necessary. In the case of clinical PD, Gd-MRI should continue until documented objective radiological progression wherever possible.
The modified Macdonald criteria for MRI response will also be documented as outlined in Appendix 8, by the central radiology review, but will not be used for treatment/management decisions by the participating sites.

Centralised, independent review of tumour progression will be performed on all relevant Gd-MRI scans. Where the patient has remained on study, but is subsequently determined to have progressed at an earlier time point, the date of progressive disease will be recorded as the date where progression was first identified on review.

6.3.3 Overall Disease Assessment

Investigators must take the radiological assessment, clinical/neurological assessment, and changes in corticosteroid dose into account in order to give a disease assessment overall evaluation of progressive disease or non-progressive disease at each disease assessment after baseline. Any assessment different from Progressive disease will be considered as non-progressive disease (including overall assessments of stable disease, no change, partial response or complete response).

Neurological Examination: Definition of clear neurological worsening is difficult to describe because progression in the brain can present in numerous ways. Accordingly, evaluation of neurological function at each disease assessment will be based purely on the investigator's assessment of the patient’s neurological state compared to baseline. Neurological function must be recorded as Improved, Stable, or Worse. In the absence of progression based on radiological assessment, patients who clearly neurologically worsen compared to baseline, and whose corticosteroids use is unchanged or increased compared with the corticosteroid use at the time of the baseline scan will be considered to have Progressive Disease. In such a case, all efforts should be made to document progression objectively at this time by performing an MRI if possible.

NOTE: Neurological deterioration independent from the disease being treated should not be considered in the context of the Disease Assessments.

Corticosteroid use: at the time of each disease assessment the corticosteroid intake will be compared to corticosteroid intake at the time of the baseline scan. The changes will be recorded as increased, stable or decreased. Increases and decreases in corticosteroid intake should be clinically justified and significant.

NOTE: Increases in corticosteroid dose for reasons other than for disease control (for example, as an anti-emetic pre and post chemotherapy dose) do not need to be taken into consideration when making this comparison.

Radiological assessment: patients who have undergone gross total resection and have no measurable disease (index or non-index lesions) will be followed for recurrence (the appearance of one or more new lesions). If no signs of progression are observed on the MRI, then these patients should have a radiological assessment recorded as No Change. However, in case of unequivocal evidence of progressive disease (major deterioration in neurological function, and unchanged or increased corticosteroid dose) the Overall Disease Assessment will be progressive disease. For index lesions, the products of the diameters of the index lesions (if multiple: maximum of 5 lesions) will be added together to determine the Sum of the Products of the Diameters (SPD). In case of progressive disease based on the index lesions evaluation, the SPD of the nadir will be used to judge the increase in size of the index lesions. Subsequent scans should not be compared to the 4-week scan; the 8-week scan should be compared with the baseline scan rather than the 4-week scan.
6.3.4 Radiological change during and post discontinuation of bevacizumab

It has been reported that post discontinuation of VEGF or VEGFR targeted therapy, a 'rebound' effect may occur\textsuperscript{33}. As bevacizumab reconstitutes the blood brain barrier, it has been reported that there can be an increase in enhancement and/or oedema with the cessation of this component of therapy. Thus it is important to be aware that such radiologic changes may be related to the withdrawal of VEGF inhibition rather than further progression of disease. This can be associated with both radiologic and clinical deterioration. Radiological change during and post discontinuation of bevacizumab in GBM has not been well studied to date, and only retrospective studies are available in the literature. A recently published retrospective study of 37 patients who had discontinued bevacizumab due to progression describes differing patterns of recurrence and shorter overall survival associated with a non-enhancing pattern of recurrence\textsuperscript{32}.

It is reasonable for these patients to continue on study despite radiological deterioration at this point, if it is felt by the Investigators that it is in the patient's best interest. The reason for this is that the 'rebound phenomenon' may be transient. An increased dose of steroids may be indicated and should be recorded. An earlier subsequent MRI may need to be performed at the discretion of the Investigators.

6.3.5 Progression-free survival

Progression-free survival is calculated from date of patient study randomisation to date of first evidence of disease progression or patient death.

6.3.6 Subsequent Progression-free survival

Subsequent progression-free survival is calculated from date of second study randomisation to date of first evidence of subsequent disease progression or patient death.

6.3.7 Overall survival

Overall survival is calculated from date of patient study randomisation to date of patient death from any cause. Patients will be followed up monthly for survival post study treatment.

6.3.8 Time to treatment failure

Time to treatment failure is calculated from the date of first (Part 1) or second (Part 2) randomisation to cessation of drug (separate for Part 1 and Part 2) due to progression, toxicity, death, patient refusal or any other cause.

6.3.9 Duration of response

Duration of response is defined as the time from the date of the first response (CR or PR, as defined by modified RANO criteria, see Appendix 10) to date of first evidence of disease progression or patient death.

6.3.10 Laboratory assessments

Approximately 20 mL of blood will be collected at each treatment cycle (excluding blood samples collected for the optional biomarker substudy).

Biological samples taken from all subjects may be infectious and will be classified as infectious specimens for dispatch purposes.
Coagulation tests, blood chemistry and urine dipstick have to be performed within 14 days prior to patient randomisation and recorded in the Screening section of the CRF. These tests do not have to be repeated on Day 1 of cycle 1 if the first dose of study drug is given within 7 days of these screening tests being performed. Subsequent laboratory tests required before starting each treatment cycle must be performed within 3 days before the start of the cycle.

All laboratory assessments will be performed locally. For each local laboratory, the reference ranges to be utilised for the laboratory parameters must be supplied before the first patient is enrolled.

Proteinuria will be monitored by urine dipstick analysis every 2 weeks (for patients receiving bevacizumab). If the dipstick shows ≥ 2+ protein, then either a UPC ratio or a 24 hour urine collection is required (see Appendix 11).

### 6.3.11 Biomarker substudy (optional)

Patient participation in this substudy is optional.

Biospecimens from patients consenting to participate in this substudy will be used for research to identify prognostic biomarkers or biomarkers that may be predictive of bevacizumab treatment response (including therapeautic response or resistance, dose, safety and tolerability) and that may help to better understand the pathogenesis, course and outcome of glioblastoma and related diseases. The collected samples might allow the generation of statistically meaningful biomarker data. Peripheral blood and tissue samples will be collected from trial patients for this biomarker research.

It is anticipated that the plasma samples will be used to identify dynamic biomarkers that are predictive of treatment response (including therapeutic response or resistance, dose, safety and tolerability). Since the identification of biomarkers of angiogenesis and tumourigenesis pathways and novel markers of response predication or safety that correlate with disease activity and the efficacy of safety of treatment is rapidly evolving, some analyses may be determined in the future.

Data from this substudy will not be captured in the (e-)CRF and will not be analysed as part of the main clinical trial.

**Peripheral blood samples** for biomarker research will be taken at the following four (4) time points:
- Baseline – prior to commencement of study treatment (anytime from screening up to and including Cycle 1 Day 1 prior to therapy being administered)
- Week 4 (Cycle 2 Day 1),
- Week 8 (Cycle 3 Day 1) and
- at first disease progression

**Tumour tissue samples** (formalin-fixed paraffin-embedded (FFPE) blocks or fresh frozen tissue) from the primary tumour and/or recurrent resection will be used for exploratory biomarker research.

NOTE: If a patient has already commenced study treatment they still may participate in the Biomarker substudy by contributing tissue and one blood sample for DNA analysis (at any time point during the study).

Biospecimens collected from each patient will be sent for analysis at both local (Australian) laboratories, and international laboratories (including the Roche Clinical Repository in Basel, Switzerland).

**Local Laboratories**

A variety of methodologies may be applied on the biomarker samples, including but not limited to
reverse transcription polymerase chain reaction (RT-PCR), in situ hybridization (ISH), gene expression profiling, immunohistochemical (IHC) analyses, enzyme-linked immunosorbent assay (ELISA) and bead-based multiplex assay (Bioplex). The tumour tissue blocks will potentially also be used to set up tissue microarray (TMA) for IHC analysis and for the extraction of DNA and ribonucleic acid (RNA).

Since the identification of new biomarkers correlating with disease activity and the efficacy or safety of treatment are rapidly evolving, the definitive list of analyses remains to be determined, but may include markers of angiogenesis and tumourigenesis pathways (e.g. VEGF, VEGFRs, sVEGFRs, angiopoietins, ephrins, EGFR, transforming growth factor (TGF), etc).

**Plasma-based biomarkers**
Plasma isolated from patients peripheral blood may be analysed for expression of the following biological markers including but not limited to:
- VEGF, interleukin-6 (IL-6), hepatocyte growth factor (HGF), VEGF-C, leukaemia inhibitory factor (LIF), Hypoxia-induced protein, insulin-like growth factor-binding protein 2 (IGFBP2)
- Proteins implicated in impaired immune defence and poor survival: SDF1α, CXCL9 and CXCL10.

**Tissue-based biomarkers**
FFPE tissue may be analysed for expression of biological markers including but not limited to: VEGF, VEGF-R1, VEGF-R2, IL-6R, EGFR, methylguanine methyltransferase (MGMT), isocitrate dehydrogenase 1 (IDH1), c-met and tissue macrophages.

**DNA-based biomarkers**
DNA will be extracted from a blood sample (at baseline, or at any time point during the study if the participant has already commenced treatment) and examined for the incidence of DNA polymorphisms that may be associated with response or resistance to therapy, or overall outcomes; and other genomic aspects of interest.

**Roche Clinical Repository (RCR)**
In conjunction with Australian laboratories, RCR samples will enable exploratory analysis of baseline and serial changes in biomarkers. Techniques used will include immunohistochemical (IHC) analyses. Additional methodologies may be applied including but not limited to: RT-PCR, in situ hybridization (ISH), DNA sequencing, DNA copy number determination, DNA methylation profiling and gene expression profiling. The tumour tissue blocks will potentially also be used for the extraction of DNA and RNA and to set up tissue microarray (TMA) for IHC analysis.

Any biospecimens sent to Roche will be stored at Roche for up to 15 years after the end of the study (final database freeze). If required by regulatory authorities, however, specimens may be maintained for a longer period. Where FFPE tissue blocks have been sent to the Roche Clinical Repository, the remaining part of the block will be returned to the site by Roche within 6-9 months of receipt.

Refer to the Biological Sampling Manual for details on collection and preparation of samples.

**6.3.12 Mini-Mental State Examination (MMSE)**
The MMSE is a brief, quantitative measure of cognitive status in adults. It can be used to screen for cognitive impairment, to estimate the severity of cognitive impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individualised response to treatment. In this protocol the MMSE score is part of the neurological examination performed in the context of the disease assessments.
The MMSE will be assessed at screening, at week 4, then every 4 weeks during treatment for both parts of the study; as well as at the end of treatment visit. The MMSE assessments must, where possible, be completed prior to announcing any radiological assessment results to the patient.

### 6.3.13 CogState assessments

This comprises approximately 20 minutes of testing on a computer. The testing involves:

1. Fixed response mapping task (helps familiarise with using the NO and YES buttons)
2. Detection (simple reaction time)
3. Identification (assessing attention)
4. One card learning test (testing visual memory)
5. One back test (testing working memory and executive function)

Patients will do a brief practice test before completing a formal test at screening. Another formal test will be completed at baseline in order to allow intra-individual test variability to be estimated. Patients will then complete a formal test every 4 weeks during treatment. All patients will be encouraged to complete CogState testing at the required assessment time points.

### 6.4 Central Radiology Assessments

Although decisions regarding disease response and progression (and thus continuation on the trial) will be made at the local research centre and by RANO criteria, all radiological investigations must be centrally reviewed and recorded. At the central review, response assessment using both modified Macdonald and modified RANO criteria will be assessed and documented by a panel of experienced neuro-radiologists who are blinded to the patient’s treatment arm allocation.

### 7 INVESTIGATIONAL PRODUCT

#### 7.1 Packaging and Formulation

**7.1.1 Bevacizumab**

Bevacizumab will be manufactured, packaged and labelled by Roche Products Pty Limited and distributed to investigational centres using Roche clinical study drug distribution procedures.

Bevacizumab will be supplied as a clear to slightly opalescent, colourless to pale brown solution in single use vials. Each vial of 100 mg bevacizumab contains 4 mL of 25 mg/mL solution and each vial of 400 mg bevacizumab contains 16 mL of 25mg/mL sterile solution. Both also contain trehalose dihydrate, monobasic sodium phosphate monohydrate, dibasic sodium phosphate, polysorbate 20 and water for injections.

**7.1.2 Other study drugs**

Institutions should follow their standard guidelines for other study drugs. Other study drugs will not be provided by Roche.

**7.1.3 Labelling**

Each vial of bevacizumab will be labelled in accordance with current good manufacturing practice (GMP) and Australian regulatory requirements for clinical trials supply.
7.1.4 Storage

**Bevacizumab**

Bevacizumab must be stored at 2-8°C in a secured area. Detailed instructions for storage of bevacizumab are contained in the Pharmacy Manual for the study.

**Carboplatin, Etoposide and Temozolomide**

Carboplatin, Etoposide and Temozolomide should be stored as per usual site practices.

7.2 Supply of Investigational Product

Roche will supply bevacizumab. Other study drugs will be prescribed, dispensed and funded as per usual practice at each site. Any chemotherapy that is used in Part 2 will be supplied as per usual hospital practices and not provided or paid for by Roche.

7.3 Drug Accountability

The Pharmacy Department at participating institutions will maintain a record of drugs dispensed for each patient. The Pharmacy will also maintain a record of drug returns and drug destruction as appropriate. The pharmacist should maintain an inventory of the investigational product (bevacizumab) at a site level and patient level. Records should include delivery, dispensing and destruction of the investigational product. Investigators should maintain records that adequately document that each patient was provided the dose specified in the protocol and reconcile all investigational products received from the sponsor.

8 STATISTICS

8.1 Sample Size

**PART 1**

The primary focus of the study is to obtain reliable estimates of progression-free survival (PFS) for treatment with bevacizumab alone (Arm A) and bevacizumab plus carboplatin (Arm B) in patients with recurrent glioblastoma multiforme.

Current estimates of 6 month PFS in Arm A are around 30-40% depending upon patient selection. With 60 patients in each arm and a minimum of 6 months follow up on all patients, this study will produce 6 month PFS estimates which, with 95% confidence, will be within ±12.5% of the true 6 month rate.

In addition to providing estimates of sufficient accuracy, if the 6 month PFS in Arm A is 35% and Arm B is 50%, the total sample size of 120 patients is sufficient to detect the difference (HR=0.62) with 70% power at the two-sided 10% significance level (based on accrual over 2 years with a minimum of 12 months follow up on all patients). All patients will be followed until death, loss to follow up or withdrawal of consent.

**PART 2**

The second randomisation to continue or cease bevacizumab will create 4 arms which will each be of separate interest:

1. Bevacizumab alone followed by carboplatin/best supportive care alone (Arm C)
2. Bevacizumab alone followed by bevacizumab + carboplatin/best supportive care (Arm D)
3. Bevacizumab plus carboplatin followed by clinician’s choice/best supportive care (Arm E)
4. Bevacizumab plus carboplatin followed by bevacizumab + clinician’s choice/best supportive care (Arm F)

It is anticipated that 15-20 patients will participate in each Part 2 arm, providing 30-40 patients continuing and 30-40 patients stopping bevacizumab. (There will be a number of patients who are not of suitable health to participate; these patients will not be randomised or included in analysis of Part 2). Analysis will focus on estimation of outcomes in each group as well as providing some comparison of continuing vs. stopping bevacizumab. 30 patients per group would provide about 79% power to detect a difference in median PFS of 2 vs. 4 months (HR 0.50).

8.2 Statistical Analysis
A statistical analysis plan (SAP) will be developed containing specific statistical instructions. The SAP will be written prior to commencement of study analysis and be approved by the trial management committee.

8.2.1 Analysis population
For analysis of all safety endpoints all patients registered who receive at least one dose of study therapies will be included in analysis. Efficacy analysis will include all randomised patients regardless of whether any treatment is received.

8.2.2 Primary analysis
The primary objective is to determine the proportion alive and progression-free at 6 months in each treatment arm. Disease progression is defined according to modified RANO criteria and is measured from date of randomisation. All patients will be followed and assessed until death, loss to follow up or withdrawal of consent.

8.2.3 Secondary analysis
Time to progression, overall survival, and time to treatment failure will be estimated using the non-parametric Kaplan-Meier method, summary statistics will be presented with appropriate confidence intervals. The nonparametric log-rank test will be used to compare the two arms of the study and, if appropriate, a Cox proportional hazard model will be used to estimate the treatment effect.

Tumour response rates will be reported as the ratio of the number of patients achieving either a complete or partial response (according to modified Macdonald and modified RANO criteria) divided by the total number of evaluable patients in each arm.

The incidence of adverse events will be summarised by type of adverse event and severity using the NCI Common Terminology Criteria for Adverse Events Version 4.0.

Other secondary endpoints will be summarised according to established guidelines specific to the measurement tool. In general, categorical variables will be tabulated and key summary statistics (mean, standard deviation, median, range, etc) will be presented for continuous measurements.

Comparisons between treatment groups will be made where appropriate, the test selected depending on the distribution. Additional details will be provided in the SAP.

8.2.4 Interim analysis
No formal interim analysis of the primary endpoint will be conducted during the course of the study. Regular reporting of safety endpoints will be made to the Safety Data Monitoring Committee (SDMC) as outlined in section 9.3.
8.3 Trial Termination

Although the CTC has every intention of completing the study, the CTC reserves the right to discontinue the study at any time for clinical or administrative reasons. Reasons for terminating the study may include:

1. Occurrence of AEs that are related to study treatment and unknown to date with respect to their nature, severity, and duration
2. Unexpected incidence of known AEs
3. Medical or ethical reasons affecting the continued performance of the study
4. Difficulties in the recruitment of patients
5. Cancellation of drug development

Following recommendation of the SDMC to discontinue the study, Regulatory Authorities and Ethics Committees (ECs) will be informed about the discontinuation of the study in accordance with applicable regulations. Ethical aspects (adequate treatment of patients on study) will be adequately covered.

If the study is not terminated for a reason given above, the study will end when each of the following is fulfilled:

- The last patient received the last dose of study medication (including a safety follow-up of 30 days)
- The study objectives could be answered, i.e. the final analysis on survival has been performed.

9 STUDY STRUCTURE

9.1 Coordinating Centre

This trial is an independent investigator-initiated multi-centre trial coordinated by the NHMRC Clinical Trials Centre (CTC), University of Sydney.

9.2 Trial Management Committee (TMC)

The NHMRC CTC, in conjunction with the Principal Investigator will appoint a Trial Management Committee (TMC), which will be led by the Study Chair. A Trial Executive Committee (TEC) may be selected from the TMC in order to expedite decision-making and will be led by the Study Chair. The TMC will meet as required, preferably at least six monthly.

The TMC responsibilities include protocol development, study planning, monitoring of progress and patient safety, review of information from related research and implementation of recommendations from other study committees and external bodies (e.g. ECs), and publications. This committee will also be responsible for co-ordination of local Investigators, and site selection. This committee will also monitor rate of recruitment and endpoint occurrence and will advise the Safety Data Monitoring Committee (SDMC) of variations.

The Trial Management Committee will monitor toxicity.

In addition, the TMC has responsibilities to hospital sites in taking all reasonable steps to ensure the proper conduct of the study as regards to ethics, protocol adherence, integrity and validity of the data recorded on the CRFs.
9.3 Safety Data Monitoring Committee (SDMC)
An independent SDMC will monitor the progress of all safety aspects of the study and will ensure that the study meets the highest standards of patient safety and related ethical issues. Data on key study outcomes will be monitored at regular intervals to ensure that the event rates meet protocol projections.

10 ADMINISTRATIVE ASPECTS

10.1 Ethics and regulatory compliance

This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC National Statement on Ethical Conduct in Human Research (© Australian Government 2007) and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2004. The Investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a subject. In this circumstance the CTC, Principal Investigator and HREC must be advised immediately.

10.2 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the NHMRC CTC, University of Sydney and will only be available to staff directly involved with the study.

The Investigator must ensure that the patient’s confidentiality is maintained to the extent permitted by Australian regulations. Records identifying the patient will not be made publicly available and no study report will contain any reference to participant’s names.

Case report forms and other study documents will not identify patients by name, but by a patient study number or identification code only. The Investigator should keep a patient enrolment log showing codes, names and addresses of patients.

In compliance with ICH GCP Guidelines, the Investigator and institution must permit authorised representatives of the sponsor, of regulatory agencies, and the Ethics Committee direct access to review the patient’s original medical records for verification of study-related procedures and data. Direct access includes examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

10.3 Protocol amendments

Changes and amendments to the protocol can only be made by the Trial Management Committee. Approval of amendments by the Institutional HREC is required prior to their implementation. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the Case Report Forms, if required, will be incorporated in the amendment.

The Investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial participant(s). Protocol waivers will not be allowed except in exceptional circumstances.
10.4 Data Handling and Record Keeping

Trial data will be recorded on the (e-)CRFs provided. All required data entry fields will be completed. Data corrections will be done according to the instructions provided. The Investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated.

Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a patient's medical records, hospital charts, clinic charts, the Investigator's patient study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The Investigator's copy of the case report forms serves as part of the Investigator's record of a patient's study-related data.

The following information should be entered into the patient's medical record:

a. Patient's name, contact information and protocol identification.
b. The date that the patient entered the study, and patient number.
c. A statement that informed consent was obtained (including the date).
d. Relevant medical history
e. Dates of all patient visits and results of key trial parameters.
f. Occurrence and status of any adverse events.
g. The date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation.

All study-related documentation will be maintained for 15 years following completion of the study.

10.5 Study Monitoring

Data from this study will be monitored by Clinical Trials Program staff from the NHMRC CTC. Monitoring will include centralised review of CRFs and other study documents for protocol compliance, data accuracy and completeness. Monitoring may include monitoring visits to investigational sites for source data verification, review of the Investigator's site file and drug handling records. The CTC will be given direct access to source documents, CRFs and other study-related documents. By signing the informed consent form, the subject gives authorised CTC staff direct access to their medical records and the study data.

10.6 Audit and Inspection

This study may be subject to audit or inspection by representatives of the collaborative group or the CTC or representatives of regulatory bodies (e.g. TGA, US FDA) or the pharmaceutical manufacturer Roche.

10.7 Clinical Study Report

The data will be entered and analysed by the CTC. Statistical analysis will be conducted by the CTC. A Clinical Study Report will be issued which may form the basis of a manuscript intended for publication. The Clinical Study Report or summary thereof will be provided to Roche.

10.8 Publication Policy

The Trial Management Committee will appoint a Writing Committee to draft manuscripts based on the trial data. Manuscripts will be submitted to peer-reviewed journal(s). The first publication will be the report of the full trial results based on the main protocol using the study group name, with subsequent publications of data subsets in the names of individual contributors. The Writing
Committee will develop a publication plan, including authorship, target journals and expected dates of publication.

Data from the study results will be retained by COGNO. The results of this study may be published or presented at scientific meetings and in journals. Roche will have the opportunity to review abstracts (28 day time frame) and manuscripts (28 day time frame) before submission.

The Trial Management Committee will also appoint a Writing Committee to draft manuscripts based on substudy data. Manuscripts will be submitted to peer-reviewed journal(s). Publication(s) will be on substudy data linked with trial data. The Writing Committee will develop a publication plan, including authorship, target journals and expected dates of publication. Roche and other research collaborators will have the opportunity to review abstracts (28 day time frame) and manuscripts (28 day time frame) before submission.
11 REFERENCES


12 LIST OF APPENDICES

Appendix 1a: Participant information sheet and informed consent form (Part 1)
Appendix 1b: Participant information sheet and informed consent form (Part 2)
Appendix 1c: Participant information sheet and informed consent form (optional biomarkers substudy for patients commencing the CABARET clinical trial)
Appendix 1d: Participant information sheet and informed consent form (optional biomarkers substudy for patients who have commenced treatment on the CABARET clinical trial)
Appendix 2: List of abbreviations and terms
Appendix 3: List of chemotherapy agents which are acceptable options for treatment in Part 2
Appendix 4: ECOG and Karnofsky performance status
Appendix 5: Health-related quality of life (HRQL) forms
Appendix 6: Mini-Mental State Examination (MMSE) form
Appendix 7: Common Terminology Criteria for Adverse Events (CTCAE)
Appendix 8: Modified Macdonald criteria
Appendix 9: Proposed T2/FLAIR grading
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Appendix 12: Cockroft-Gault equation for calculation of creatinine clearance
Appendix 13: Relative potencies of commonly used steroids
PARTICIPANT INFORMATION AND CONSENT FORM

Study Title: A randomised phase II study of Carboplatin and Bevacizumab in Recurrent Glioblastoma Multiforme (CABARET study): PART 1

Principal Investigator: [name]

This Participant Information and Consent Form is 11 pages long. Please make sure that you have all the pages.

You are being invited to take part in a research study.

This Participant Information contains detailed information about the research study. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in the study before you decide whether or not to take part in it.

Please read this Participant Information carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the study with a relative or friend or your local health worker.

Once you understand what the study is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project.

You will be given a copy of the Participant Information and Consent Form to keep as a record.

1. What is the purpose of this study?

The purpose of this study is to investigate the effectiveness of a drug called bevacizumab in combination with carboplatin compared with bevacizumab alone for patients with glioblastoma multiforme (GBM) (advanced brain tumour) that has recurred after previous treatment.

**Bevacizumab**

Bevacizumab is approved for use in Australia and many other countries in combination with chemotherapy for the treatment of bowel, breast, lung and renal cancers that have spread to other parts of the body, and GBM (advanced brain tumour) after relapse or disease progression.

Bevacizumab has recently been approved by the Therapeutic Goods Administration (TGA) in Australia as a single agent, for the treatment of patients with GBM after relapse or disease progression following standard therapy, including chemotherapy.

Bevacizumab is a humanised antibody that has been made in a laboratory. Antibodies are proteins that can be found circulating in your blood stream. Antibodies are normally made by the body to attack a foreign substance that the body thinks is harmful. The growth of brain tumours may be promoted by a growth factor called vascular endothelial growth factor (VEGF) which acts on a receptor located on the surface of cancer cells. Bevacizumab works against VEGF by blocking the binding of VEGF to its receptors on cancer cells, hence potentially stopping the growth of the tumour.

To date several studies have investigated the effect of bevacizumab in patients with recurrent GBM. These studies have shown that bevacizumab may provide a clinical benefit for patients with recurrent GBM, particularly in terms of delaying disease progression.

Despite the results of these studies, significant outstanding questions still remain regarding the use of bevacizumab in patients with recurrent GBM. The overall benefit of bevacizumab for these patients is still unclear. To address this issue, this study will examine the effect of bevacizumab on your cognitive
function (e.g. memory, attention, problem solving), quality of life, and functional status (e.g. how much
time you need to spend resting) as markers of overall benefit.

**Carboplatin**

Carboplatin is a form of chemotherapy which is currently used by many Australian oncologists for
patients with recurrent GBM. It is also commonly used for many other types of cancer, such as lung
cancer and ovarian cancer. Research has investigated the use of carboplatin in patients with
recurrent GBM and has demonstrated response rates of approximately 14%. Furthermore, in patients
who do respond, the response can be prolonged up to 12-18 months in some patients. Since there is
currently no accepted standard care for patients with recurrent GBM, this treatment is often prescribed
for patients whose disease continues to progress during or following treatment with temozolomide (a
form of oral chemotherapy).

**Combination of bevacizumab and carboplatin**

Whilst bevacizumab has been tested in combination with other forms of chemotherapy, to date the
combination of bevacizumab and carboplatin has only been tested in small numbers of patients with
recurrent GBM. The combination of treatment appears to be relatively safe and quite effective in these
small numbers of patients. However, the combination has not been compared with bevacizumab
alone to see if giving the two medications together is more effective than giving bevacizumab by itself.
We also need to make sure that the potential side effects of combining the two medications together
are manageable and not severe.

There is currently no standard care for patients with recurrent GBM. The treatment being investigated
in this study is therefore considered experimental.

2. **Who is conducting this study?**

This study is being sponsored by the University of Sydney, and coordinated by the National Health
and Medical Research Council (NHMRC) Clinical Trials Centre (CTC), for the Cooperative Trials
Group for Neuro-Oncology (COGNO), which runs studies to improve the treatment of patients with
brain tumours.

Your study doctor’s department will be paid a nominal amount to assist with the costs of your
participation in the study. The company that makes bevacizumab, Roche, is providing this drug and
some additional funding to help cover the costs of conducting the study. Roche has a financial interest
in the outcome of this study. The University of Sydney, NHMRC Clinical Trials Centre, COGNO and
your study doctor and their team do not have a financial interest in the outcome of this study. Some of
the doctors involved in this study have connections with Roche. This may include membership on
Roche advisory boards, participation (paid or non-paid) at Roche meetings and conferences, and
receipt of funding from Roche to attend scientific conferences.

3. **Why have I been asked to participate in this study?**

You have been invited to participate in this study because you have been diagnosed with a brain
tumour (GBM) which has been previously treated with radiotherapy and temozolomide (a form of
chemotherapy), but has now returned. Your doctor believes that you may benefit from further drug
treatment, which may shrink your brain tumour or lengthen the time that your brain tumour is
controlled.

A total of 120 people will participate in this study in Australia.
4. What are the alternatives to participating in this study?

A number of other drugs and regimens may be suitable for you. Your doctor can discuss the alternatives with you. You may ask your study doctor for information about your cancer and the benefits and risks of the other treatments available. You may choose one or more of these treatments rather than participate in this study. You may decide to receive treatment for your symptoms only or you may decide not to be treated at all. You should discuss your condition and the likely course of your cancer with your physician or the study doctor.

5. What if I don’t want to take part in this study, or if I want to withdraw later?

Participation in this study is voluntary. It is completely up to you whether or not you wish to participate. Your choice not to participate will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you.

Before you make your decision, your study doctor or a member of the study team will be available so you can ask any questions you have about the study. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

New information about the treatment being studied may become available during the course of the study. You or your legally acceptable representative will be kept informed of any significant new findings that may affect your willingness to continue in the study.

If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason. Your decision to withdraw from the study will not affect your future care or your relationship with the staff caring for you.

If you decide to withdraw from this study, please notify a member of the research team before you withdraw. This notice will allow your doctor to inform you if there are any health risks or special requirements linked to withdrawing.

If you decide to discontinue the study treatment, you will be asked to attend follow-up visits to allow collection of information regarding your health status. Alternatively, the investigator or sponsor will request your permission to access your medical records for collection of follow-up information for research and analysis.

In the event that you withdraw your consent, the effective date of the notification will be the date on which your withdrawal is received by your study doctor, and that information about you collected prior to that date will continue to be used and form part of this project.

Your study doctor may withdraw you from the study if:

- You decide to discontinue taking the study drug/s, fail to attend scheduled assessments or develop another illness which affects your participation in the study
- An event occurs which is clinically important and affects your safety (e.g. pregnancy)
- An adverse event occurs that requires discontinuation of the study treatment
- He/she does not think it is in your best interests to continue

Although the investigators have every intention of completing the study, they reserve the right to discontinue the study at any time due to clinical or administrative reasons.

6. What does this study involve?

This study has 2 parts (Part 1 and Part 2). This information sheet relates to Part 1 of the study. If you decide to participate in Part 1 of the study, you will be expected to attend the clinic for study visits every two weeks whilst on study treatment. It is important to tell your doctor and the study staff about any treatments or medications you may be taking, including non-prescription medicines, vitamins or herbal remedies and any changes to these during the study.

Initially you will be assessed to ensure that you are suitable to join the study.
If you agree to participate, initial assessments will involve:

- Physical examination (including assessment of your blood pressure, heart rate, temperature, weight, height, current functional status e.g. ability to carry out normal daily activities, a medical assessment); and a brief neurological examination
- Medical history (including current medications and adverse events)
- MRI scan to measure your brain tumour
- ECG (electrocardiogram) to check your heart function
- Blood sample for routine testing of kidney, liver and bone marrow function
- Urine sample for routine testing of kidney function
- Pregnancy test (for women of childbearing potential)
- Questionnaires to assess your quality of life (how you are feeling and functioning in everyday life)
- Tests of your cognitive function (e.g. memory, attention, problem solving)

Following the initial assessment, if you are suitable and agree to take part in the study, you will enter Part 1 of the study and be randomised into one of the treatment groups described below.

Randomisation means that you are put into a group by chance. A computer program will choose which group you are allocated to. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either group. You will be told which treatment you will receive.

**Treatments**

In Part 1 of the study you will be randomised to receive:

1. Bevacizumab alone (Arm A) OR
2. Bevacizumab and carboplatin (Arm B)

If you are randomised to Arm A, you will receive bevacizumab on day 1 and day 15 of every 28 day treatment cycle. Bevacizumab is given by injection, into a vein, usually in your arm or hand (also known as an intravenous injection, IV or drip).

If you are randomised to Arm B, you will receive bevacizumab on day 1 and day 15 of every 28 day treatment cycle, and carboplatin on day 1 of every 28 day treatment cycle. Bevacizumab and carboplatin are both given by injection, into a vein, usually in your arm or hand (also known as an intravenous injection, IV or drip).

Treatment in Part 1 will be stopped when it becomes clear that the treatment is no longer controlling your cancer, or if it is causing excessive side effects that cannot be treated or controlled by reducing the dose. For patients in Arm B, if you are required to cease carboplatin due to excessive side-effects, you will still continue to take bevacizumab until it becomes clear that the treatment is no longer...
controlling your cancer. If all treatment is withdrawn in Part 1 due to excessive side-effects, you will continue to be assessed until your cancer is no longer controlled.

When it is clear that the study treatment in Part 1 is no longer controlling your cancer you will stop receiving the study treatment. If your study doctor assesses you as suitable, you will be given the opportunity to participate in Part 2 of the study. This part of the study will involve continuing or stopping bevacizumab as well as the option of receiving other chemotherapy based on discussion between you and your doctor at that time. Your study doctor will provide you with this additional information about Part 2 of the study at that time. As in Part 1, you will be given an opportunity to read this information and ask any questions you may have. If you decide to continue onto Part 2 of the study you will be asked to sign an additional consent form.

If you decide not to continue onto Part 2 of the study, or your doctor assesses that you are unsuitable to continue onto Part 2, your doctor will continue to follow you up at monthly intervals, unless you decide to withdraw your consent to participate in the study. You and your doctor will decide on what is the most suitable treatment for you at this time.

**Assessments**

In Part 1 of the study you will attend the clinic for treatment every 2 weeks. You will generally see your doctor before every treatment, or more frequently if necessary.

Assessments during treatment in Part 1 will be completed according to the following schedule:

**Day 1 and 15 of every cycle of study treatment (every 14 days)**

- Blood sample (20mL, approximately 4 teaspoons) for routine testing of kidney, liver and bone marrow function
- Urine sample
- Questions relating to your current medications and any adverse events
- Physical examination (including assessment of your blood pressure, heart rate, temperature, weight, current functional status e.g. ability to carry out normal daily activities, a medical assessment); and a brief neurological examination (physical and neurological examination, weight and functional status completed on day 1 and 15 of cycle 1 and then day 1 only thereafter)
- Tests of your cognitive function (day 1 only)
- Questionnaires to assess your health-related quality of life (how you are feeling and functioning in everyday life) (day 1 only).

**Day 1 of cycles 2 and 3 (4 and 8 weeks after commencing study treatment) and then 8 weekly during study treatment**

- MRI scan to assess your brain tumour

**End of study treatment**

- Blood sample (20mL, approximately 4 teaspoons) for routine testing of kidney, liver and bone marrow function
- Physical examination (including assessment of your blood pressure, heart rate, temperature, weight, current functional status e.g. ability to carry out normal daily activities, a medical assessment); and a brief neurological examination
- Tests of your cognitive function
- Questionnaires to assess your health-related quality of life (how you are feeling and functioning in everyday life)
- MRI scan to assess your brain tumour (only if previous MRI scans have not shown progression of your tumour)
- Questions relating to your current medications and adverse events (adverse events will be monitored until at least 30 days after your last study treatment)
Follow-up

After you have completed all study treatment your doctor will continue to follow you up once per month for life. Your doctor will ask you about any treatments that you may be having for your brain tumour including any steroid medications. At your first follow-up assessment your doctor will ask you about any adverse events that have occurred since your End of Treatment visit. Follow-up assessments may occur via a clinic visit, phone call, or by your doctor contacting your general practitioner or reviewing your medical records.

Every 2 months after end of study treatment

- You may be required to have an MRI scan to assess your brain tumour once every 2 months after the end of your study treatment (only if previous MRI scans have not shown progression of your tumour)

7. Are there risks to me in taking part in this study?

All medical procedures involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. In spite of all reasonable precautions, you might develop medical complications from participating in this study.

Patients in Arm A (bevacizumab only) may experience some, all, or none of the following side effects from bevacizumab (as bevacizumab is often used in combination with chemotherapy in other types of cancer, some of these side effects may be related to the chemotherapy that bevacizumab is combined with):

Very Common (more than 1 in 10 patients i.e. >10%)

- Gastrointestinal effects including: nausea and vomiting, constipation, diarrhoea, loss of appetite, change in the sense of taste
- Changes to the blood including: low numbers of white blood cells, potentially associated with fever, low numbers of platelets
- Cardiovascular effects including: high blood pressure
- Effects on the kidneys including: protein in the urine
- Neurological effects including: numbness in the fingers or toes, headache
- Respiratory effects including: shortness of breath
- Effects on the skin including: dry skin, flaking and inflammation, change in skin colour
- Bleeding effects including: nosebleeds or easy bruising
- General effects including: pain, joint pain, eye problems including making more tears, runny nose, lack of energy, weakness, fever, mucosal inflammation (for example, ulcers in the mouth)

Common (between 1 in 10 and 1 in 100 patients i.e. between 1 and 10%)

- Gastrointestinal effects including: gastrointestinal disorder, a tear or a hole in the gut (perforation), blockage in the intestine
- Changes to the blood including: lower levels of oxygen in the blood, low numbers of red blood cells which can make you feel tired
- Cardiovascular effects including: blocking of the arteries by a blood clot, including stroke or heart attack, clogging of a vessel in the lung, blood clots in the veins, heart failure, and rapid beating of the heart
- Neurological effects including: sleepiness, feeling tired
- Infection: presence of bacteria in the blood, collection of pus in tissue or organs
- Bleeding effects including: bleeding associated with the tumour
- General effects including: voice changes, hoarseness, muscular pain and muscular weakness, abdominal pain
- Delay in wound healing, failure of a wound to heal or spontaneous opening of a wound
- Abnormal tube-like connection (fistula) between internal organs and skin or other tissues that are not normally connected
- Pain, tenderness, or blistering on the fingers or feet
- Allergic reaction, including allergic reaction to the drug during the infusion
Uncommon (between 1 in 100 and 1 in 1000 patients i.e. <1%)
- Abnormal connection (fistula) between the windpipe (trachea) and the oesophagus (the tube that connects the mouth to the stomach)

Rare (between 1 in 1000 and 1 in 10000 patients i.e. <0.1%)
- Reversible posterior leukoencephalopathy syndrome. This may include symptoms of impaired brain function (headaches, vision changes, confusion, or seizures), and often, high blood pressure
- Hypertensive encephalopathy. This may include symptoms of impaired brain function (headaches, vision changes, confusion, or seizures), and often, high blood pressure

Very Rare (fewer than 1 in 10000 patients i.e. <0.01%)
- A hole in the nasal passage

Bevacizumab may also cause changes in laboratory tests carried out by your doctor such as decreased blood potassium (electrolyte) and sodium (electrolyte), increased blood sugar, or altered coagulation (blood clotting) values.

Some side effects are more common in elderly patients than in younger patients. These side effects include blood clots in the arteries which can lead to a stroke or a heart attack. In addition, elderly patients have a higher risk of a reduction in the number of white cells in the blood which can increase risk of infection.

Patients in Arm B (bevacizumab and carboplatin) may experience some, all, or none of the following side effects from carboplatin:

Very common (more than 1 in 10 patients i.e. >10%):
- Changes to the blood including: decreased levels of haemoglobin (anaemia), white blood cells, platelets, magnesium and potassium
- Gastrointestinal effects including: nausea and vomiting
- Effects on the kidneys including: mildly decreased creatinine clearance, increased uric acid, increased urea in the blood
- Effects on the liver including: mildly increased liver enzymes
- Decreased hearing acuity

Common (between 1 in 10 and 1 in 100 patients i.e. between 1 and 10%):
- Gastrointestinal effects including: diarrhoea, constipation
- Effects on the kidneys including: increased creatinine in the blood
- Changes to the blood including: decreased calcium in the blood
- Neurological effects including: mild effects on the nerves in the arms and legs (may affect strength, ability to feel and reflexes)
- Allergic reaction (rash, fever, hives, itching, decreased blood pressure, difficulty breathing)
- General effects including: ringing in the ears, hair loss and flu-like symptoms

Uncommon (between 1 in 100 and 1 in 1000 patients i.e. <1%):
- Acute kidney failure
- Altered sense of taste
- Dermatitis (irritation of the skin)
- Blurred vision
- Combination of anaemia, decreased platelets in the blood and acute kidney failure (haemolytic uraemic syndrome)

Pre-existing pins and needles may worsen during treatment with carboplatin. Similarly pre-existing hearing impairments may persist or worsen during treatment with carboplatin. Decreased sodium levels in the blood and adverse respiratory and genitourinary effects have also been reported with carboplatin treatment.
In addition, patients in Arm B may also experience some, all, or none of the side effects related to bevacizumab alone (see page 6).

While the combination of chemotherapy and bevacizumab has been investigated in many research studies, these studies have often involved another drug in addition to bevacizumab and carboplatin, or a different chemotherapy drug instead of carboplatin. As such, limited information is available regarding the risks associated with the combined effects of bevacizumab and carboplatin. In one study that reported limited information about the side effects of this drug combination, a decrease in the number of platelets and sodium in the blood was reported. There were no deaths or bleeding within the head associated with the combined effects of carboplatin and bevacizumab in this study.

Other risk information
Following the administration of the study drugs, you may experience infusion/hypersensitivity reactions. Infusion reactions may be mild or serious, and there is a possibility that you may develop a severe infusion reaction. You may also develop an allergic reaction such as itching, hives, shortness of breath, wheezing, sudden drop in blood pressure, swelling around the mouth or eyes, palpitation (fast pulse), headache, flushing, or sweating. Your study doctor will monitor you for any adverse effects. Severe allergic reactions may rarely occur and if they do, may cause an injury or even lead to death.

Risks related to blood sampling
There may be some discomfort, swelling or bruising around the vein that was used to draw your blood. You may experience light-headedness; and fainting at the time of blood drawing could occur. Infection at the blood drawing site may also occur.

Risks related to intravenous (into the vein) infusions
If you have an intravenous catheter inserted, you can expect to experience pain at the moment the needle containing the plastic catheter goes into your arm. In addition to this pain, there will be the discomfort of having the catheter taped to your arm. Other risks associated with catheter insertion include: a small amount of bleeding under the skin producing a bruise, temporary clotting of the vein from an intravenous catheter, infection, and significant blood loss. Finally, you may experience dizziness during the catheter insertion.

Risks related to MRI Scans
An MRI is an imaging test used to measure the size of your tumour. You may feel claustrophobic or anxious inside the MRI scanner. You may experience some discomfort and fatigue from lying in a confined space within the scanner. There are no known effects from exposure to the magnetic fields. The contrast agent will be injected into the vein and may cause a few people to experience nausea, headache, hot flushes, dizziness and irregular heartbeat as well as discomfort from the injection needle. Please tell your doctor if you have a pacemaker or any metal plates or clips in your body and if you have any allergies. The contrast material (dye) that is injected into your vein may cause you to get a metallic taste in your mouth, to feel warm, and may cause rare nausea or vomiting.

Risks related to ECGs
An electrocardiogram (ECG) generally has no risks. Because this procedure only records the electrical activity of the heart and does not send out electricity, there is no risk of shock. Occasionally, there may be some minor skin irritation or slight discomfort from ECG electrodes (disposable adhesive tabs placed on top of the skin in the chest area and then removed from the skin at the end of the procedure).

Risks related to pregnancy
It is important that women participating in this study are not pregnant and do not become pregnant during the study as the study drugs may damage an unborn baby. Furthermore, it is important that partners of men participating in this study do not become pregnant during the study as the study drugs may damage an unborn baby. The effect of the study drugs on an unborn baby is unknown. If you are a woman of childbearing potential and there is any possibility that you are pregnant, your doctor will need to perform a pregnancy test before you start in the study. If necessary, women, or partners of women participating in this study should use reliable contraception (such as oral or implanted contraceptive or an IUD) during the course of the study and for 6 months after the
completion of study treatment. If you think you or your partner may be pregnant, it is important to let your doctor know immediately.

Breastfeeding should be discontinued during the study.

Chemotherapy may cause temporary or permanent sterility. Please discuss this with your doctor if you have any concerns about future fertility.

8. What happens if I suffer injury or complications as a result of the study?

If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment. Treatment for the injury or complication will be provided free-of-charge at a public hospital.

You may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies.

You do not give up any legal rights to compensation for your injury or compensation by participating in this study. If you are not eligible for compensation for your injury or complication under law, but are eligible for Medicare, then you can receive any medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

9. Will I benefit from the study?

The study aims to further medical knowledge and may improve future treatment of recurrent GBM. We hope that the treatment combinations examined in this study will benefit some patients with recurrent GBM, but we cannot guarantee that taking part in the trial may be of direct benefit to you. Your participation in this study may help other patients with recurrent GBM in the future.

10. Will taking part in this study cost me anything?

Your study visits and procedures will be provided at no extra cost. You may be required to make a co-payment for some of the drugs involved in this study. This will depend on the processes at your local hospital. If you wish to find out more about co-payments that may be required at your hospital, please discuss this further with your doctor. You will not be paid for participation in this study.

11. How will my confidentiality be protected?

Nursing and medical staff involved in your care will know whether or not you are participating in this study. Any identifiable information that is collected about you in connection with this study will remain confidential and will not be disclosed without your permission, except as required by law.

Your health records and any information obtained during the study may be examined by authorised representatives of the hospital’s Health Research Ethics Committee, the study sponsor (The University of Sydney), Roche Products Pty Limited, or by regulatory authorities such as the Australian Government’s Therapeutic Goods Administration (TGA) or the Food and Drug Administration (FDA) of the United States of America (USA) or as required by law, for the purposes of verifying the study procedures or data. By signing the Consent Form, you authorise access to this confidential information to the relevant study personnel and regulatory authorities as noted above.
12. What happens with the results?

Your doctor will inform you about your own results where relevant.

If you give us your permission by signing the Consent Form, we plan to publish the results in a medical journal, at scientific conferences or at other professional forums. In any publication, information will be provided in such a way that you cannot be identified.

Results of the study will be provided to you, if you wish, by your study doctor.

13. What happens to my treatment when the study is finished?

When it is clear that the study treatment in Part 1 is no longer controlling your cancer you will stop receiving the study treatment. If your study doctor assesses you as suitable, you will be given the opportunity to participate in Part 2 of the study and receive further study treatment.

If you decide not to continue onto part 2 of the study, or your doctor assesses that you are unsuitable to continue onto part 2, you and your doctor will decide on what is the most suitable treatment for you at this time.

If you do continue on to Part 2 of the study it is planned that the study will continue for the entire duration during which you are receiving treatment. In the event that the study is terminated whilst you are still receiving treatment, those patients who are continuing to benefit from bevacizumab will have the opportunity to continue that treatment. This decision will be made in consultation with you and your treating doctor.

14. Further Information or Any Problems

If you require further information or if you have any problems concerning this study (for example, any side effects), you can contact the principal investigator or study staff. The investigator/s responsible for this study are [list the names and contact phone numbers, including after hours numbers].

Name: [Principal investigator or study team contact person]

Position: 

Telephone: 

15. Who should I contact if I have concerns about the conduct of this study?

This study has been approved by the Cancer Institute New South Wales Clinical Research Ethics Committee. If you have concerns or complaints about the conduct of this study, you should contact the Ethics Coordinator who is the person nominated by the Human Research Ethics Committee to receive complaints from research participants. You should contact them on (02) 8374 5600 and quote 2010C/07/135.

Position: Ethics Coordinator

Telephone: 02 8374 5600

Thank you for taking the time to consider being part of this study.

If you wish to take part in this study, please sign the attached consent form.

This information sheet is for you to keep.
PARTICIPANT CONSENT FORM: PART 1

I, ....................................................................................................................... [name]
Of......................................................................................................................[address] have read and understood the Information for Participants on the above named research study. I understand that I am agreeing to participate in a research study.
I have been made aware of the procedures involved in the study, including any known or expected inconvenience, risk, discomfort or side effect, and of their implications as far as they are currently known by the researchers.
I understand that the research project will be carried out according to the principles in the National Health & Medical Research Council National Statement on Ethical Conduct in Human Research.
I freely choose to participate in this study and understand that I can withdraw at any time.
I also understand that the research study is strictly confidential.
I hereby agree to participate in this research study.

NAME: ......................................
SIGNATURE: .................................
DATE: .................................

NAME OF INVESTIGATOR: ........................................
SIGNATURE OF INVESTIGATOR: ........................................
DATE: .................................
PARTICIPANT INFORMATION AND CONSENT FORM

Study Title: A randomised phase II study of Carboplatin and Bevacizumab in Recurrent Glioblastoma Multiforme (CABARET study): PART 2

Principal Investigator: [name]

This Participant Information and Consent Form is 9 pages long. Please make sure that you have all the pages.

You have been invited to participate in Part 2 of the CABARET research study because you have completed study treatment in Part 1, and have been assessed by your study doctor as suitable to continue onto Part 2. Your doctor believes that you may benefit from further drug treatment as part of this study. It is anticipated that approximately 60-80 patients will continue onto Part 2 of this study across Australia.

Please note when the information is the same in Part 2 as Part 1 of this study you will be referred to the Part 1 Participant Information and Consent Form.

The remainder of this Participant Information and Consent Form contains detailed information specific to the treatments and assessments required for Part 2 of the research study. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in Part 2 of the study before you decide whether or not to participate. You may also wish to discuss the study with a relative or friend or your local health worker.

Participation in Part 2 of this study is voluntary. It is completely up to you whether or not you wish to participate. Your choice not to participate will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you.

Please read this Participant Information carefully. Once you understand what Part 2 of the study is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in Part 2 of this research study.

You will be given a copy of this Participant Information and Consent Form to keep as a record.

1. What is the purpose of Part 2 of this study?

The purpose of Part 2 of this study is to determine whether there is any additional benefit of continuing or stopping bevacizumab after your tumour has progressed during Part 1 of the study. Bevacizumab is currently not standard care for patients with recurrent Glioblastoma Multiforme (GBM) and is therefore considered experimental. In Part 2 of this study you may also receive further chemotherapy (a decision that will be made between you and your study doctor).

2. What does Part 2 of this study involve?

If you decide to participate in Part 2 of this study, you will be expected to attend the clinic for study visits every two or four weeks (depending on which treatment you are allocated to) whilst on study treatment. You will also be followed up monthly following the end of study treatment. These follow-up assessments may be visits with your study doctor or alternatively may occur via a telephone call from your doctor or by your doctor contacting your GP or reviewing your medical records.

It is important to tell your doctor and the study staff about any treatments or medications you may be taking, including non-prescription medicines, vitamins or herbal remedies and any changes to these during the study.
If you agree to participate in Part 2 of this study you will be randomised into one of the treatment groups described below. Randomisation means that you are put into a group by chance. You will have an equal chance of being placed in either group. You will be told which treatment you will receive.

**Treatments**

**Arm A**

If you were in Arm A in Part 1 of the study you will be randomised as follows:

1. **Tumour progression on Bevacizumab only**
2. **Patient/doctor decision to start chemotherapy (carboplatin) or best supportive care**

   - **Arm C**
     - Cease Bevacizumab
   - **Arm D**
     - Continue Bevacizumab

If you and your doctor decide that you are not suitable to receive the additional chemotherapy (carboplatin) you may choose to have best supportive care alone. This decision will be made before the randomisation (to continue or stop bevacizumab) occurs.

‘Best supportive care’ involves treatments to assist with controlling the symptoms of your cancer, such as pain medication or anti-nausea medications. Everyone on this study (including those receiving chemotherapy) will also be receiving best supportive care.

After you and your doctor have made the decision regarding additional chemotherapy (carboplatin) or best supportive care, you will then be randomly allocated to:

1. **Stop bevacizumab (Arm C) OR**
2. **Continue bevacizumab (Arm D)**

If you are allocated to Arm C you will receive carboplatin on day 1 of every 28 day treatment cycle, given by injection, into a vein, usually in your arm or hand (also known as an intravenous injection, IV or drip) OR best supportive care.

If you are allocated to Arm D you will continue to receive bevacizumab on day 1 and day 15 of every 28 day treatment cycle. You will also start carboplatin on day 1 of every 28 day treatment cycle OR start best supportive care. Bevacizumab and carboplatin are both given by injection, into a vein, usually in your arm or hand (also known as an intravenous injection, IV or drip).
Arm B

If you were in Arm B in Part 1 of the study you will be randomised as follows:

If you have been receiving bevacizumab and carboplatin in Part 1 of this study, you will stop taking carboplatin and you and your doctor will choose from one of the following treatments:

i) Oral temozolomide (chemotherapy) OR
ii) Oral etoposide (chemotherapy) OR
iii) Best supportive care alone

This decision will be made before the randomisation (to continue or stop bevacizumab) occurs.

You will then be randomly allocated to:

i) Stop bevacizumab (Arm E) OR
ii) Continue bevacizumab (Arm F)

‘Best supportive care’ involves treatments to assist with controlling the symptoms of your cancer, such as pain medication and antinausea medication. Everyone on this study (including those receiving chemotherapy) will also be receiving best supportive care.

If you are allocated to Arm E you will stop bevacizumab and carboplatin. You will commence the treatment decided on by you and your doctor (oral temozolomide, oral etoposide or best supportive care). If you choose oral temozolomide or oral etoposide you will be required to take a tablet or capsule for either 5 or 20 days out of every 28 day treatment cycle.

If you are allocated to Arm F you will stop carboplatin and continue to receive bevacizumab on day 1 and day 15 of every 28 day treatment cycle, given by injection, into a vein, usually in your arm or hand (also known as an intravenous injection, IV or drip). You will also commence the treatment decided on
by you and your doctor (oral temozolomide, oral etoposide or best supportive care). If you choose oral temozolomide or oral etoposide you will be required to take a tablet or capsule for either 5 or 20 days out of every 28 day treatment cycle.

Treatment in Part 2 will continue until your tumour is no longer controlled or if you have excessive side effects. If you are having problems with your treatment, then your doctor may need to stop the study treatment until the problems improve, and may need to change the dose for future treatments. Follow-up assessments will be completed at monthly intervals once you have finished study treatment, unless you decide to withdraw your consent to participate in the study.

Assessments

In Part 2 of the study, you will continue to attend the clinic every 2 weeks for assessment unless you are receiving ‘best supportive care’ only. If you are receiving ‘best supportive care’ only (i.e. if you choose not to have further chemotherapy and are randomised to stop bevacizumab) you will attend the clinic every 4 weeks, but will receive a telephone call from one of the study staff between visits to obtain information about your medications and any adverse events.

For Part 2 of the study assessments will be completed according to the following schedule:

Day 1 and 15 of every cycle of study treatment (every 14 days)
- Blood sample (20mL, approximately 4 teaspoons) for routine testing of kidney, liver and bone marrow function
- Urine sample (only for patients receiving bevacizumab)
- Questions relating to your current medications and any adverse events
- Physical examination (including assessment of your blood pressure, heart rate, temperature, weight, current functional status e.g. ability to carry out normal daily activities, a medical assessment); and a brief neurological examination** (physical and neurological examination, weight and functional status completed on day 1 and 15 of cycle 1 and then day 1 only thereafter)
- Tests of your cognitive function (day 1 only)
- Questionnaires to assess your health-related quality of life (how you are feeling and functioning in everyday life) (day 1 only).

If you are receiving best supportive care only, you will have a physical examination at Day 1 (blood pressure, heart rate and temperature, weight and medical assessment, including cognitive function) and will answer questionnaires related to quality of life but will not undergo blood or urine tests as described above. On Day 15, you will not need to visit the clinic but you will receive a telephone call from a member of the study team, who will ask you about your current health status and medications, and any adverse events.

Every 8 weeks during study treatment
- MRI scan to assess your brain tumour

End of study treatment (or for patients receiving best supportive care only, when your tumour has shown signs of progression)
- Blood sample (20mL, approximately 4 teaspoons) for routine testing of kidney, liver and bone marrow function (not required for patients receiving best supportive care only)
- Physical examination (including assessment of your blood pressure, heart rate, temperature, weight, current functional status e.g. ability to carry out normal daily activities, a medical assessment); and a brief neurological examination
- Tests of your cognitive function
- Questionnaires to assess your health-related quality of life (how you are feeling and functioning in everyday life)
- MRI scan to assess your brain tumour (only if previous MRI scans have not shown progression of your tumour)
- Questions relating to your current medications and adverse events (adverse events will be monitored until at least 30 days after your last study treatment)
Follow-up

After you have completed all study treatment (when your tumour has shown signs of progression), your doctor will continue to follow you up once per month for life. Your doctor will ask you about any treatments that you may be having for your brain tumour including any steroid medications. At your first follow-up assessment your doctor will ask you about any adverse events that have occurred since your End of Treatment visit. This may be via a clinic visit, phone call, or by your doctor contacting your general practitioner or reviewing your medical records.

Every 2 months after end of study treatment

- You may be required to have an MRI scan to assess your brain tumour once every 2 months after the end of your study treatment (only if previous MRI scans have not shown progression of your tumour)

3. Are there risks to me in taking part in this study?

All medical procedures involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. In spite of all reasonable precautions, you might develop medical complications from participating in this study.

The side effects of the following treatments; carboplatin only, bevacizumab only, and carboplatin and bevacizumab in combination are the same as the information supplied in the Participant Information and Consent Form for Part 1 of the study. Please refer to the Part 1 Participant Information and Consent Form or ask the study team for a copy of this document for more information on the treatments discussed above. Please feel free to ask your doctor to repeat or further explain this information.

If you receive etoposide alone, you may experience some, all, or none of the following side effects:

Very common (more than 1 in 10 patients i.e. >10%):
- Changes to the blood including: decreased levels of platelets and white blood cells
- Gastrointestinal effects including: nausea, vomiting, loss of appetite (anorexia), diarrhoea
- Baldness/hair loss

Common (between 1 in 10 and 1 in 100 patients i.e. between 1 and 10%):
- Changes to the blood including: a decrease in the levels of red blood cells, white blood cells and/or platelets
- Gastrointestinal effects including: inflammation within the mouth
- Cardiovascular effects including: low blood pressure

Uncommon (between 1 in 100 and 1 in 1000 patients i.e. <1%):
- Allergic effects including: anaphylactic reaction (fevers, chills, increased heart rate, airway narrowing, shortness of breath and low blood pressure)
- Increased blood pressure, flushing and/or seizures may also occur
- Neurological effects including: effects on the nerves in the arms and legs (may affect strength, ability to feel and reflexes)
- Central nervous system effects including: seizures, drowsiness and fatigue
- Respiratory effects including: fibrosis (scarring) of the lungs, airway narrowing, pauses in breathing for a short time
- Gastrointestinal effects including: abdominal pain, constipation
- Effects on the skin including: rash, pigmentation, itching, hives, dermatitis, soft tissue inflammation, toxic epidermal necrolysis (a skin condition where the top layer of the skin separates from the lower layers), Stevens-Johnson syndrome (a condition characterised by blisters of the skin and mucous membranes (e.g. the mouth) and conjunctivitis which in very rare circumstances results in corneal damage leading to blindness)
- Visual disturbances including: transient loss of vision due to either effects on the brain or inflammation of the optic nerve
• Cardiovascular effects including: heart attack, heart failure
• Effects on the liver including: transient jaundice, increased liver enzymes
• Effects on the kidneys including: increased urea, increased uric acid in the blood
• General effects including: infection/septicaemia, aftertaste, inflammation of mucous membranes (including the oesophagus), difficulty swallowing, weakness and generally feeling unwell (malaise)
• Death due to myelosuppression (a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets)

If you receive temozolomide alone, you may experience some, all, or none of the following side effects:

**Very common** (more than 1 in 10 patients i.e. >10%):
• Gastrointestinal effects including: nausea, vomiting, constipation, poor appetite
• Changes to the blood including: abnormal white blood cell or platelet count
• General effects including: headache, rash, tiredness

**Common** (between 1 in 10 and 1 in 100 patients i.e. between 1 and 10%):
• Neurological effects including: drowsiness, dizziness, pins and needles, weakness
• Gastrointestinal effects including: diarrhoea, abdominal pain, indigestion, altered taste
• Respiratory effects including: breathlessness
• Cardiovascular effects including: palpitations
• Changes to the blood including: decreased levels of haemoglobin (anaemia)
• Effects on the skin including: dermatitis, dry skin, itching
• Abnormal liver function tests
• General effects including: fever, muscle aches and pains, weight loss, thrush, cold sores, sore throat, infection, anxiety, insomnia, cough
• Hair loss (usually mild)

**Uncommon** (between 1 in 100 and 1 in 1000 patients i.e. <1%):
• Shingles
• Serious infection requiring hospital admission and antibiotics
• Dry eyes or eye pain
• Pneumonia
• Serious skin rash, significant damage to the skin or linings of body cavities
• Menstrual abnormalities
• Flushing
• Shakes
• Exhaustion
• Significant abnormalities of liver function tests
• Secondary cancers (cancers possibly caused by the treatment of a previous cancer)
• Allergic reactions (including anaphylaxis which is a sudden and severe allergic reaction and may include breathing difficulty and drop of blood pressure, leading to loss of consciousness or death)

A substantial decrease in white blood cells related to temozolomide may increase your risk of infections. Low platelets related to temozolomide treatment may also increase your risk of bleeding. There is a risk that these blood counts will not return to normal which may further increase your risk of a severe infection or bleed (this is a condition called aplasia). This condition may be prolonged and result in a disease called aplastic anaemia. This is rare but occurs more often when temozolomide is given for a longer period of time.

Other side effects of temozolomide may include chills, upset stomach, redness and oedema (swelling), deep vein thrombosis (blood clots in large veins usually in legs) and pulmonary embolism (blood clots in large blood vessels in the lungs).
If you receive etoposide plus bevacizumab, you may experience some, all or none of the side effects associated with etoposide alone (see page 5) or bevacizumab alone (refer to Patient Information for Part 1 of the study).

In addition, you may experience some, all or none of the following side-effects reported in previous tests of this combination of drugs:

**Very common** (more than 1 in 10 patients i.e. >10%):
- Effects on the blood including: anaemia, decreased levels of white blood cells
- Cardiovascular effects including: fatigue, high blood pressure, blood clots
- Gastrointestinal effects including: nausea, vomiting, elevated levels of liver enzymes
- Genitourinary effects including: excess protein in the urine
- General effects including: infection, inflammation of mucous membranes (linings of body organs and cavities e.g. nose, mouth, eyes)

**Common** (between 1 in 10 and 1 in 100 patients i.e. between 1 and 10%):
- Gastrointestinal effects including: anorexia, diarrhoea
- General effects including: rash

**Uncommon** (between 1 in 100 and 1 in 1000 patients i.e. <1%):

Only adverse events that occurred in at least 10% of patients receiving the combination of etoposide and bevacizumab have been reported in the research testing this combination of drugs. Adverse events occurring in less than 10% of patients receiving etoposide and bevacizumab (in addition to either drug alone) are unknown and therefore cannot be given.

If you receive temozolomide plus bevacizumab, you may experience some, all or none of the side-effects associated with temozolomide alone (see page 6) or bevacizumab alone (refer to Patient Information for Part 1 of the study).

In addition, you may also experience some, all or none of the following side effects reported in previous tests of this combination of drugs:

**Very common** (more than 1 in 10 patients i.e. >10%):
- Effects on the blood including: decreased levels of platelets, anaemia
- Cardiovascular effects including: high blood pressure, fatigue, blood clots in the deep veins, usually legs (deep vein thrombosis) or lungs (pulmonary embolism)
- Gastrointestinal effects including: constipation, nausea, vomiting, elevated levels of liver enzymes
- Neurological effects including: dizziness, seizures, headache
- Respiratory effects including: cough, sinus infection
- Genitourinary effects including: urinary tract infection, excess protein in the urine
- General effects including: oral thrush, hair loss (usually mild)

**Common** (between 1 in 10 and 1 in 100 patients i.e. between 1 and 10%):
- Effects on the blood including: decreased levels of white blood cells
- Gastrointestinal effects including: anorexia
- Bleeding abnormalities including: nosebleed, coughing blood
- Neurological effects including: mood alteration
- Respiratory effects including: vocal changes, pneumonia
- Effects on the skin including: skin or wound infection, wound healing complications, cellulitis (inflammation) and ulceration of the legs
- Other effects including: muscle weakness

**Uncommon** (between 1 in 100 and 1 in 1000 patients i.e. <1%):
- Pancreatitis (inflammation of the pancreas)
Other risk information

Other risk information, including risks associated with blood sampling, intravenous (into the vein) infusions, MRI scans and pregnancy are outlined in the Participant Information for Part 1 of the study and are also applicable to Part 2 of this study.

4. What happens to my treatment when the study is finished?

If you decide not to continue onto Part 2 of the study you and your doctor will decide on what is the most suitable treatment for you at this time.

If you do continue on to Part 2 of the study it is planned that the study will continue for the entire duration during which you are receiving treatment. In the event that the study is terminated whilst you are still receiving treatment, those patients who are continuing to benefit from bevacizumab will have the opportunity to continue that treatment. This decision will be made in consultation with you and your treating doctor.

5. Further Information or Any Problems

If you require further information or if you have any problems concerning this study (for example, any side effects), you can contact the principal investigator or study staff who were involved in Part 1 of this study. The investigator/s responsible for this study are [list the names and contact phone numbers, including after hours numbers]:

Name: [Principal investigator or study team contact person]
Position:
Telephone:

6. Who should I contact if I have concerns about the conduct of this study?

This study has been approved by the Cancer Institute New South Wales Clinical Research Ethics Committee. If you have concerns or complaints about the conduct of this study, you should contact the Ethics Coordinator who is the person nominated by the Human Research Ethics Committee to receive complaints from research participants. You should contact them on (02) 8374 5600 and quote 2010C/07/135.

Position: Ethics Coordinator
Telephone: 02 8374 5600

Thank you for taking the time to consider being part of this study.

If you wish to take part in this study, please sign the attached consent form.

This information sheet is for you to keep.
PARTICIPANT CONSENT FORM: PART 2

I, ....................................................................................................................... [name]
Of.......................................................................................................................[address] have read and understood the Information for Participants on the above named research study. I understand that I am agreeing to participate in a research study.

I have been made aware of the procedures involved in the study, including any known or expected inconvenience, risk, discomfort or side effect, and of their implications as far as they are currently known by the researchers.

I understand that the research project will be carried out according to the principles in the National Health & Medical Research Council National Statement on Ethical Conduct in Human Research.

I freely choose to participate in this study and understand that I can withdraw at any time.

I also understand that the research study is strictly confidential.

I hereby agree to participate in this research study.

NAME: ......................................
SIGNATURE: ......................................
DATE: ......................................

NAME OF INVESTIGATOR: ......................................
SIGNATURE OF INVESTIGATOR: ......................................
DATE: ......................................
PARTICIPANT INFORMATION AND CONSENT FORM

Study Title: A randomised phase II study of Carboplatin and Bevacizumab in Recurrent Glioblastoma Multiforme (CABARET study)

Translational Substudy

Principal Investigator: [name]

This Participant Information and Consent Form is 4 pages long. Please make sure that you have all the pages.

You are being asked to take part in this translational research substudy because you have consented to participate in the CABARET clinical trial: A randomised phase II study of Carboplatin and Bevacizumab in Recurrent Glioblastoma Multiforme.

This Participant Information contains detailed information about the optional translational research substudy. Its purpose is to explain to you as openly and clearly as possible all the procedures involved before you decide whether or not to take part in it.

Please read this Participant Information carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the study with a relative or friend or your local health worker. Feel free to do this.

Once you understand what the substudy is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent form, you indicate that you understand the information and that you give your consent to participate in the substudy.

You will be given a copy of the Participant Information and Consent form to keep as a record.

1. What is the purpose of this study?

We wish to conduct research into all aspects of glioblastoma multiforme (GBM). This includes research into possible biomarkers. A biomarker is a specific trait which can be used to measure the effects of treatment on a disease, or the progress of a disease. We are requesting your consent to allow us to collect tissue and blood samples from you to help identify such biomarkers in patients with GBM.

Up to 120 people in Australia will participate in this translational substudy.

2. What does the study involve?

We are requesting your consent to allow us to collect from you:

- tumour tissue which may have been taken from you previously as a biopsy or during surgery. These tissue samples are routinely stored in pathology departments as required by law. Tumour tissue will be obtained from the hospital/s where your tumour sample is currently stored.
- any other tumour tissue taken from you during your participation on the CABARET clinical trial.
- blood samples: when you first start the study, at 4 and 8 weeks following commencement of study treatment and when your tumour first shows signs of progression. Approximately 10mL or 2 teaspoons of blood will be taken at each collection. At the start of the study, the amount of blood collected will be higher, 20mL (4 teaspoons). These blood tests will be performed at the same time as other routine blood tests.
Participation in this optional translational substudy is voluntary. The choice to participate is entirely up to you. Your ability to participate in the main clinical trial will not be affected in any way by your decision.

3. What will be done with my samples?

Your tissue and blood samples will be sent to Australian and/or International laboratories and/or research organisations for research. This will include research investigating proteins and genes relevant to your cancer. The samples will be used for research purposes only and will not be sold.

Your samples will be stored only with your study number, initials and date of birth. Your samples can only be identified by accessing your medical records. Staff at the research laboratories will not have access to your medical records.

Your samples will be stored at the laboratories for the duration required for the researchers to complete the analysis of the samples. Some tests may not be done until after the CABARET clinical trial has been completed.

Rapid advances in technology make it impossible to predict what new tests or studies may be possible in the future. The tissue and blood samples will only be used for research studies that have been approved by the CABARET trial management committee and a human research ethics committee (HREC).

Whilst the aim of our research is to improve the health of our community, sometimes research may lead to findings that result in the development of a commercial test or treatment. There is no financial reward or payment to you in this event.

4. Protecting your privacy

We seek your consent to access medical information kept about you that is relevant to medical research, including information that may come from hospital case notes and your GP records.

Your details will be held in strict confidence at all times. Tissue and blood samples will be identified by your study number, initials and date of birth and it will not be possible for researchers using them to link this to your personal information themselves. We will abide by all state and Federal Privacy legislation at all times.

5. What will happen with the results?

The tests results from your tissue and blood samples are experimental and not suitable for guiding treatment or decision-making.

You will not be informed of your individual results from these tests.

If you give us your permission by signing the Consent Form, we plan to discuss/publish the results in a medical or scientific journal, at medical or scientific conferences or at other professional meetings. In any publication, information will be provided in such a way that you cannot be identified.

6. What are the potential risks?

**Risks related to tissue sampling** Obtaining your tumour tissue for research involves no further risk to you. The tissue sample for research is obtained from the hospital and will be a sample of your brain tumour tissue that was taken from you previously, either during surgery or a biopsy. This tissue is preserved as formalin-fixed paraffin-embedded blocks. If other tumour material is taken from you during the CABARET clinical trial, it will also be collected and stored by the hospital. In the event that a tumour tissue sample is not available from the hospital, you will not be subjected to any procedures to obtain a sample.

**Risks related to blood sampling** There may be some discomfort, swelling or bruising around the vein that was used to draw your blood. You may experience light-headedness; and fainting at the time of blood drawing could occur. Infection at the blood drawing site may also occur.
7. What are the potential benefits?

It is unlikely that this research will be of direct benefit to you. The results may help us to better understand how to diagnose or treat patients with recurrent GBM more effectively in the future.

8. What if I change my mind?

Your tissue and blood for research will be stored until it is used up or you contact your doctor to request its destruction.

You will retain the right to have the sample material destroyed at any time by notifying your study doctor in writing. If you decide to have your samples destroyed, any data or analyses that were done before the request cannot be removed; however, no additional analysis will be done on your samples, and all of your remaining samples will be destroyed.

9. What happens to my tissue and blood if I die?

In the event of your death, we will continue to store your tissue and blood and make it available to researchers. Your tissue and blood will continue to be used in cancer research subject to the conditions described in section 3.

10. Further Information or Any Problems

If you require further information or if you have any problems concerning this project, you can contact the principal investigator or study staff. Contact details are:

Name:  [Principal Investigator or study team contact person]
Position:
Telephone:

11. Other Issues

This substudy has been approved by the Cancer Institute New South Wales Clinical Research Ethics Committee. If you have concerns or complaints about the conduct of this substudy, you should contact the Ethics Coordinator who is the person nominated by the Human Research ethics Committee to receive complaints from research participants. You should contact them on (02) 8374 5600 and quote 2010C/07/135.

Position:  Ethics Coordinator
Telephone:  (02) 8374 5600

12. Ethical Guidelines

This project will be carried out according to the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research. This statement has been developed to protect the interests of people who agree to participate in human research studies.

Thank you for taking the time to consider being part of this substudy.
If you wish to take part in this substudy, please sign the attached consent form.
This information sheet is for you to keep.
A randomised phase II study of Carboplatin and Bevacizumab in Recurrent Glioblastoma Multiforme (CABARET study)

Translational Substudy

PARTICIPANT CONSENT FORM

I, ....................................................................................................................... [name]

Of........................................................................................................................[address] have read and understood the Information for Participants on the above named research study (Translational Substudy).

I understand that I am agreeing to participate in a research study.

I have been made aware of the procedures involved in the study, including any known or expected inconvenience or risk and of their implications as far as they are currently known by the researchers.

I understand that the research project and any future research projects will be carried out according to the principles in the National Health & Medical Research Council National Statement on Ethical Conduct in Human Research.

I freely choose to donate my tissue and blood samples for research and understand that I can withdraw them at any time.

I also understand that the results of the research studies and data may be published provided that I cannot be identified.

I understand that I will not benefit financially if this research leads to development of a new treatment or medical test.

I hereby agree to participate in this research study and consent to my tissue and blood being stored and made available for research.

NAME: ..............................................................................................................

SIGNATURE: ......................................................................................................

DATE: ..................................................................................................................

NAME OF INVESTIGATOR: ...............................................................................

SIGNATURE OF INVESTIGATOR: .................................................................

DATE: ..................................................................................................................
PARTICIPANT INFORMATION AND CONSENT FORM

Study Title: A randomised phase II study of Carboplatin and Bevacizumab in Recurrent Glioblastoma Multiforme (CABARET study)

Principal Investigator: [name]

This Participant Information and Consent Form is 4 pages long. Please make sure that you have all the pages.

You are being asked to take part in this translational research substudy because you have consented to participate in the CABARET clinical trial: A randomised phase II study of Carboplatin and Bevacizumab in Recurrent Glioblastoma Multiforme.

This Participant Information contains detailed information about the optional translational research substudy. Its purpose is to explain to you as openly and clearly as possible all the procedures involved before you decide whether or not to take part in it.

Please read this Participant Information carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the study with a relative or friend or your local health worker. Feel free to do this.

Once you understand what the substudy is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent form, you indicate that you understand the information and that you give your consent to participate in the substudy.

You will be given a copy of the Participant Information and Consent form to keep as a record.

1. What is the purpose of this study?

We wish to conduct research into all aspects of glioblastoma multiforme (GBM). This includes research into possible biomarkers. A biomarker is a specific trait which can be used to measure the effects of treatment on a disease, or the progress of a disease. We are requesting your consent to allow us to collect tissue and blood samples from you to help identify such biomarkers in patients with GBM.

Up to 120 people in Australia will participate in this translational substudy

2. What does the study involve?

We are requesting your consent to allow us to collect from you:

- tumour tissue which may have been taken from you previously as a biopsy or during surgery. These tissue samples are routinely stored in pathology departments as required by law. Tumour tissue will be obtained from the hospital/s where your tumour sample is currently stored.
- any other tumour tissue taken from you during your participation on the CABARET clinical trial.
- one blood sample of approximately 10mL (2 teaspoons) of blood taken during one of your scheduled study visits. This blood test will be performed at the same time as a routine blood tests.
3. What will be done with my samples?

Your tissue and blood samples will be sent to Australian and/or International laboratories and/or research organisations for research. This will include research investigating proteins and genes relevant to your cancer. The samples will be used for research purposes only and will not be sold.

Your samples will be stored only with your study number, initials and date of birth. Your samples can only be identified by accessing your medical records. Staff at the research laboratories will not have access to your medical records.

Your samples will be stored at the laboratories for the duration required for the researchers to complete the analysis of the samples. Some tests may not be done until after the CABARET clinical trial has been completed.

Rapid advances in technology make it impossible to predict what new tests or studies may be possible in the future. The tissue and blood samples will only be used for research studies that have been approved by the CABARET trial management committee and a human research ethics committee (HREC).

Whilst the aim of our research is to improve the health of our community, sometimes research may lead to findings that result in the development of a commercial test or treatment. There is no financial reward or payment to you in this event.

4. Protecting your privacy

We seek your consent to access medical information kept about you that is relevant to medical research, including information that may come from hospital case notes and your GP records.

Your details will be held in strict confidence at all times. Tissue and blood samples will be identified by your study number, initials and date of birth and it will not be possible for researchers using them to link this to your personal information themselves. We will abide by all state and Federal Privacy legislation at all times.

5. What will happen with the results?

The tests results from your tissue and blood samples are experimental and not suitable for guiding treatment or decision-making.

You will not be informed of your individual results from these tests.

If you give us your permission by signing the Consent Form, we plan to discuss/publish the results in a medical or scientific journal, at medical or scientific conferences or at other professional meetings. In any publication, information will be provided in such a way that you cannot be identified.

6. What are the potential risks?

Risks related to tissue sampling Obtaining your tumour tissue for research involves no further risk to you. The tissue sample for research is obtained from the hospital and will be a sample of your brain tumour tissue that was taken from you previously, either during surgery or a biopsy. This tissue is preserved as formalin-fixed paraffin-embedded blocks. If other tumour material is taken from you during the CABARET clinical trial, it will also be collected and stored by the hospital. In the event that a tumour tissue sample is not available from the hospital, you will not be subjected to any procedures to obtain a sample.

Risks related to blood sampling There may be some discomfort, swelling or bruising around the vein that was used to draw your blood. You may experience light-headedness; and fainting at the time of blood drawing could occur. Infection at the blood drawing site may also occur.
7. What are the potential benefits?
It is unlikely that this research will be of direct benefit to you. The results may help us to better understand how to diagnose or treat patients with recurrent GBM more effectively in the future.

8. What if I change my mind?
Your tissue and blood for research will be stored until it is used up or you contact your doctor to request its destruction.
You will retain the right to have the sample material destroyed at any time by notifying your study doctor in writing. If you decide to have your samples destroyed, any data or analyses that were done before the request cannot be removed; however, no additional analysis will be done on your samples, and all of your remaining samples will be destroyed.

9. What happens to my tissue and blood if I die?
In the event of your death, we will continue to store your tissue and blood and make it available to researchers. Your tissue and blood will continue to be used in cancer research subject to the conditions described in section 3.

10. Further Information or Any Problems
If you require further information or if you have any problems concerning this project, you can contact the principal investigator or study staff. Contact details are:

Name: [Principal Investigator or study team contact person]
Position:
Telephone:

11. Other Issues
This substudy has been approved by the Cancer Institute New South Wales Clinical Research Ethics Committee. If you have concerns or complaints about the conduct of this substudy, you should contact the Ethics Coordinator who is the person nominated by the Human Research ethics Committee to receive complaints from research participants. You should contact them on (02) 8374 5600 and quote 2010C/07/135.

Position: Ethics Coordinator
Telephone: (02) 8374 5600

12. Ethical Guidelines
This project will be carried out according to the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research. This statement has been developed to protect the interests of people who agree to participate in human research studies.

Thank you for taking the time to consider being part of this substudy.
If you wish to take part in this substudy, please sign the attached consent form.
This information sheet is for you to keep.
A randomised phase II study of Carboplatin and Bevacizumab in Recurrent Glioblastoma Multiforme (CABARET study)

Translational Substudy

PARTICIPANT CONSENT FORM

I, ....................................................................................................................... [name]

Of........................................................................................................................[address] have read and understood the Information for Participants on the above named research study (Translational Substudy).

I understand that I am agreeing to participate in a research study.

I have been made aware of the procedures involved in the study, including any known or expected inconvenience or risk and of their implications as far as they are currently known by the researchers.

I understand that the research project and any future research projects will be carried out according to the principles in the National Health & Medical Research Council National Statement on Ethical Conduct in Human Research.

I freely choose to donate my tissue and blood samples for research and understand that I can withdraw them at any time.

I also understand that the results of the research studies and data may be published provided that I cannot be identified.

I understand that I will not benefit financially if this research leads to development of a new treatment or medical test.

I hereby agree to participate in this research study and consent to my tissue and blood being stored and made available for research.

NAME: ...........................................................................................................

SIGNATURE: ..............................................................................................

DATE: .........................................................................................................

NAME OF INVESTIGATOR: ...........................................................................

SIGNATURE OF INVESTIGATOR: ..............................................................

DATE: .........................................................................................................
## Appendix 2: List of abbreviations and terms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADRs</td>
<td>Adverse Drug Reactions</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ANC</td>
<td>Absolute neutrophil count</td>
</tr>
<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>COGNO</td>
<td>Cooperative Trials Group for Neuro-Oncology</td>
</tr>
<tr>
<td>CR</td>
<td>Complete response</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>CTC</td>
<td>NHMRC Clinical Trials Centre</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>CVAD</td>
<td>Central venous access device</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>EGF</td>
<td>Epidermal Growth Factor</td>
</tr>
<tr>
<td>EGFR</td>
<td>Epidermal Growth Factor Receptor</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>(e-)CRFs</td>
<td>(Electronic) case report forms</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>FBC</td>
<td>Full Blood Count</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FFPE</td>
<td>Formalin-fixed paraffin-embedded</td>
</tr>
<tr>
<td>GBM</td>
<td>Glioblastoma multiforme</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>Gd-MRI</td>
<td>Gadolinium-enhanced MRI</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>HGF</td>
<td>Hepatocyte growth factor</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>HRQL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IDH</td>
<td>Isocitrate dehydrogenase</td>
</tr>
<tr>
<td>IGFBP2</td>
<td>Insulin-like growth factor-binding protein 2</td>
</tr>
<tr>
<td>IHC</td>
<td>Immunohistochemistry</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>INR</td>
<td>International Normalised Ratio</td>
</tr>
<tr>
<td>ISF</td>
<td>Investigator site file</td>
</tr>
<tr>
<td>ISH</td>
<td>In situ hybridization</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>L</td>
<td>Litre</td>
</tr>
<tr>
<td>LIF</td>
<td>Leukaemia inhibitory factor</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low molecular weight heparin</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>MGMT</td>
<td>Methylguanine methyltransferase</td>
</tr>
<tr>
<td>mL</td>
<td>Millilitre</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-Mental State Examination</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>mTOR</td>
<td>Mammalian target of rapamycin</td>
</tr>
<tr>
<td>NABTC</td>
<td>North American Brain Tumor Coalition</td>
</tr>
<tr>
<td>NCF</td>
<td>Neurocognitive function</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>OR</td>
<td>Overall response</td>
</tr>
<tr>
<td>ORR</td>
<td>Objective response rate</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression-free survival</td>
</tr>
<tr>
<td>PICC</td>
<td>Peripherally inserted central catheter</td>
</tr>
<tr>
<td>PR</td>
<td>Partial response</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin time</td>
</tr>
<tr>
<td>PTT</td>
<td>Partial thromboplastin time</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RANO</td>
<td>Response Assessment in Neuro-Oncology</td>
</tr>
<tr>
<td>RCR</td>
<td>Roche Clinical Repository</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumours</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>RPLS</td>
<td>Reversible posterior leucoencephalopathy syndrome</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>reverse transcription polymerase chain reaction</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical analysis plan</td>
</tr>
<tr>
<td>SD</td>
<td>Stable disease</td>
</tr>
<tr>
<td>SDMC</td>
<td>Safety Data Monitoring Committee</td>
</tr>
<tr>
<td>SPD</td>
<td>Sum of the products of the diameters</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected unexpected serious adverse reaction</td>
</tr>
<tr>
<td>TEC</td>
<td>Trial Executive Committee</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
</tr>
<tr>
<td>TGF</td>
<td>transforming growth factor</td>
</tr>
<tr>
<td>TMA</td>
<td>tissue microarray</td>
</tr>
<tr>
<td>TMC</td>
<td>Trial Management Committee</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
</tr>
<tr>
<td>VEGFR</td>
<td>Vascular endothelial growth factor Receptor</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Appendix 3: List of chemotherapy agents which are acceptable options for treatment in Part 2

1. Temozolomide (oral)
   a. 150-200mg/m\(^2\) daily for 5 days out of every 28 day treatment cycle,
   OR;
   b. 75mg/m\(^2\) daily for 20 days out of every 28 day treatment cycle.

2. Etoposide (oral)
   50mg/m\(^2\) daily for 20 days out of every 28 day treatment cycle.

We recommend rounding down to the nearest capsule size, at site Investigator discretion.
## Appendix 4: ECOG and Karnofsky performance status

### ECOG Performance Status

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Source:

### Karnofsky Performance Status

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some signs or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or to do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most of his personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; required special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospital admission is indicated although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospital admission necessary; active supportive treatment necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Source:
## Appendix 5: Health-related quality of life (HRQL) forms

### EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: 

Your birthdate (Day, Month, Year):  

Today's date (Day, Month, Year):  

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Do you have any trouble taking a long walk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Do you have any trouble taking a short walk outside of the house?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Do you need to stay in bed or a chair during the day?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Do you need help with eating, dressing, washing yourself or using the toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Were you limited in doing either your work or other daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Were you limited in pursuing your hobbies or other leisure time activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Were you short of breath?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Have you had pain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Did you need to rest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Have you had trouble sleeping?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Have you felt weak?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Have you lacked appetite?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Have you felt nauseated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Have you vomited?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16. Have you been constipated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please go on to the next page
### During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Have you had diarrhea?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Were you tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Did pain interfere with your daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21. Did you feel tense?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Did you worry?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. Did you feel irritable?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. Did you feel depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25. Have you had difficulty remembering things?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. Has your physical condition or medical treatment interfered with your family life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27. Has your physical condition or medical treatment interfered with your social activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>28. Has your physical condition or medical treatment caused you financial difficulties?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

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EORTC QLQ - BN20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>31. Did you feel uncertain about the future?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32. Did you feel you had setbacks in your condition?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33. Were you concerned about disruption of family life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>34. Did you have headaches?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>35. Did your outlook on the future worsen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>36. Did you have double vision?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>37. Was your vision blurred?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>38. Did you have difficulty reading because of your vision?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>39. Did you have seizures?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>40. Did you have weakness on one side of your body?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>41. Did you have trouble finding the right words to express yourself?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>42. Did you have difficulty speaking?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>43. Did you have trouble communicating your thoughts?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>44. Did you feel drowsy during the daytime?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>45. Did you have trouble with your coordination?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>46. Did hair loss bother you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>47. Did itching of your skin bother you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>48. Did you have weakness of both legs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>49. Did you feel unsteady on your feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>50. Did you have trouble controlling your bladder?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

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Health Questionnaire

(English version for Australia)
By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

<table>
<thead>
<tr>
<th>Mobility</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no problems in walking around</td>
<td>✔️</td>
</tr>
<tr>
<td>I have some problems in walking around</td>
<td></td>
</tr>
<tr>
<td>I am confined to bed</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Personal Care</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no problems with personal care</td>
<td>✔️</td>
</tr>
<tr>
<td>I have some problems washing or dressing myself</td>
<td></td>
</tr>
<tr>
<td>I am unable to wash or dress myself</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Usual Activities (e.g. work, study, housework, family or leisure activities)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no problems with performing my usual activities</td>
<td>✔️</td>
</tr>
<tr>
<td>I have some problems with performing my usual activities</td>
<td></td>
</tr>
<tr>
<td>I am unable to perform my usual activities</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain/Discomfort</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no pain or discomfort</td>
<td>✔️</td>
</tr>
<tr>
<td>I have moderate pain or discomfort</td>
<td></td>
</tr>
<tr>
<td>I have extreme pain or discomfort</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anxiety/Depression</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I am not anxious or depressed</td>
<td>✔️</td>
</tr>
<tr>
<td>I am moderately anxious or depressed</td>
<td></td>
</tr>
<tr>
<td>I am extremely anxious or depressed</td>
<td></td>
</tr>
</tbody>
</table>

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To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.
Appendix 6: Mini-Mental State Examination (MMSE) form

**Date of Examination / /** Examiner ____________________________ Years of
Name ____________________________ Age ______ School Completed ______

**Instructions:** Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee’s primary language. Circle 0 if the response is incorrect, or 1 if the response is correct. Begin by asking the following two questions:

Do you have any trouble with your memory? **May I ask you some questions about your memory?**

**ORIENTATION TO TIME**

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the... year?</td>
<td>0</td>
</tr>
<tr>
<td>season?</td>
<td>0</td>
</tr>
<tr>
<td>month of the year?</td>
<td>0</td>
</tr>
<tr>
<td>day of the week?</td>
<td>0</td>
</tr>
<tr>
<td>date?</td>
<td>0</td>
</tr>
</tbody>
</table>

**ORIENTATION TO PLACE**

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Where are we now? What is the... state (province)?</td>
<td>0</td>
</tr>
<tr>
<td>county (or city/town)?</td>
<td>0</td>
</tr>
<tr>
<td>city/town (or part of city/neighborhood)?</td>
<td>0</td>
</tr>
<tr>
<td>building (name or type)?</td>
<td>0</td>
</tr>
<tr>
<td>floor of the building (room number or address)?</td>
<td>0</td>
</tr>
</tbody>
</table>

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and scored.

**REGISTRATION**

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are... APPLE [pause], PENNY [pause], TABLE [pause]. Now repeat those words back to me. [Repeat up to 5 times, but score only the first trial.]

APPLE
PENNY
TABLE

Now keep those words in mind. I am going to ask you to say them again in a few minutes.

*Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and scored when retesting an examinee.

**ATTENTION AND CALCULATION [Serial 7s]**

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7? [93]
If needed, say: Keep going.
If needed, say: Keep going.
If needed, say: Keep going.
If needed, say: Keep going.

*Alternative item (WORLD backward) should only be administered if the examinee refuses to perform the Serial 7s task.

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Appendix 6: Mini-mental state examination form   ©NHMRC Clinical Trials Centre

Substitute and score this item only if the examinee refuses to perform the Serial 7s task.

**Spell WORLD forward, then backward.**
Correct forward spelling if misspelled, but score only the backward spelling.

<table>
<thead>
<tr>
<th>RECALL</th>
<th>RESPONSE</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(D = 1)</td>
<td>(L = 1)</td>
</tr>
<tr>
<td></td>
<td>(R = 1)</td>
<td>(W = 1)</td>
</tr>
<tr>
<td></td>
<td>(O = 1)</td>
<td>(0 to 5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What were those three words I asked you to remember? [Do not offer any hints.]

| APPLE  | 0  |
| PENNY  | 1  |
| TABLE  | 0  |

**Naming**

What is this? [Point to a pencil or pen.]

What is this? [Point to a watch.]

*Alternative common objects (e.g., eyeglasses, chair, keys) may be substituted and noted.

**Repetition**

Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that.

[Repeat up to 5 times, but score only the first trial.]

| NO IFS, ANDS, OR BUTS. | 0  |

Detach the next page along the lengthwise perforation, and then tear it in half along the horizontal perforation. Use the upper half of the page (blank) for the Comprehension, Writing, and Drawing items that follow. Use the lower half of the page as a stimulus form for the Reading ("CLOSE YOUR EYES") and Drawing (intersecting pentagons) items.

**Comprehension**

Listen carefully because I am going to ask you to do something.
Take this paper in your right hand [pause], fold it in half [pause], and put it on the floor (or table).

| TAKE IN RIGHT HAND | 0  |
| FOLD IN HALF | 0  |
| PUT ON FLOOR (or TABLE) | 0  |

**Reading**

Please read this and do what it says. [Show examinee the words on the stimulus form.]

| CLOSE YOUR EYES | 0  |

**Writing**

Please write a sentence. [If examinee does not respond, say: Write about the weather.]

Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.

**Drawing**

Please copy this design. [Display the intersecting pentagons on the stimulus form.]

Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure.

Assessment of level of consciousness.

<table>
<thead>
<tr>
<th>Alert/Responsive</th>
<th>Drowsy</th>
<th>Stuporous</th>
<th>Comatose/Unresponsive</th>
</tr>
</thead>
</table>

Total Score = 

(Sum all item scores.) (30 points max.)
CLOSE YOUR EYES
In the present study, adverse events and/or adverse drug reactions (ADRs) will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address:


Grading of AEs not listed in NCI CTC v4.0:

<table>
<thead>
<tr>
<th>CTC grade</th>
<th>Equivalent to</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Mild</td>
<td>Discomfort noticed but no disruption of normal daily activity</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate</td>
<td>Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the subject</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe</td>
<td>Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the subject at direct risk</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life threatening/disabling</td>
<td>An immediate threat to life or leading to a permanent mental or physical condition that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death</td>
<td>AE resulting in death</td>
</tr>
</tbody>
</table>
Appendix 8: Modified Macdonald criteria

Modified Macdonald Criteria Quick Reference

Definitions

Measurable Disease - the presence of at least one bi-dimensionally measurable lesion.

Measurable Lesions - Bi-dimensionally contrast-enhancing lesions with clearly defined margins by MRI scan, with two perpendicular diameters of at least 10mm, visible on 2 or more axial slices that are preferably, at most, 5mm thick with 0mm skip (or at least two times the slice thickness if the MRI is performed with thicker slices).

Non-measurable Lesions – Either unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10mm. Cysts and surgical cavities should be considered non-measurable unless there is a nodular component measuring ≥ 10mm.

Methods of Measurement

- MRI is the best currently available and reproducible method to measure target lesions selected for response assessment.

Baseline Documentation of Enhancing Lesions

- All measurable lesions up to a maximum of 5 lesions should be identified as target lesions and recorded and measured during screening.
- Enhancing lesions should be selected on the basis of their size (lesions with the largest cross sectional area) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the cross sectional areas for all enhancing lesions will be calculated and reported as the baseline sum cross-sectional areas. The baseline cross sectional areas will be used as reference by which to characterise the objective tumour.

Response Criteria

Evaluation of Lesions

Complete Response (CR): Disappearance of all enhancing tumour on consecutive MRI imaging scans at least 4 weeks apart, off steroids and neurologically stable or improved.

Partial Response (PR): ≥ 50% reduction in size of enhancing tumour on consecutive MRI scans at least 4 weeks apart, steroids stable or reduced and neurologically stable or improved.

Progressive Disease (PD):
≥ 25% increase in size of enhancing tumour
OR any new tumour on MRI scans,
OR neurologically worse, and steroids stable or increased.

Stable Disease (SD): All other situations
Evaluation of Best Overall Response

The best overall response (OR) is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of measurable disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

Duration of Overall Response

- The duration of overall response is measured from the time measurement criteria are met for complete response or partial response (whichever status is recorded first) until the first date that recurrence or progressive disease is objectively documented, taking as reference for progressive disease the smallest measurements recorded since the treatment started.

- SD is measured from the start of the treatment until the criteria for measurable disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

Neurological Evaluation: will be recorded as:

1. Improved
2. Stable
3. Worse
## Appendix 9: Proposed T2/FLAIR grading

### Proposed T2 / FLAIR grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>&gt;50% decrease in size of T2 / FLAIR abnormality</td>
</tr>
<tr>
<td>-1</td>
<td>25-50% decrease in size of T2 / FLAIR abnormality</td>
</tr>
<tr>
<td>0</td>
<td>Stable (±/ - 25% from nadir T2/FLAIR appearance)</td>
</tr>
<tr>
<td>+1</td>
<td>25-50% increase in size of T2 / FLAIR abnormality</td>
</tr>
<tr>
<td>+2</td>
<td>&gt;50% increase in size of T2 / FLAIR abnormality</td>
</tr>
</tbody>
</table>

Changes in T2 / FLAIR abnormality which are clearly due to non-gliomatous pathology e.g. stroke should be documented but excluded from the grading assessment.
Appendix 10: Modified RANO criteria

The following information is taken from Wen et al JCO 2010 with inclusion of proposed T2 / FLAIR grading.

Criteria for Response Assessment Incorporating MRI and Clinical Factors

Complete Response requires all of the following:

a) Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan ≥ 4 weeks later, this scan will be considered only stable disease*
b) No new lesions
c) All measurable and non-measurable lesions must be assessed using the same techniques as baseline
d) Patients must be on no steroids or physiologic replacement doses only
e) Stable or improved non-enhancing (T2/FLAIR) lesions (T2 / FLAIR grade -2 to 0)
f) Stable or improved clinically

Note: Patients with non-measurable disease cannot have a complete response. The best response possible is stable disease.

Partial Response requires all of the following:

a) Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan ≥ 4 weeks later, this scan will be considered only stable disease*
b) No progression of non-measurable disease
c) No new lesions
d) All measurable and nonmeasurable lesions must be assessed using the same techniques as baseline
e) The steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan
f) Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan (T2 / FLAIR grade -2 to 0)
g) Stable or improved clinically

Note: Patients with non-measurable disease cannot have a partial response. The best response possible is stable disease.

Stable Disease requires all of the following:

a) Does not qualify for CR, PR, or progression
b) All measurable and non-measurable sites must be assessed using the same techniques as baseline
c) Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose has been increased, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose (T2 / FLAIR grade -2 to 0)
d) Stable clinically

Abbreviations: CR, complete response;  
MRI, magnetic resonance imaging;  
PR, partial response.
Criteria to Determine Progression

**Progression is defined by any of the following:**

a) ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumour measurement obtained either at baseline (if no decrease) or best response on stable or increasing doses of corticosteroids (Note: the 4-week MRI should not be used as a comparator scan for disease assessments)

b) Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events (radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects) *(T2 / FLAIR grade +1 or +2)*

c) Any new lesion

d) Clear clinical deterioration not attributable to other causes apart from the tumour (e.g., seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.). The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decrease in 20% of KPS or from baseline to 50% or less be considered, unless attributable to co-morbid events

e) Failure to return for evaluation due to death or deteriorating condition

f) Clear progression of non-measurable disease

In general, if there is doubt about whether there is progression, continued treatment and close follow-up evaluation is recommended.

Abbreviation: KFS, Karnofsky Performance Status.

*Confirming scan can be ≥ 4 weeks later rather than 4 weeks later, as per personal communication with Dr Wen (19 January 2011).

**Source:**

**Appendix 11: Procedures for obtaining urine protein/creatinine (UPC) ratio**

Proteinuria will be monitored by urine dipstick analysis every 2 weeks (for patients receiving bevacizumab). If the dipstick shows ≥ 2+ protein, then either a UPC ratio or a 24 hour urine collection is required.

Obtaining the UPC ratio requires at least 4 mL of a random urine sample (does not have to be a 24-hour urine).

The local laboratory will determine the urine protein/creatinine ratio by using the following formula:

\[
\text{Urine protein/creatinine ratio} = \frac{\text{protein concentration}}{\text{creatinine concentration}}
\]

The UPC ratio directly correlates with the amount of protein excreted in the urine per 24 hours (i.e., a UPC ratio of 1 should be equivalent to 1 g of protein in a 24-hour urine collection). Protein and creatinine concentrations should be available on standard reports of urinalyses, not dipsticks. If protein and creatinine concentrations are not routinely reported at an institution, their measurements and reports may need to be requested.
Appendix 12: Cockcroft-Gault equation for calculation of creatinine clearance

Cockroft Gault GFR/creatinine clearance (mL/min) = \(\frac{(140 - \text{age}) \times \text{weight in kg}}{0.814 \times \text{Cr} \,[\mu\text{mol/L}]}\) \times (0.85 \text{ if female})

Source:
Cockcroft D, Gault MD. Nephron, 16:31-41, 1976
## Appendix 13: Relative potencies of commonly used steroids

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>Relative glucocorticoid potency</th>
<th>Equivalent dose for glucocorticoid effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>20mg</td>
</tr>
<tr>
<td>Cortisone acetate</td>
<td>0.8</td>
<td>25mg</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25-50</td>
<td>400-800 micrograms</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4</td>
<td>5mg</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>4mg</td>
</tr>
</tbody>
</table>

**Source:**
Appendix 2: Field et al: Review Article (Bevacizumab in glioma)
Bevacizumab and Glioblastoma: Scientific Review, Newly Reported Updates, and Ongoing Controversies

Kathryn M. Field, MD1; Justin T. Jordan, MD2; Patrick Y. Wen, MD2; Mark A. Rosenthal, MD1; and David A. Reardon, MD2

Antiangiogenic therapy for glioblastoma has been in the spotlight for several years, as researchers and clinicians strive to find agents with meaningful efficacy against glioblastoma. Bevacizumab in particular, in the second half of the last decade, became the most significant breakthrough in anti-glioblastoma therapy since temozolomide. Optimism for bevacizumab has been somewhat challenged given recent clinical trials that have raised questions regarding its clinical effectiveness, the optimal timing of its use and the validity of endpoints, among other issues. In addition, uncertainty has recently arisen regarding the effects of bevacizumab on quality of life and neurocognitive function, two key clinical endpoints of unquestionable significance among glioblastoma patients. In this review, we highlight these controversies and other recent work related to bevacizumab for glioblastoma.


KEYWORDS: glioblastoma, bevacizumab, angiogenesis, vascular endothelial growth factor, malignant glioma.

INTRODUCTION

Glioblastoma is the most common and most aggressive primary parenchymal brain tumor. Despite our best known therapy (using concurrent radiotherapy and chemotherapy with temozolomide followed by at least 6 months of adjuvant temozolomide), the average survival is only approximately 15 months. In the inevitably recurrent setting of this disease, to our knowledge arguably no chemotherapy regimen has provided reliable or meaningful clinical benefit. In light of these suboptimal outcomes, ongoing investigations aim to identify alternative therapies to complement or replace older cytotoxic therapies. Along these lines, antiangiogenic therapy for glioblastoma has been in the spotlight for several years.

Angiogenesis and the Role of Antiangiogenesis in Patients With Glioblastoma

Tumor angiogenesis correlates to the pathologic grade of gliomas, and is controlled through a complex balance of angiogenic factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor, hypoxia-inducible factor 1α, and others. Considered chief among these is VEGF, which may be upregulated via multiple angiogenesis-promoting pathways. In hypoxic conditions, commonly found as tumors outgrow their intrinsic blood supply, hypoxia-inducible factor 1α accumulates and ultimately increases VEGF stabilization. However, even in the absence of hypoxia, VEGF is often upregulated in glioblastoma through constitutive activation of mitogenic pathways such as Ras/mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/akt, which increase VEGF downstream.

An additional means by which angiogenesis occurs in glioblastoma is through so-called vascular mimicry. Separate from blood vessels produced through the angiogenic signaling described above, glioma stem-like cells have been shown to differentiate into vascular endothelial cells both in culture and in xenografts. These non-VEGF-dependent endothelial cells hold genetic markers similar to the surrounding glioma tissue, such as amplification of epidermal growth factor receptor or mutation of TP53.

Early studies regarding antiangiogenic therapy were based on the hypothesis of inflicting direct endothelial injury to vessels, inducing blood vessel pruning and therefore reduced delivery of nutrients and oxygen to highly metabolic tumor cells. However, over the ensuing decades, subsequent studies suggested that tumor blood vessels are intrinsically abnormal in both structure and function. Based on this understanding, another potential mechanism of antiangiogenic therapy...
that has emerged is vascular normalization, which leads to increased chemotherapy delivery and improved radiation effect through enhanced oxygen delivery.\textsuperscript{9,15-17}

**Early Study of Bevacizumab in Patients With Recurrent Glioblastoma**

Because of its importance in angiogenesis, targeted efforts to block VEGF pathways have been ongoing for the past several years, focusing on monoclonal antibodies and tyrosine kinase inhibitors. To the best of our knowledge, the earliest and most resonant clinical successes involve bevacizumab, a recombinant humanized monoclonal antibody against VEGF-A, composed of human immunoglobulin (Ig) G1 constant and murine VEGF-binding regions.\textsuperscript{18} In preclinical models, bevacizumab inhibited angiogenesis and tumor growth, and was noted to augment the antitumor effects of chemotherapy and radiotherapy.\textsuperscript{19-23} Phase 1 studies in various solid tumors demonstrated a half-life of nearly 3 weeks, and no dose-limiting toxicities.\textsuperscript{24,25} With this safety information, and in light of remarkable successes in other cancers including those of the breast and colon, oncologists began to use bevacizumab for the treatment of patients with recurrent glioblastoma. In the first such report, 21 patients were presented who received bevacizumab and irinotecan as salvage therapy for recurrent glioblastoma.\textsuperscript{26} An unusually robust rate of radiographic response was reported in 9 of 21 patients, and 11 of 21 patients achieved stable disease. With these early positive data and little toxicity, further study was proposed.

Two single-arm, prospective, phase 2 studies by Vredenburgh et al followed, describing the use of bevacizumab and irinotecan as salvage therapy for recurrent high-grade gliomas in a total of 67 patients.\textsuperscript{27,28} Radiographic response in these studies was demonstrated in approximately 60% of patients, and the 6-month progression-free survival (PFS) rate was 38% to 46%. In comparison, contemporary data for other salvage regimens at that time demonstrated radiographic response in 5% to 10% of patients, and a 6-month PFS rate of 9% to 15%.\textsuperscript{2,29,30}

---

**Figure 1.** XRT indicates radiotherapy; TMZ, temozolomide; BEV, bevacizumab; GBM, glioblastoma multiforme; EORTC, European Organization for Research and Treatment of Cancer.
Propelled further by this clinical success, the pivotal AVF3708g/BRAIN trial came next, which was a randomized, noncontrolled, phase 2 study evaluating the activity of bevacizumab monotherapy and bevacizumab plus irinotecan in 167 patients. In this study, using the criteria of Macdonald et al,\textsuperscript{31} radiographic response was noted in 28% and 38% of patients, respectively, and the 6-month PFS rate was reported at 42.6% and 50.3%, respectively.\textsuperscript{32} An additional single-arm phase 2 study of bevacizumab monotherapy in 48 patients published the same year demonstrated radiographic response in 35% of patients, and a 6-month PFS rate of 29%.\textsuperscript{33} A total of 19 patients went on to receive bevacizumab plus irinotecan at the time of second disease progression, but no subsequent responses were observed. The combination of these findings, along with minimal reported toxicity, led to the accelerated approval by the US Food and Drug Administration (FDA) in 2009 for the use of bevacizumab in the treatment of recurrent glioblastoma, pending further phase 3 study.\textsuperscript{34} However, it is interesting to note that the European Medicines Agency did not approve bevacizumab for use in recurrent glioblastoma at that time, and still had not as of early 2014. The lack of European approval is cited to be a result of there being no placebo-controlled data, and due to uncertain validity of the demonstrated outcome measures as a surrogate for true clinical benefit.\textsuperscript{35,36}

**Bevacizumab-Based Regimens in Patients With Recurrent Glioblastoma**

Multiple subsequent studies have been reported since provisional FDA approval, seeking to better define outcomes for bevacizumab, as well as to improve on them with alternative chemotherapy combinations. A prospective phase 2 study using every-3-week dosing of bevacizumab at a dose of 15 mg/kg in 61 patients with World Health Organization grade 3 or grade 4 glioma demonstrated no obvious differences in patient outcomes compared with contemporary studies using every-2-week dosing at 10 mg/kg,\textsuperscript{37} thus allowing for flexibility in patient scheduling without clinical detriment. Several phase 2 trials of bevacizumab-based combinations have also been reported for recurrent glioblastoma (Table 1),\textsuperscript{27,28,32,38-58} including bevacizumab with irinotecan, irinotecan plus cetuximab, irinotecan plus carboplatin, etoposide, fotemustine, sorafenib, temozolomide, erlotinib, and temsirilimus.\textsuperscript{27,28,32,38-41} In addition, several retrospective studies have also been reported combining bevacizumab and irinotecan; carboplatin; carboplatin and cetuximab; carboplatin, etoposide, and ifosfamide; lomustine; carbustine; etoposide; or temozolomide.\textsuperscript{48-58}

Although these small studies are not easily compared due to their size and various patient populations, the consensus to date has been that no combination significantly surpasses the outcomes of bevacizumab monotherapy for recurrent glioma.\textsuperscript{9}

**Newly Reported Bevacizumab Trials**

Preliminary results of several other trials involving bevacizumab for the treatment of glioblastoma have recently been presented (Table 2).\textsuperscript{32,59-68} The randomized phase 2 GLARIUS trial compared bevacizumab, irinotecan, and radiotherapy versus standard temozolomide and radiation in patients with O\textsuperscript{6}-methylguanine-methyltransferase (MGMT)-unmethylated, newly diagnosed glioblastoma.\textsuperscript{59} This study found the combination of bevacizumab and irinotecan with radiotherapy to be more favorable than standard therapy, with the 6-month PFS rate reported at 79.5% versus 41.3%, and a mean PFS of 9.7 months versus 6 months, respectively. Preliminary overall survival (OS) results were statistically significant, with a median OS of 16.6 months versus 14.8 months.

In the recurrent glioblastoma setting, the BELOB phase 2 study randomized 148 patients at the time of first recurrence into 3 treatment arms of bevacizumab monotherapy, lomustine monotherapy, or bevacizumab plus lomustine.\textsuperscript{60} In this study, patients in the combination arm had better outcomes than patients in either of the monotherapy arms, with the primary endpoint of 9-month OS rate of 38% versus 43% versus 59%, respectively. In addition, the median OS was 8 months versus 8 months versus 11 months, respectively, with an impressive improvement in the 6-month PFS rate at 18% versus 11% versus 41%, respectively. This is an important study in that it included a control arm that did not receive bevacizumab, thus providing the first randomized comparison between bevacizumab and chemotherapy. In addition, we also believe it to be the first study to demonstrate a survival benefit of chemotherapy added to bevacizumab in comparison with single-agent bevacizumab. The authors concluded that a phase 3 follow-up study was warranted based on these findings, and the current European Organization for Research and Treatment of Cancer (EORTC) 26101 study has been modified accordingly to a 2-arm phase 3 trial comparing lomustine plus bevacizumab versus lomustine monotherapy.

It is notable that the 6-month PFS rate for bevacizumab monotherapy in the BELOB trial was only 18%, which is substantially lower than the rate of 43% that was reported in the BRAIN study.\textsuperscript{32} This may be partly related to the BELOB study using the more sensitive...
Response Assessment in Neuro-Oncology (RANO) criteria for the assessment of disease progression, rather than the McDonald criteria used in the BRAIN study.31 The RANO criteria take into account nonenhancing tumor volume in addition to contrast-enhancing tumor measurements.69 This is of key importance, especially in the setting of antiangiogenic therapies such as bevacizumab, which alter vascular permeability and may therefore result in a decrease in radiological contrast enhancement that is not necessarily an antitumor effect. Thus, taking nonenhancing tumor into consideration in response assessment may be a more accurate determination of tumor status.

In addition, the 6-month PFS of 11% noted for lomustine monotherapy in the BELOB trial was considerably lower than the rate of 25% for lomustine plus placebo reported in the phase 3 REGAL study comparing cediranib, cediranib plus lomustine, or lomustine monotherapy. Similarly, this represents a noteworthy difference from the PFS rate of 19% in the phase 3 trial of enzastaurin versus lomustine.70,71 Although the reasons for these differences are unknown, they do highlight the potential limitations of phase 2 studies with relatively small sample sizes in each arm.

### Bevacizumab in Patients With Newly Diagnosed Glioblastoma: AVAglio and Radiation Therapy Oncology Group 0825

Data from 2 pivotal studies assessing the efficacy of bevacizumab in the upfront setting were recently reported. These 2 large-scale, first-line, randomized phase 3 studies (AVAglio and Radiation Therapy Oncology Group [RTOG] 082561,62) were reported along with a variety of substudies arising from both. In many respects, the studies were similar and yet there are essential differences that are worth noting (Table 3).61,62,72-74 Both studies represent significant achievements in terms of size, accrual, and conduct.

The AVAglio trial, which was an international, industry-sponsored, randomized phase 3 trial, examined bevacizumab versus placebo when added to standard radiation and temozolomide chemotherapy. The coprimary endpoints were PFS and OS; the overall alpha significance

### TABLE 1. Phase 2 and Retrospective Studies of Bevacizumab Combinations in Patients With High-Grade Gliomas

<table>
<thead>
<tr>
<th>Chemotherapy Combination</th>
<th>No.</th>
<th>Radiographic Response Rate, %</th>
<th>PFS, Weeks</th>
<th>6-Month PFS, %</th>
<th>OS, Weeks</th>
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<td>83</td>
<td>19</td>
<td>22</td>
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</tbody>
</table>

Abbreviations: NR, not reported; OS, overall survival; PFS, progression-free survival.
The predefined PFS endpoint was met, with a median PFS of 10.6 months versus 6.2 months (hazard ratio [HR], 0.64; 95% confidence interval [95% CI], 0.55-0.74 \( P < .0001 \)), although the OS endpoint was not met. Although crossover on disease progression was not planned on the AVAglio trial, it is estimated that up to 30% of participants not randomized to receive bevacizumab ultimately did receive the drug at the time of disease progression, thus potentially distorting any potential OS benefits.

Although its protocol was slightly different from that of the AVAglio trial, the RTOG 0825 study had a similar design and coprimary endpoints of PFS and OS. Two notable differences in design include a planned crossover from placebo to bevacizumab in RTOG 0825, as well as eligibility criteria excluding patients who underwent biopsy only, which was not the case in the AVAglio trial. The prespecified alpha significance level was also split differently, with .004 allocated to PFS and .046 to OS. In addition, the HRs used for sample size calculations estimated a slightly larger difference between treatment arms than in the AVAglio trial (Table 3). The bevacizumab arm demonstrated longer PFS than placebo (10.7 months vs 7.3 months; HR, 0.79; 95% CI, 0.66-0.94 \( P = .007 \)), although this did not meet the predefined PFS significance level. Similar to the AVAglio trial, no difference in OS was noted between treatment arms, with a median OS of 15.7 months versus 16.1 months (HR, 1.13; 95% CI, 0.93-1.37 \( P = .21 \)). The authors of RTOG 0825 also noted increased risks of grade 3 or higher toxicity in the bevacizumab arm, including neutropenia, hypertension, and venous thromboembolic events.

### Quality of Life and Neurocognitive Function

Health-related quality of life (QOL) findings were reported from the AVAglio trial, although neurocognitive...
function was assessed only in a small number of patients in this trial. Specifically, 5 domains from the EORTC QLQ-C30 and BN20, both of which are validated QOL assessment tools, were preselected as secondary endpoints. All patients were required to complete the questionnaires. The study’s definition of time to definitive deterioration (TDD) or deterioration-free survival was from randomization to a 10-point deterioration from baseline with no improvement, progressive disease, or death. The median TDD was compared between the 2 treatment arms and reported. In all 5 prespecified domains (Global Health Status, Physical and Social Functioning, Motor Dysfunction, and Communication Deficit), the median TDD was significantly improved for patients on the bevacizumab arm. Similar findings were observed favoring the bevacizumab arm for most non-prespecified domains of the QOL questionnaires. Maintenance of a stable QOL was extended for 3 to 4 months for patients treated on the bevacizumab arm compared with the control arm during the PFS period. It should be noted that QOL testing included data at the time of disease progression, which permitted separate analyses to be performed assessing QOL before disease progression and up to the point of disease progression. The exploratory longitudinal analysis demonstrated no difference in QOL score changes over time between treatment arms; in other words, neither harm nor benefit from bevacizumab was noted in the scores.

The AVAglio trial also reported that the addition of bevacizumab resulted in the significantly prolonged maintenance of Karnofsky performance status and increased steroid discontinuation or delay in initiating steroids. The AVAglio investigators concluded that these findings represented a “clinically meaningful” improvement in PFS.

This is in contrast to findings from the RTOG 0825 study, which similarly used the EORTC QLQ-C30 and BN20 questionnaires, as well as The University of Texas MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT) to assess patient-reported outcomes. Testing was not a mandatory component of this trial. In this study, also different from the AVAglio trial, longitudinal collection of data was assessed only before disease progression. Both discrete time points were compared as well as general linear modeling. The majority of QOL domains were no different between arms, but the placebo group was more likely to be stable for certain symptom domains.
at certain time points. Some symptom groupings in the MDASI-BT were reported as being significantly deteriorated in the bevacizumab arm and others improved in the placebo arm at particular time points, although these were not found to be sustained at all time points. The longitudinal modeling, controlling for recursive partitioning analysis class and MGMT methylation status, found that from 0 to 46 weeks on trial, patients treated on the bevacizumab arm experienced significant worsening in cognitive functioning, motor dysfunction, and communication deficits compared with patients treated on the placebo arm, as well as several subscales using the MDASI-BT. The authors concluded that there was overall more deterioration in symptoms and QOL in the bevacizumab arm.\textsuperscript{73,74}

To the best of our knowledge, steroid dosing and changes in Karnofsky performance status have not yet been formally reported for the RTOG study.

In a separate presentation, neurocognitive function outcomes for the RTOG study were reported.\textsuperscript{74} Three measures were used: the Hopkins Verbal Learning Test-Revised, Trail Making Test, and Controlled Oral Word Association Test. A composite score was created to ascertain global neurocognitive function. Again, data were compared for patients who had not yet progressed using a longitudinal analysis. Overall, no statistically significant differences between treatment arms were noted regarding frequency of improvement, but over time a greater rate of neurocognitive function decline for patients on the bevacizumab arm was observed for some measures, including Global Cognitive Function, Processing Speed, and Executive Function, but not in measures of learning and memory function.

The cause of the apparent differences in QOL outcomes between these 2 studies is likely multifactorial. First, there was substantial dropout among RTOG participants as the QOL assessments proceeded. Conversely, questionnaire completion was a requirement in the AVAglio trial, and therefore the majority of randomized patients had data available for analysis at most time points, although there was also some attrition at the time of disease progression. Second, the statistical methodology was different. The AVAglio trial used the median TDD as previously defined, with other exploratory statistical testing including sensitivity and longitudinal analyses confirming the robustness of the primary analysis. This compares to the RTOG 0825 study, which compared patients who had not yet progressed using both discrete time point analyses and general linear modeling (longitudinal analysis). Finally, the AVAglio trial used a radiologic response criteria similar to the RANO criteria,\textsuperscript{69,75} which took into account nonenhancing disease progression, whereas RTOG 0825 used the traditional criteria of Macdonald et al that evaluated only enhancing disease.\textsuperscript{31} Thus, there is concern that RTOG 0825 data regarding QOL and neurocognitive function may have been biased by including a disproportionate percentage of patients with early progressive disease on the bevacizumab arm compared with the control arm. However, it is interesting to note that in the AVAglio trial, sensitivity analyses excluding the disease progression endpoint still resulted in similar findings for 3 of the 5 prespecified scales and for multiple other non-prespecified questionnaire domains.

Given the clear differences in QOL outcomes between these 2 studies, and the increasing recognition that this is a critically important endpoint for consideration in clinical trials, it seems apparent that these data must be analyzed objectively, perhaps by an independent review committee, before any definitive conclusions can be made regarding this important issue. Unfortunately, data were not collected for QOL after disease progression had occurred; this would be valuable information that could be built into future clinical trials, although requiring ongoing patient participation beyond study drug delivery poses potential ethical challenges for trial design.

**PFS as an Endpoint**

PFS has been considered a surrogate endpoint in clinical trials, meaning that on its own it is not a meaningful endpoint unless it translates ultimately to a valid clinical endpoint such as OS benefit. A surrogate endpoint should thus only be used if it is found to reliably predict the true clinical endpoint of interest. Herein lies one of the key difficulties with the 2 large first-line bevacizumab studies: although both demonstrated substantially improved PFS for bevacizumab, neither study indicated that this translated to an OS benefit. It is acknowledged that the preplanned crossover to bevacizumab at the time of disease progression in the RTOG 0825 study and the likely high percentage of participants receiving placebo who subsequently received bevacizumab in the AVAglio trial may have at least partly contributed to the failure to detect an OS benefit for the drug, despite the seemingly promising PFS findings. This conundrum is reminiscent of the withdrawal of bevacizumab in late 2011 from its previously accelerated FDA approval for metastatic breast cancer after additional studies and reviews concluded that the drug failed to improve OS or QOL despite improving PFS.\textsuperscript{76}
In considering the data from the AVAglio and RTOG 0825 trials, as well as subsequent studies, an important consideration is whether PFS should be regarded as purely a primary endpoint in neurooncology trials. Whereas malignant gliomas are inherently invasive and destructive within the central nervous system, tumor progression inevitably affects neurologic function, including very important considerations for patients and caregivers such as interpersonal interactions, the ability to partake in meaningful activities, and the capacity to care for self and others. As such, many may argue that for patients with malignant gliomas, time without tumor progression (provided that this time is of good quality and not at the expense of intolerable or dangerous side effects) is perhaps equally or more meaningful than OS. Maintaining disease, and therefore symptomatic stability, could therefore arguably be considered to be a meaningful clinical benefit.

Another contentious issue in neurooncology that predates antiangiogenic and other targeted therapies is whether PFS should be regarded as purely a primary endpoint in neurooncology trials. Whereas malignant gliomas are inherently invasive and destructive within the central nervous system, tumor progression inevitably affects neurologic function, including very important considerations for patients and caregivers such as interpersonal interactions, the ability to partake in meaningful activities, and the capacity to care for self and others. As such, many may argue that for patients with malignant gliomas, time without tumor progression (provided that this time is of good quality and not at the expense of intolerable or dangerous side effects) is perhaps equally or more meaningful than OS. Maintaining disease, and therefore symptomatic stability, could therefore arguably be considered to be a meaningful clinical benefit.

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Another contentious issue in neurooncology that predates antiangiogenic and other targeted therapies is whether PFS serves as a surrogate marker of OS. Data from the AVAglio and RTOG 0825 trials argue that PFS benefit may not translate into downstream survival improvement. Data from meta-analyses performed in the current era suggest that PFS predicts survival benefit, although these analyses are limited by the finding that they reflected essentially negative clinical trials. Similarly, PFS may not be objectively associated with improved/stable QOL or symptom control. In fact, even predating these studies, some contentiously argued that the effect of bevacizumab on PFS could simply be a reflection of the drug masking radiologic disease progression or altering the recurrence pattern without having a substantial impact on the disease process itself. As such, the usefulness of PFS as a clinical trial endpoint for patients with glioblastoma will need to be explored further, both in its usefulness as a clinically meaningful endpoint as well as its association with QOL and neurocognitive functions. Furthermore, similar to the AVAglio trial, reliable correlation between PFS and maintenance of performance status may be worth exploring further. Finally, alternative endpoints for such trials may also be worth consideration. As an example, the secondary endpoints of steroid discontinuation and delay to initiation of steroids in the bevacizumab arm in the AVAglio trial should be considered clinically significant given the morbidity and toxicity associated with prolonged steroid use.

### The Search for Biomarkers

Parallel to efforts to best understand and maximize clinical effectiveness with bevacizumab in patients with glioblastoma, others are searching for biomarkers to predict which patients will respond best to this therapy. To our knowledge, no predictive biomarker for bevacizumab responsiveness has been validated in any tumor type to date.

At the 2013 annual meeting of the American Society of Clinical Oncology, there were several presentations related to biomarker searches in glioblastoma (Table 4) that not only provided intriguing clinical insights but also highlighted the importance of biomarkers in clinical trial design. Both the AVAglio and RTOG 0825 trials included an optional biomarker component. Preliminary
cancer, albeit with reservations and some disappointments. 

Separate from the search for predictive tools, several other blood and tissue biomarker studies were presented at the American Society of Clinical Oncology meeting identifying potential prognostic indicators. Among these were transcriptional subclasses, single nucleotide polymorphism of the VEGF-A gene (rs2010963), and matrix metalloproteinase 2 levels. Similarly, early results in imaging biomarkers were reported, including enhancing tumor volume measurements, relative cerebral blood volume variation, perfusion maps, and contrast-enhanced T1-weighted subtraction maps.

**Looking Forward**

Despite the initial optimism and much ensuing research, there remains uncertainty and many unanswered questions in relation to the use of bevacizumab in the treatment of patients with glioblastoma. We now know that it does not confer an OS benefit when used in the de novo setting, despite having clinical efficacy in the recurrent setting. However, it is worth noting that only one trial to date, the BELOB study, demonstrated objective randomized evidence of an OS benefit in the recurrent setting of glioblastoma. Before this, clinical decisions were made based on single-arm, phase 2 studies and retrospective data with historical controls.

The conflicting QOL data presented in the AVAglio and RTOG 0825 trials further confound the issue, and unless we obtain data connecting PFS and QOL, the application of either of these endpoints will remain uncertain. Other unanswered questions include the optimal dose and schedule of bevacizumab, and whether it should be used as a single agent or in combination with chemotherapy or other molecular-targeting agents.

Although opinions differ in the neurooncology community, albeit with reservations and some disappointments, bevacizumab nevertheless remains the only targeted therapy to have objective evidence of clinical efficacy compared withchemotherapy alone among patients with recurrent disease (Fig. 1). We should take careful note of the results we will obtain from the EORTC 26101 study, which will become the second trial to date to directly compare bevacizumab and chemotherapy. At least anecdotally, and in the tails of Kaplan-Meier survival curves, some patients do appear to benefit greatly. Identifying those patients who may fall into this category is a continuing issue and the search for predictive biomarkers is currently ongoing. In addition, determining the best method of tumor assessment after antiangiogenic therapy is important. The ability to select those patients who are most likely to benefit, and understanding how best to follow their disease, would be ideal. Given that bevacizumab is not the panacea we hoped for all patients, the search for other, newer agents and combinations that may help to combat glioblastoma will continue.

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**CONFLICT OF INTEREST DISCLOSURES**

Dr. Field received conference travel grants from Roche and Merck Sharp and Dohme and has received Speaker’s honoraria from Roche and acted as Principal Investigator of a clinical trial funded by Roche (Roche was not a sponsor of the trial) for work performed outside of the current study. Dr. Wen received research support from Genentech for work performed as part of the current study and is a member of the Roche Advisory Board. Dr. Rosenthal has received honoraria from Roche as a member of the Roche Advisory Board. Dr. Reardon is a member of the Roche Advisory Board and has received personal fees from Genentech/Roche, EMD Serono, Merck/Schering, Novartis, and Amgen for work performed outside of the current study.

**REFERENCES**


Appendix 3: Field et al: Review Article: Brain tumours
BRAIN TUMOURS: SUCCESSES AND CHALLENGES ON THE OTHER SIDE OF THE BLOOD-BRAIN BARRIER

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Abstract

Tumours of the central nervous system encompass a large variety of cancers, ranging from slow-growing to rapidly progressive. Although comparatively rare in adults, central nervous system malignancies are relatively common in children, adolescents and young adults, resulting in substantial and ongoing morbidity, significant loss of effective life-years and a heavy burden on family and carers. In fact, more children and adults under the age of 40 die from a brain tumour than from any other cancer. As such, their effect on the community is greater than the apparent low incidence would otherwise indicate. This article focuses on adult brain tumours and in particular glioblastoma. Glioblastoma is rare, but is an example of a disease where treatment has been improved through better understanding of its molecular characteristics, as well as through international clinical trials. We will also discuss some challenges in rare tumours where level one evidence for optimal management is unlikely to ever exist.

Brain tumours are a heterogenous group of diseases, with over 100 types and subtypes, benign and malignant. Figure 1 shows the types of malignant brain tumours operated on most commonly at Royal Melbourne and Melbourne Private Hospitals, both busy tertiary referral centres.

In this paper, we focus on adult malignant brain tumours, accounting for 1.5% of all new cancers diagnosed annually in Australia. The most recent Australian Institute of Health and Welfare cancer incidence and mortality data indicate that in 2010, 1680 Australians were diagnosed with a malignant brain tumour and in 2011, over 1200 died from the disease, a sobering observation that incidence is closely matched by mortality.

Aetiology and molecular biology

For the most part, the aetiology and risk factors for brain cancers remain unknown. Only 5% of brain tumours are attributable to rare familial cancer syndromes such as Turcot or Li-Fraumeni Syndromes. Ionizing radiation exposure may increase brain tumour risk, more commonly at least 10-15 years after radiation. There is no clear association between mobile phone use and brain tumours, despite some contention in the literature. As is the case for many other cancer types, histological description of brain tumours is now transitioning to molecular characterisation and, importantly, treatment strategies are being modified accordingly. Table 1 describes some of these molecular markers and their significance and utility.

Rare tumours but effective management

The management of brain tumours has evolved over the last decade with the advent of improved neuro-surgical and radiation techniques, new systemic therapies, increasing numbers of clinical trials and the introduction of multi-disciplinary care. Among the most important
has been the addition of temozolomide chemotherapy to radiotherapy following surgery for glioblastoma (GBM). However, beyond chemotherapy and promising developments in targeted therapies, there are several other aspects of neuro-oncology that have developed and strengthened in recent years. This exemplifies optimal management of rare tumours.

In the Australian context, collaboration among the relatively small group of clinicians treating brain tumours has been facilitated by the development of several groups. Examples include: the Cooperative Trials Group for Neuro-Oncology (COGNO), established in 2007 to co-ordinate management of neuro-oncology trials and facilitate discussion of potential investigation into more rare central nervous system (CNS) malignancies; the Clinical Oncology Society of Australia Neuro-oncology Group, established in 2000 which among other activities, has developed comprehensive Australian clinical practice guidelines for brain tumour management; and Cancer Council Victoria’s Clinical Network Neuro-Oncology committee, established in 1999, which has produced several patterns of care studies for Victorian patients in collaboration with the Victorian Cancer Registry. Co-operative groups in Australia are mirrored overseas with North American, European and Asian groups providing education, scientific and clinical development in the field.

At many hospitals, brain tumours are managed in a multidisciplinary context, with regular multidisciplinary team meetings discussing complex cases, as well as multidisciplinary neuro-oncology clinics. Like other tumour streams, a care co-ordinator is an essential focal point for clinicians and patients.

### Table 1: Select molecular markers in adult malignant brain tumours*

<table>
<thead>
<tr>
<th>Molecular marker</th>
<th>Description</th>
<th>Impact</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGMT (O6-methylguanine-DNA methyltransferase) methylation</td>
<td>Methylation inactivates repair enzyme and renders cells more sensitive to damage from chemotherapy.</td>
<td>Predictive and prognostic biomarker in GBM.</td>
<td>32,33</td>
</tr>
<tr>
<td>IDH-1 and IDH-2 (isocitrate dehydrogenase) mutations</td>
<td>Krebs cycle enzyme Mutation is early molecular event. More common in grade II/III glioma (50-80%) and secondary GBM Associated with improved prognosis (PFS and OS).</td>
<td>May be associated with improved outcomes with chemotherapy in WHO III oligodendroglioma and oligoastrocytoma.</td>
<td>21,34-36</td>
</tr>
<tr>
<td>1p/19q codeletion or loss of heterozygosity</td>
<td>Very common in oligodendroglial tumours (up to 70%). Often but not always associated with IDH-1 mutation.</td>
<td>Associated with improved sensitivity to chemotherapy in WHO II and III tumours. Rare in GBM.</td>
<td>19,20</td>
</tr>
<tr>
<td>Molecular variants/subtypes of GBM</td>
<td>Distinct subclasses with difference genomic alterations.</td>
<td>Could potentially be used as predictive biomarkers or drug targets in future.</td>
<td>37-39</td>
</tr>
<tr>
<td>• proneural, • classical/proliferative • mesenchymal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potential therapeutic target 3 molecular variants:</td>
<td>Distinct differences in demographics and prognosis for each subtype. SHH pathway activated in over 50% of adult medulloblastomas.</td>
<td>Potential therapeutic target.</td>
<td>30</td>
</tr>
<tr>
<td>• sonic hedgehog (SHH)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• subtype C</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• subtype D</td>
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</tbody>
</table>

*This table is not exhaustive; many more molecular markers exist and are under investigation for their prognostic, predictive and/or targetable value.

### Standards of care and gaps in current knowledge

The traditional standards of care for many brain tumours have been largely dictated by the histopathology of the tumour, coupled with the clinical context (age and performance status). This is beginning to change, albeit slowly although in some contexts, without robust prospective evidence to guide us. Management of several brain tumours is discussed below.
Glioblastoma

Although rare, glioblastoma (GBM) is the most common CNS malignancy and data from a number of randomised clinical trials is available. The EORTC-NCIC trial reported by Stupp et al, published in 2005, remains the ‘gold standard’ management of patients with GBM under 70 years.\(^6\) Several trials have attempted without success to add additional medications in the de novo setting – bevacizumab, cediranib and cilengitide.\(^{13-16}\) In Australia, there is no standard of care for patients with recurrent GBM. Patients often receive single agent carboplatin or lomustine. Enrolment on a clinical trial is appropriate. Bevacizumab is approved by the US Food and Drug Administration, but is not Pharmaceutical Benefits Advisory Committee approved in Australia and is only available on an access program.

The most pressing clinical issues in the management of GBM include: the treatment of de novo disease in patients aged over 70 years or those with poorer performance status; the management of recurrent GBM; and the management of patients who have a non-methylated O6-Methylguanine-DNA methyltransferase (MGMT), a DNA repair enzyme. This group of patients has a poorer prognosis and is less likely to respond to current therapies including temozolomide.\(^{17}\)

Grade 3 glioma

This term encompasses pure astrocytomas, oligodendrogliomas and mixed oligoastrocytomas. Until recently, these tumours were grouped as one and standard management was surgery, radiotherapy, then temozolomide chemotherapy at disease progression. However, the prognostic and predictive value of 1p/19q co-deletion – seen in up to 70% of patients with an oligodendrogial component,\(^{16}\) – is now recognised and two randomised trials reported striking overall survival improvements for those 1p/19q co-deleted patients who received PCV chemotherapy in addition to radiotherapy. In one study, the benefit was 14.7 years versus 7.3 years in and in the other study: 123 versus 23 months.\(^{19,20}\) Early post-radiotherapy chemotherapy is now considered routine for patients with 1p/19q codeletions. Isocitrate dehydrogenase (IDH) mutations may also confer benefit from chemotherapy compared with non-mutated tumours.\(^{21}\) Of interest, these two studies evaluated PCV (procarbazine, lomustine and vincristine) chemotherapy, an old fashioned and complex regimen. Many believe that temozolomide is likely to provide equivalent results to PCV with less toxicity.\(^{22}\)

Low grade glioma

Low grade glioma (LGG) is much less common than GBM in adults, and tends to affect young adults. After surgery, management options include watching and waiting or up-front radiotherapy, with chemotherapy traditionally reserved until progression. However, updated data from RTOG 9802, comparing radiotherapy + PCV chemotherapy, versus radiotherapy alone, reported a striking overall survival benefit (13.3 versus 7.8 years, HR 0.59, p=0.03) with the combination arm.\(^{23}\) The data are not yet available for 1p/19q co-deletion status, but given that 42% of participants had oligodendroglioma and 32% were mixed gliomas, it is assumed that much of the benefit is driven by the co-deleted tumours responding to chemotherapy. The trial also does not tell us whether co-deleted patients would do just as well with up-front chemotherapy, reserving radiotherapy for later progression. The obvious advantage of such a strategy is that the potential neurocognitive sequelae of radiotherapy, especially in a young patient population, would be delayed. As such, we favour early chemotherapy in those with 1p/19q co-deletions. In Australia, temozolomide is restricted to recurrent grade 3 or grade 4 tumours and is not routinely available for LGG.

Rare brain tumours

Medulloblastoma is a rare cancer representing only 5% of all adult CNS malignancies.\(^{24,25}\) Much of the literature on adult medulloblastoma is in the form of case reports and small cohort studies. Management has largely been extrapolated and modified from the paediatric population, with no accepted standard of care world-wide. A recently published international patterns of care survey, mainly from Australia, reported that cranio-spinal irradiation was common, as was post-radiotherapy chemotherapy, but the regimens varied considerably – up to 10 different regimens were described – reflecting the uncertainty as to optimal management of this disease in adults.\(^{26}\)

Ependymoma, a rare tumour involving the spinal cord more frequently than brain, represents only around 3% of CNS malignancies.\(^{27}\) While surgery with or without radiotherapy is the predominant management strategy for ependymoma, chemotherapy is considered for recurrent disease. However, to date, chemotherapy has not been shown to improve outcome in this disease, and clearly improvements are needed.

Clinical trials: feasible, possible, and do-able for rare tumours in Australia

Despite their rarity, there are many successful clinical trials for CNS malignancies. Further, Australian centres have contributed significantly. These range from large international phase III studies to local phase I studies. A number of Australian sites are participating in early phase studies in which experimental drugs are attempting to inhibit molecular targets such as EGFR, EGFR\(_V3\), FGF\(_R\), PI3 Kinase and others. COGNO has conducted a number of Australian studies, including the recently
completed CABARET study that recruited over 120 patients in 12 months across Australia.\textsuperscript{28}

For rarer tumours such as ependymoma and medulloblastoma, the difficulty lies in the fact that it is unlikely that large scale randomised studies will ever be conducted, and trials, where available, would ideally need to be multi-centre and multi-national studies. To this end, the US-based Collaborative Ependymoma Research Network foundation has established two clinical trials for chemotherapy and targeted therapy in adults with ependymoma.\textsuperscript{29} It may be possible in the future for Australian centres to collaborate with overseas foundations in order to involve Australian patients in these research efforts.

Ongoing challenges

A major challenge for neuro-oncology is applying limited objective evidence to routine clinical practice. Clinical information and direction often comes from retrospective post hoc subgroup analyses from clinical trials while at the same time, novel biomarkers come to light. Do we accept the limitations of retrospective review and change our practice, or should we await prospective confirmation? In some cases for example, there appears to be compelling benefit of chemotherapy for 1p/19q co-deleted oligodendrogliomas. In other diseases, such as management of medulloblastoma or ependymoma, we need to accept that there will never be robust randomised phase III trial data to support our management decisions.

Another challenge is the potential danger of ‘leaping ahead’ for patients with incurable aggressive tumours such as GBM, and attempting to incorporate drugs into clinical practice where evidence does not yet exist. It is understandable that even clinicians may clutch at straws if there is a small chance of benefit when faced with a patient in front of us. This is exemplified by the use of bevacizumab in GBM. After favourable single arm studies and non-comparative randomised phase 2 trials in the recurrent disease setting indicated benefit, at least anecdotally, many clinicians in the US began using the drug in de novo GBM. However, the subsequent AvaGlio and RTOG 0825 studies did not show an overall survival benefit when using bevacizumab in this context.\textsuperscript{13,14}

Prognostic and predictive biomarkers should play a stronger role in the future to tailor and guide clinical practice, but in some ways they are still in their infancy. 1p/19q status is now routinely used to guide treatment decisions in grade 2 and 3 gliomas, whereas IDH mutations and MGMT methylation status have yet to reach a tipping point of guiding decisions.

The field of neuro-oncology has many of the same issues and hindrances as that of other rare tumours. First, rare tumours such as medulloblastoma are more common in the paediatric patient population, but the management of these patients cannot be extrapolated to the adult population due to fundamental differences in tumour biology and tolerability of therapies.\textsuperscript{30} Secondly, tumours must undergo expert neuropathology review. Indeed a review of ependymoma patients demonstrated that 14.6% were reclassified on expert neuropathology review.\textsuperscript{31} Third, there has been a reluctance to allow neuro-oncology patients access to generic phase 1 studies.

Finally, within Australia, access to drugs is not the same as in the US. Thus, evidence and recommendations from US studies and organisations such as the National Comprehensive Cancer Network Clinical Practice Guidelines may not always be relevant in the Australian context. This may be frustrating, but is occasionally overcome by compassionate drug access (e.g. via a hospital or a pharmaceutical company) if available evidence is deemed to warrant it for individual circumstances.

Summary and conclusion

Brain tumours are rare in adults, but significant progress has occurred in recent years, changing the face of neuro-oncology in Australia and worldwide. The ongoing challenges are not simply because these tumours are rare, but also resistant to many therapies and in most cases incurable. However, continuing discoveries and clinical trials, as well as substantial work in collaboration and networking, will continue to facilitate progress in all aspects of CNS oncology, from diagnosis through to management and supportive care.

References


Appendix 4: Bennett, Field et al: Early perfusion MRI on CABARET patients
Early perfusion MRI predicts survival outcome in patients with recurrent glioblastoma treated with bevacizumab and carboplatin

Iwan E. Bennett1 · Kathryn M. Field3 · Christopher M. Hovens1 · Bradford A. Moffat2 · Mark A. Rosenthal3 · Katharine Drummond1,4 · Andrew H. Kaye1,4 · Andrew P. Morokoff1,4

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Abstract Bevacizumab, an anti-angiogenic agent, is FDA-approved for use in patients with recurrent glioblastoma multiforme (rGBM). The radiologic evaluation of tumor response to bevacizumab is complex and there is no validated method of monitoring tumor vascularity during therapy. We evaluated perfusion-weighted MR imaging (PWI) in our cohort of patients enrolled in the CABARET trial, which examined the effectiveness of bevacizumab with or without carboplatin in patients with rGBM. Pretreatment and early follow-up (4- and 8-week) PWI were used to calculate relative cerebral blood volume (rCBV) histogram statistics of the contrast-enhancing and FLAIR hyperintense tumor volumes. A novel rCBV measurement (load) was developed to estimate the total volume of perfused tumor blood vessels. Changes in all rCBV measures were examined for correlations with progression-free (PFS) and overall survival (OS). All of our 15 patients enrolled in the CABARET trial were included. Median PFS and OS were 23 and 45 weeks respectively. Kaplan–Meier analysis of pre-treatment PWI revealed an 18 week reduction in median OS in patients with high tumor rCBV (p = 0.031). Changes in rCBV measures, especially load, correlated significantly with PFS and OS at both follow-up time-points. Patients with the greatest reduction in rCBVload by 8-weeks of therapy had a significantly increased median OS (30 weeks; p = 0.013). PWI may be of significant clinical utility in managing patients with rGBM, particularly those treated with anti-angiogenic agents such as bevacizumab. These findings need to be confirmed prospectively in larger studies.

Keywords Bevacizumab · Glioblastoma · DSC · MRI · rCBV · Perfusion

Introduction

Bevacizumab is a humanized murine monoclonal antibody targeting vascular endothelial growth factor-A, and is approved for the treatment of recurrent glioblastoma multiforme (rGBM) based on initial reported response rates of 46% [1]. Subsequent phase II studies have further demonstrated its efficacy in salvage therapy [2]. However, the progression-free survival (PFS) benefits of bevacizumab have not yet translated into improved overall survival (OS) in either the de novo or recurrent disease settings.

One concern is that MRI based assessment of bevacizumab response may be inaccurate and misleading. Pseudo-response is well described when tumors are assessed by conventional MacDonald criteria due to decreasing tumor vessel permeability causing decreased contrast enhancement [2]. The RANO criteria were introduced to specifically account for this issue [3]. Newer imaging modalities...
not dependent on contrast-enhancement are also being investigated for determining outcome measures in GBM [4].

Perfusion MRI, or perfusion-weighted imaging (PWI), rapidly obtains images to serially measure the movement of a tracer agent within a tissue of interest to give estimates of its haemodynamic properties. Reductions in PWI parameters such as permeability coefficients (e.g. $K_{trans}$) and cerebral blood volume (CBV) have been demonstrated with bevacizumab administration in both pre-clinical studies [5–7] and phase II clinical trials [8]. The ability of PWI to predict patient outcome remains uncertain, with mixed results being reported from the small number of studies investigating this relationship [9–11].

This study retrospectively examined the prognostic value of PWI specifically in patients with rGBM treated with bevacizumab. In particular, the analysis included pre-treatment scans and an “early” time-point scan undertaken after only 4 weeks of treatment.

**Materials and methods**

**Patient selection and follow-up**

Study participants were those patients recruited from The Royal Melbourne and Melbourne Private Hospitals for the CABARET randomized phase II clinical trial. Inclusion and exclusion criteria for the CABARET trial are listed in the supplementary material. Briefly, patients eligible for inclusion were those over 18 years old with a tissue diagnosis of GBM and disease recurrence on post-contrast MRI or confirmed histologically. Previous treatment with temozolomide and radiotherapy was mandatory. Patients were excluded if there was any evidence of recent intracerebral hemorrhage or an inability to undergo MRI. The study was conducted with institutional Human Research Ethics Committee approval.

Patient age, gender, and presenting functional status (KPS, Karnofsky Performance Status) were recorded at enrolment. Patients were followed prospectively to determine PFS and OS. PFS was defined as the time from randomization to clinical or radiographic progression. OS was determined by the time from randomization to death.

**CABARET trial protocol**

The CABARET trial is a randomized phase II multi-center study in patients with rGBM consisting of two parts. Part 1 randomized patients to bevacizumab alone or bevacizumab plus carboplatin. At disease progression, Part 2 randomized patients suitable for further therapy to either continuation of bevacizumab or discontinuation. Part 2 allowed patients to be treated with physicians’ choice chemotherapy (carboplatin, temozolomide or etoposide).

**MR imaging**

MRI findings from pre-treatment scans, as well as the initial two follow-up scans during Part 1 of the trial were assessed for their ability to predict outcome. The first two follow-up scans were undertaken at 4- and 8-weeks following randomization as per trial protocol. While 8-week follow-up imaging is not unusual in studies of this kind as well as in clinical practice, the 4-week follow-up MRI represented a deliberate early time-point for radiographic assessment of treatment response, and was included to assess the value of early MRI in disease monitoring.

Patients underwent conventional MRI as part of the CABARET trial protocol. These studies normally also included PWI. The majority of investigations were undertaken on a 3-T scanner, with the remainder performed on 1.5-T machines. Although specific MRI protocols differed slightly between patients, they typically included T1 pre- and post-contrast administration, FLAIR, DWI and T2-weighted scans.

Dynamic susceptibility-weighted MRI was used for PWI whereby dynamic MR images were acquired during a bolus IV administration of contrast agent. A pragmatic attempt was made to acquire the data in accordance with previous recommendations [12] whilst keeping the total contrast agent dose within recommended limits, and obtaining acceptable slice coverage and image signal-to-noise ratio. To reduce the effect of contrast leakage on CBV calculations, a 5 mL bolus of gadolinium contrast agent (Magnevist®, Bayer, Germany) was administered to the patient 5 min prior to the PWI acquisition at a rate of 1 mL/s followed by a 15 mL saline flush. For PWI, dynamic gradient-echo EPI images were then acquired every 1.5–3 s. After approximately 10 to 15 s of scanning, a 10 mL bolus of contrast agent was administered at a rate of 5 mL/s followed by a 30 mL saline flush. Due to the differences in MR system configurations the TR (1.2–3 s), TE (30–60 ms), in-plane resolution (1.2–3 mm), slice thickness (4–7 mm), slice number (14–20) and total acquisition times (70–100 s) were scanner dependent.

**Post-acquisition imaging analysis**

All imaging was transferred to an external computing station for post-acquisition processing. Using Analyze 10.0 (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN), tumor regions of interest (ROIs) were created from contrast-enhancing regions on T1-weighted sequences (T1+C ROI) and hyperintense regions on FLAIR sequences (FLAIR ROI). Cystic cavities and necrotic...
cores were not included. A further ROI was created from T2-weighted normal-appearing white matter (NAWM) of the contralateral centrum semiovale.

PWI data were converted to maps proportional to contrast agent concentration to correct for blood vessel leakage in Matlab® 7.11 (Mathworks, Inc., MA, USA), and maps proportional to CBV were then created by numerical integration on a voxel by voxel basis [12]. The tumor and NAWM ROIs were then co-registered and re-sampled onto the CBV map frame of reference via a nine-parameter affine co-registration (MINC tools, Montreal Neurological Institute) of the T1 post-contrast, FLAIR and T2 scans to the first phase of the PWI images. Relative CBV (rCBV) maps were subsequently created, relative to the NAWM ROI, again using Matlab®. Tumor voxel rCBV histograms were then created for the T1 + C and FLAIR ROIs.

Interval and serial imaging characteristics

For each patient, T1 contrast-enhancing and FLAIR-hyperintense tumor volumes (cm$^3$) were calculated for the three (pre-treatment, and 4- and 8-week follow-up) imaging time-points by integrating the number of voxels within each corresponding ROI by the voxel volumes within Matlab®. Traditional tumor rCBV histogram statistics (mean, median, mode and maximum) were obtained from the histogram data of each tumor ROI. Additionally, a novel rCBV measurement was calculated to give a volumetric indicator of total tumor perfusion load. This was achieved by determining the numerical integral of the voxel rCBV histogram for a given tumor ROI (rCBV$_{load}$).

Values of traditional tumor rCBV histogram statistics, and rCBV$_{load}$ for each imaging time-point were then compared to determine serial changes in these characteristics, expressed as a percentage. Definitions of volumetric progression (>40% increase in volume) and response (>65% reduction in volume) were applied to changes in tumor volumes, as well as the volumetric perfusion measurement rCBV$_{load}$ to determine rates of radiographic progression and response [13, 14].

Statistical analysis

Statistical analysis was performed using Prism 5 for Mac OS X (GraphPad Software, Inc., San Diego). Correlations between rCBV measures and outcome were investigated using the Spearman correlation test. Patients surviving at time of analysis were censored at that date. Patients were also dichotomized to low and high rCBV$_{mean}$, rCBV$_{median}$, rCBV$_{mode}$, rCBV$_{max}$, and rCBV$_{load}$ groups based on the median value of each of the five parameters, at each imaging timepoint log-rank tests were then used to compare the Kaplan–Meier survival curves of these groups. The same analyses were applied to the percentage change in rCBV values at each follow-up imaging time-point. Statistical significance was considered to be p < 0.05 for all tests.

Results

Patient demographics and outcome

A total of 122 patients were enrolled in the CABARET trial, including 15 from our institutions between April 2011 and Feb 2012. For these 15 patients, the mean patient age was 49 years, with more males recruited (n = 9). Tumors were most commonly located in the frontal lobe (n = 5). The majority of patients (n = 12) exhibited good functional status at enrolment (KPS score 80–100), with three patients displaying moderate functional status (KPS score 50–70).

At the time of analysis only one patient was alive and was censored for outcome analyses. One patient underwent further resection prior to commencement of treatment to confirm recurrence rather than radiation necrosis. This patient was excluded from response analyses as any change in tumor volume would be the result of treatment plus surgery. One patient discontinued treatment after 4 months due to acute renal impairment potentially caused by bevacizumab. Outcome data from this patient has been included. PFS and OS data was available for all patients. Median PFS and OS was 23 weeks [standard deviation (SD) ±24 weeks] and 45 weeks (SD ±22 weeks) respectively.

Pre-treatment MRI

All patients had conventional pre-treatment MRI available for analysis. Nine out of 15 MR scans were performed on the same 3 T machine. Scans were undertaken on average 24 days (SD ±23 days) prior to commencing treatment. The average contrast-enhancing tumor volume was 27 cm$^3$ (SD ±23 cm$^3$), while the average FLAIR hyperintense volume was 137 cm$^3$ (SD ±56 cm$^3$).

Pre-treatment MR imaging also included PWI for 13 patients. Based on Spearman analysis, no rCBV measure was found to significantly correlate with PFS or OS. However, Kaplan–Meier analysis demonstrated a significant difference in OS curves between patients with low vs. high rCBV$_{median}$ (Fig. 1a). Median survival was reduced by 18 weeks in patients with high rCBVs (53 vs. 35 weeks).

4-week follow-up MRI

All patients had the initial follow-up MRI available for analysis, undertaken on average 26 days (SD ±3 days) following commencing treatment. 14 out of 15 4-week MR scans were performed on the same 3 T machine. The
average contrast-enhancing tumor volume was 10 cm$^3$ (SD ±10 cm$^3$), while the average FLAIR hyperintense volume was 70 cm$^3$ (SD ±27 cm$^3$).

Spearman analysis of PWI revealed significant negative correlations between tumor rCBVs and both PFS and OS (Table 1). Kaplan–Meier analysis demonstrated a significant reduction in PFS in patients with large rCBV$_{\text{load}}$ (median PFS 23 vs. 15 weeks; Fig. 1b). Significant reductions in OS were demonstrated in patients with high tumor rCBVs (Fig. 1c, d). High rCBV$_{\text{median}}$ and rCBV$_{\text{max}}$ decreased median OS by 14 (52 vs. 38) and 21 (52 vs. 31) weeks respectively.

8-week follow-up MRI

One patient had clinical and radiographic evidence of disease progression after 4-weeks follow-up and was excluded from analysis of the 8-week follow-up MRI. The remaining 14 patients all had MRI (including PWI) available, which was undertaken on average 55 days (SD ±7 days) following commencing treatment, and 13/14 were perfomed on the 3 T machine. The average contrast-enhancing tumor volume was 6 cm$^3$ (SD ±9 cm$^3$), while the average FLAIR hyperintense volume was 60 cm$^3$ (SD ±27 cm$^3$).

Spearman analysis of PWI revealed significant negative correlations between tumor rCBVs and both PFS and OS (Table 1). Kaplan–Meier analysis demonstrated a significant reduction in PFS in patients with large rCBV$_{\text{load}}$ (median PFS 32 vs. 16 weeks; Fig. 2a). Significant reductions in OS were also demonstrated in patients with high tumor rCBVs based on T1 + C ROIs (Fig. 2b–d). Median OS was reduced by 13 (54 vs. 41) weeks in patients with high rCBV$_{\text{mean}}$, and by 16 (54 vs. 38) weeks in patients with high rCBV$_{\text{mode}}$ and large rCBV$_{\text{load}}$ (Fig. 2b–d).

Predicting response to bevacizumab based on volumetric criteria and PWI

Comparing pre-treatment to follow-up MRIs gave volumetric response rates of 50% at 4 weeks and 69% at 8 weeks using conventional T1 post-contrast imaging. FLAIR imaging gave lower response rates (14 and 35%), whilst including changes in perfusion through rCBV$_{\text{load}}$ returned higher response rates (45 and 91%). Volumetric progression was
Table 1 Correlation of follow-up perfusion MRI with outcome

<table>
<thead>
<tr>
<th></th>
<th>4-week MRI</th>
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<th>8-week MRI</th>
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<tr>
<td></td>
<td>r valuea</td>
<td>p value</td>
<td>r valuea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>r valueb</td>
</tr>
<tr>
<td><strong>T1 + C ROI histogram statistics</strong></td>
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</tr>
<tr>
<td>rCBV mean</td>
<td>−0.197</td>
<td>0.483</td>
<td>−0.500</td>
</tr>
<tr>
<td>rCBV median</td>
<td>−0.166</td>
<td>0.555</td>
<td>−0.433</td>
</tr>
<tr>
<td>rCBV mode</td>
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<td>0.182</td>
<td>−0.561</td>
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<tr>
<td>rCBV maximum</td>
<td>−0.420</td>
<td>0.119</td>
<td>−0.643</td>
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<tr>
<td>rCBV load</td>
<td>−0.456</td>
<td>0.089</td>
<td>−0.532</td>
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<td><strong>FLAIR ROI histogram statistics</strong></td>
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<tr>
<td>rCBV mean</td>
<td>−0.408</td>
<td>0.132</td>
<td>−0.443</td>
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<tr>
<td>rCBV median</td>
<td>−0.523</td>
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<td>rCBV mode</td>
<td>−0.061</td>
<td>0.830</td>
<td>−0.218</td>
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<td>rCBV maximum</td>
<td>−0.477</td>
<td>0.072</td>
<td>−0.486</td>
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<tr>
<td>rCBV load</td>
<td>−0.558</td>
<td>0.031</td>
<td>−0.364</td>
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</tbody>
</table>

Bold values are significant at the p < 0.05 level

rCBV relative cerebral blood volume, T1 + C ROI contrast-enhancing tumor, FLAIR ROI hyperintense tumor

*a* Spearman correlation test, degrees of freedom = 14

*b* Spearman correlation test, degrees of freedom = 13

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**Fig. 2** Kaplan–Meier analyses of 8-week follow-up PWI with respect to survival. 

a Significantly reduced progression-free survival is demonstrated in patients with high rCBVload. 

b-d Overall survival is significantly reduced in patients with high rCBVmean, high rCBVmode, and high rCBVload. rCBV relative cerebral blood volume, PWI perfusion-weighted imaging
demonstrated only on conventional T1 post-contrast imaging for one patient, giving a rate of progression of 7%.

Comparisons between outcome and changes in rCBV at 8 weeks, based on T1+C ROIs are shown in Fig. 3 and Table 2. Spearman and Kaplan–Meier analyses both demonstrated that patients with the greatest reductions in rCBV had improved PFS and OS. Median OS was increased by 30 weeks in patients with the greatest reduction in rCBV load at 8 weeks compared to pre-treatment imaging (Fig. 3b). No significant correlations were seen at the 4-week MRI or using changes in FLAIR ROI rCBVs.

**Discussion**

Imaging-based assessment of response to therapy in GBM has traditionally involved two-dimensional measurements of contrast-enhancing tumor regions as recommended by MacDonald and colleagues in 1990 [15]. Limitations with this criteria became increasingly apparent as therapy-induced pseudo-progression and pseudo-response gained recognition. This prompted an updated response criteria (RANO) to be published in 2010, including non-enhancing

| Table 2 Correlation of changes in PWI\(a\) at 8 weeks with outcome |
|------------------|----------|------------------|----------|
|                  | Versus progression-free survival |       | Versus overall survival |
|                  | r value | p value | r value | p value |
| Compared to pre-treatment MRI |       |       |       |
| rCBV mean | −0.501 | 0.122 | −0.447 | 0.173 |
| rCBV median | 0.646 | 0.037 | −0.500 | 0.122 |
| rCBV mode | −0.182 | 0.595 | −0.182 | 0.595 |
| rCBV maximum | −0.555 | 0.082 | −0.464 | 0.155 |
| rCBV load | 0.898 | 0.0004 | −0.770 | 0.007 |
| Compared to 4-week follow-up MRI |       |       |       |
| rCBV mean | −0.639 | 0.019 | −0.402 | 0.174 |
| rCBV median | 0.671 | 0.012 | −0.434 | 0.138 |
| rCBV mode | −0.430 | 0.143 | −0.451 | 0.122 |
| rCBV maximum | −0.278 | 0.358 | −0.038 | 0.901 |
| rCBV load | 0.801 | 0.001 | −0.614 | 0.026 |

Bold values are significant at the p<0.05 level. 

MRI, magnetic resonance imaging. PWI, perfusion-weighted imaging. rCBV, relative cerebral blood volume.

\(a\)Based on contrast-enhancing tumor volumes.

---

Fig. 3 Kaplan–Meier analyses of changes in PWI at 8-week follow-up MRI with respect to survival. 8-week PWI is compared with both pre-treatment (a, b) and 4-week follow-up (c, d) PWI. All rCBVs are based on contrast-enhancing tumor volumes (T1+C ROIs).
regions of tumor in the imaging-based assessment of response [3]. As volumetric analysis and advanced imaging techniques such as PWI become more accessible it is likely that they will become incorporated into future revisions [14].

The current study investigated the ability of PWI to predict outcome in patients with rGBM treated with bevacizumab. Pre-treatment as well as early follow-up imaging were examined for associations with PFS and OS. Changes in perfusion imaging over time were also analyzed for links with outcome.

Fifteen patients were recruited for the CABARET trial from our institutions, and all were included in this analysis. Follow-up for all patients was complete and median PFS and OS were 23 and 45 weeks respectively. Compared with historical data, this cohort did far better than expected for patients with rGBM (PFS ~10 weeks; OS ~30 weeks [16]). However, their outcomes are comparable to results from other phase II trials of bevacizumab therapy in rGBM patients [17–21].

In this study, patients with higher median rCBV within FLAIR hyperintense tumor volumes on pre-treatment MRI were found to have significantly reduced OS compared to those with lower values (53 vs. 35 week; Fig. 1a). This may simply reflect the poorer prognosis seen in patients with more vascular tumors, though it also suggests that these patients may be less likely to benefit from anti-angiogenic therapies such as bevacizumab. Perfusion MRI at the time of GBM recurrence may therefore be useful in selecting which patients should be considered for anti-angiogenic therapy.

Following the commencement of anti-angiogenic agents, PWI analysis of the contrast-enhancing tumor regions, rather than FLAIR hyperintense regions, appears to become more important in monitoring response and predicting outcome. After 4 weeks of therapy with bevacizumab, median rCBV on FLAIR ROIs correlated with both PFS and OS, but stronger and more significant correlations with OS were seen with T1 + C ROI rCBV histogram statistics. By 8 weeks of therapy, all correlations were lost with FLAIR ROI rCBV histogram statistics, but became stronger with T1 + C ROIs. The reason for this shift in significance from FLAIR to T1 + C during treatment is uncertain, but may relate to a greater sensitivity of contrast-enhancing tumor to the effects of anti-angiogenic agents. Changes in tumor volume with treatment were also greatest on T1 post-contrast imaging.

Follow-up PWI as early as 4 weeks was able to predict outcome in patients receiving bevacizumab. At this imaging time point, patients with high rCBVs demonstrated reductions in OS between 14 and 21 weeks compared to patients with low values. This predictive value persisted and strengthened by the 8-week follow-up MRI. Again, these findings may reflect the poorer prognosis associated with more highly vascular tumors, but it is interesting to note that also patients with the smallest reductions, or any increase, in tumor rCBV measures following commencement of treatment were demonstrated to have worse PFS and OS.

The strongest and most significant correlations between these PWI changes with bevacizumab therapy and outcome were seen with rCBVload. This novel rCBV measurement was developed to estimate the total volume of blood vessels within a given tumor. Unlike histogram statistics, which do not vary with tumor size, rCBVload takes into account the entire mass of abnormal tumor vasculature that is responding to treatment. Increases in rCBVload at the 4- and 8-week follow-up MRIs were associated with both poorer PFS and OS.

Imaging response rates were also assessed using true volumetric analysis. Using RECIST criteria, response rates of 50 and 69 % were seen at 4- and 8-week follow-up respectively. Response rates from other phase II trials of bevacizumab for rGBM using MacDonald imaging criteria range from 23 to 57 % following long-term follow-up [10, 17–21]. The increased response rate seen in the current study may relate to a number of factors including differences in treatment regimens and patient populations. However, one phase II study of bevacizumab in rGBM patients has directly compared MacDonald criteria to volumetric analysis of imaging response at early timepoints (3 and 21 days), and also reported higher response rates with the volumetric analysis [8]. This suggests that volumetric analysis may be a more sensitive way of monitoring GBM response to therapy.

A shortcoming of this study was that 9 of 15 subjects had baseline scans on a 1.5 T scanner and underwent further MRI studies on a 3 T scanner. This was a result of all baseline scans for this clinical trial being taken from the subjects standard clinical MRI exams which were spread over our institution’s three MRI scanners and some external Radiology sites. For the perfusion scanning the main effect of this would have been lower image resolution and thicker slices at 1.5 T. The effect on rCBV measures would have been minimal as the main difference would have been the differing T1 contamination of the rCBV values. This was carefully corrected for as previously recommended. In a recent study, 1.5 and 3 T rCBV values were found to be highly correlated (ICC = 0.92 [95% CI 0.85–0.97]) [22].

Although the CABARET trial is a large, well designed, multi-center, prospective clinical trial, this report represents an essentially retrospective ad hoc analysis of the data obtained from one of its recruiting centers. This leads to a number of inherent limitations including small sample size.
The lack of PWI in the CABARET protocol also meant that not all patients in the current study underwent pre-treatment PWI (13 of 15). Despite these problems, highly significant correlations and differences in outcome were still observable.

Conclusion

Findings from this study suggest that PWI may be of significant clinical utility in managing patients with rGBM treated with anti-angiogenic agents such as bevacizumab. We have demonstrated that pre-treatment PWI may be able to help in selecting which patients are likely to benefit most from bevacizumab. We have also shown that early follow-up imaging, even at 4 weeks, may help in identifying which patients are less likely to gain from continued use of anti-angiogenic agents and for whom other treatments should be sought. Monitoring changes in the entire tumor blood vessel volume, with rCBVload, appears to be the most useful way to identify such patients. These findings will necessarily need to be confirmed in larger studies.

Acknowledgments The authors wish to thank Luisa Barassi, Linda Garrett, Simon Salinas and Chris Steward for their assistance in this project.

Funding The CABARET trial was conducted by The Cooperative Trials Group for Neuro-Oncology (COGNO), and was funded in part by Roche. This analysis was supported in part by funding received from The Brain Foundation, the Neurosurgical Society of Australasia, the Cure for Life Foundation, and the Royal Australasian College of Surgeons.

Compliance with ethical standards

Conflict of interest The CABARET trial was funded in part by Roche. No other potential conflicts of interest regarding the submission of this manuscript have been identified by any of the authors.

References


Appendix 5: Main trial poster (ASCO, SNO, COGNO Annual Meetings)

A randomized phase II study of carboplatin and bevacizumab in recurrent glioblastoma multiforme (CABARET)

Chi M Field1, J Simms2, H Wheeler3, RJ Howe4, AK Nowak5, L Chie6, C Brown7, A Livingston7, K Sawkins7, MA Rosenthal7, CABARET/COGNO Investigators

1 Royal Melbourne Hospital, Melbourne, Australia; 2 RMMIC Clinical Trials Centre, University of Sydney, Sydney, Australia; 3 Royal North Shore Hospital, Sydney, Australia; 4 Prince of Wales Hospital, Sydney, Australia; 5 Sir Charles Gairdner Hospital, Perth, Australia; 6 Austin Hospital, Melbourne, Australia

BACKGROUND
- Glioblastoma multiforme (GBM) is the most aggressive malignant brain tumor, and overall survival remains short
- Treatment with standard chemotherapies is limited
- Bevacizumab (BSC) has been approved for GBM, but the role of carboplatin has not been definitively determined
- Systemic bevacizumab has not been associated with significant CNS leakage, enabling the use of escalating dosing without increased risk of CNS toxicity

METHODS
- Study Design: multi-centre, sequential, stratified, randomized
- Recruitment: 122 patients randomized to Part 1 between November 2010 and March 2012
- Stratification factors:
  - Measureable disease or resected recurrence
  - ECOG performance status 0-2
  - ≥ 12 weeks since radiotherapy
- Treatment groups:
  - ARM A: Bevacizumab
  - ARM B: Carboplatin + bevacizumab
  - ARM C: Carboplatin
  - ARM D: Placebo

RESULTS
- Lotter et al. 2012: OS, response rate
-Statistical Analyses: Stratification (1:1)
- Statistical Analysis: Deaths in Part 1 were as expected in 30-35% (122 patients, 45% male)
-Secondary Endpoints:
  - Time to treatment failure
  - Toxicity (National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE))
  - Objective radiological response rate (according to modified Macdonald criteria)
  - Correlation of MRI response at 4 weeks with clinical outcome (PFS and OS)
  - Correlation between blood and tissue biomarkers and clinical outcome (including PFS, OS)
  - Documentation of the location and type of radiological progression on and after radiological progression
  - Statistical Analyses (Part 1):
    - Median follow-up: 14.7 months
    - Time to treatment failure: Median not reached in all arms
    - Time to treatment failure: Median not reached in all arms
    - Toxicity: 10% episodes of grade 3-4 thrombocytopenia
    - Objective radiological response rate: 26% (combination) versus 13% (monotherapy)
    - Correlation between blood and tissue biomarkers and clinical outcome: Not yet available
    - Correlation of MRI response at 4 weeks with clinical outcome: Not yet available

CONCLUSIONS
- This study of patients with recurrent GBM, the addition of carboplatin to bevacizumab did not result in additional clinical benefit compared to bevacizumab monotherapy
- Ongoing follow-up of patients on bevacizumab beyond progression, and novel secondary endpoints to determine the effect of bevacizumab on the secondary endpoints (listed below)

Table 1: Baseline Characteristics

<table>
<thead>
<tr>
<th>Trait</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>61% (35)</td>
<td>60% (27)</td>
<td>60% (20)</td>
<td>60% (20)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63 ± 11</td>
<td>63 ± 11</td>
<td>63 ± 11</td>
<td>63 ± 11</td>
</tr>
<tr>
<td>ECOG</td>
<td>11 (18%)</td>
<td>13 (20%)</td>
<td>12 (20%)</td>
<td>12 (20%)</td>
</tr>
<tr>
<td>Treatment</td>
<td>25 (50%)</td>
<td>25 (50%)</td>
<td>25 (50%)</td>
<td>25 (50%)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>25 (50%)</td>
<td>25 (50%)</td>
<td>25 (50%)</td>
<td>25 (50%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>25 (50%)</td>
<td>25 (50%)</td>
<td>25 (50%)</td>
<td>25 (50%)</td>
</tr>
</tbody>
</table>
| Ongoing follow-up of patients on bevacizumab beyond progression, and novel secondary endpoints to determine the effect of bevacizumab on the secondary endpoints (listed below)

*Acknowledgments
This study was supported by the Cancer Council of South Australia, the Cancer Council of Victoria, and the Cancer Council of Western Australia. Financial support from the National Health and Medical Research Council (NHMRC) and Cancer Council of South Australia is acknowledged. The study was coordinated at the NHMRC Clinical Trials Centre, University of Sydney as a multi-centre study, supported by Roche Products Pty Limited (Australia)
Appendix 6: Quality of Life poster (COGNO Annual Meeting 2016)

Health-related quality of life outcomes from CABARET: A randomized phase 2 trial of carboplatin and bevacizumab in recurrent glioblastoma

KM Field (1,2), MT King (3), J Simes (4), D Espinoza (4), EH Barnes (4), K Sawkins (4), MA Rosenthal (1,2), L Cher (5), Royal Melbourne Hospital (1), Department of Medicine, University of Melbourne (2), Psycho-oncology Co-operative Research Group (PoCoG), University of Sydney (3), National Health and Medical Research Council Clinical Trials Centre, University of Sydney (4), Austin Health (5), Prince of Wales Hospital (6), Royal North Shore Hospital (7), Sir Charles Gairdner Hospital and School of Medicine and Pharmacology, University of Western Australia (8).

Background

- In recurrent glioblastoma (GBM) prognosis is poor
- Understanding the effects of treatments on health-related quality of life (HRQL) is important
- In the CABARET randomised phase 2 clinical trial, we compared bevacizumab plus carboplatin with bevacizumab monotherapy in adults with recurrent GBM. The primary outcome, progression-free survival (PFS), showed no difference between arms.
- We assessed HRQL completion rates and outcomes between arms as a secondary outcome.

Methods

- Questionnaires: European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLC-C30) and Brain Cancer Module (BN20)
- We calculated changes from baseline for each HRQL measure. Proportions with a 10-point or more change, and time to 10-point or more deterioration from baseline were compared
- Eight key domains were pre-specified in the HRQL analysis plan: global HRQL, social functioning, role functioning, physical functioning, cognitive function, drowsiness, communication deficit and motor dysfunction
- Assessment timing: baseline, day 1 of each 4-week cycle, and end of treatment. Reasons for non-completion were documented wherever possible.
- Logistic regression was used to estimate odds ratios (OR) for the effect of treatment on proportions of patients with a ≥10 point improvement, and separately for a ≥10 point deterioration. The Kaplan-Meier method was used to determine the median time to HRQL scale deterioration (≥10 points), progression or death, whichever came first, for the eight domains.

Results

- Participation rates were >90% of patients still on study, except at end of treatment when 72 (64% of eligible participants) returned a HRQL form
- There were no differences in completion rates between arms
- No difference was observed between arms for mean change scores for any HRQL domain (Global QOL: Figure 1)
- No difference between arms comparing odds ratios for improvement or deterioration from baseline for 8 pre-specified domains (Table 1)
- Sustained improvements (≥10 points for at least two time points) were most commonly reported in motor dysfunction and cognitive, role and social function in both arms, likely reflecting a therapeutic effect of treatment
- Deterioration in HRQL was seen earlier than the median PFS of 3.5 months in all pre-specified domains, with no difference between arms (Figure 3). Approximately two thirds of patients had either a single or sustained HRQL deterioration preceding radiological/clinical disease progression and cessation of treatment
- Adding carboplatin to bevacizumab did not alter HRQL outcomes in the CABARET trial
- For each pre-specified domain, more than 50% of patients experienced at least one HRQL deterioration before documented disease progression
- Close to 50% reported clinically relevant improvements in at least one symptoms domain during treatment, indicating potential therapeutic benefit
- Given attrition in HRQL completion at end of treatment, time to HRQL deterioration is a robust clinical trial endpoint in this population

Conclusions

- Close to 50% reported clinically relevant improvements in at least one symptoms domain during treatment, indicating potential therapeutic benefit
- Almost half (53/115, 46%) symptomatic patients reported an improvement of 10 or more points in at least one of these domains

Acknowledgements: This is an independent investigator-initiated study conducted under the auspices of the Cooperative Trials Group for Neuro-Oncology (COGNO), coordinated at the NHMRC Clinical Trials Centre, University of Sydney as a multi-centre study, supported by Roche Products, Pty. Limited

For enquiries please contact:
Dr Kathryn Field
CABARET Study Chair
Email: Kathryn.Field@mh.org.au
Phone: (03) 93427000
Comparison between site and central radiological assessments for patients with recurrent glioblastoma on a clinical trial (CABARET)

KM Field (1), G Fitt (3), MA Rosenthal (1,2), J Simes (4), AK Nowak (5,6), H Wheeler (7), EJ Hovey (8), PM Phal (1)
Royal Melbourne Hospital (1), Department of Medicine, University of Melbourne (2), Austin Hospital (3), National Health and Medical Research Council Clinical Trials Centre, University of Sydney (4), Sir Charles Gardiner Hospital (5), School of Medicine and Pharmacology, University of Western Australia (6), Royal North Shore Hospital (7), Prince of Wales Hospital (8)

Background
- Assessment of magnetic resonance imaging (MRI) in glioblastoma (GBM) can be challenging
- The Australian Cancer Network Clinical Practice Guidelines for Neuro-oncology recommend central radiological review for clinical trials due to reported inter-observer variability in response assessment
- However, central review does not generally occur in real-time, and prior studies have documented that discordance between site and central radiological reviews is common
- Our aims were to compare central radiology review with site-determined date of progression and disease response assessment for patients on a recurrent GBM clinical trial (CABARET)

Methods
- MRI and clinical status at specified time points for patients on the CABARET trial were used to compare results of site versus central assessment of disease status
- Central review consisted of three expert neuro-radiologists who received specific training prior to assessing scans on trial
- Response Assessment in Neuro-Oncology (RANO) criteria were used both by sites and the central reviewers
- 10% of patients (n=12) were reviewed by neuro-radiologists who received specific training prior to assessing scans on trial
- Progression-free survival (PFS) and response rates were compared for site and central assessments
- The Kaplan-Meier method was used to describe PFS times. Proportional hazards regression was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) to compare rates of progression
- The weighted kappa statistic 0.31 indicating fair agreement overall

Results
- Differences in PFS date are shown in Table 1
- Where a discrepancy occurred, median difference = 1.8 months (approximate time between sequential scans on trial)
- Range up to 20.5 months for difference between site and central review

Table 1: Differences in PFS date between site and central radiology review

<table>
<thead>
<tr>
<th>Site</th>
<th>Central</th>
<th>Difference (m)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>0.0</td>
<td>0.86</td>
</tr>
<tr>
<td>PR</td>
<td>PR</td>
<td>0.0</td>
<td>0.53</td>
</tr>
<tr>
<td>SD</td>
<td>SD</td>
<td>0.0</td>
<td>0.86</td>
</tr>
<tr>
<td>PD</td>
<td>PD</td>
<td>0.0</td>
<td>0.53</td>
</tr>
</tbody>
</table>

- For 54 of 89 patients (61%) there was agreement for best response
- For 35 (39%) there was disagreement
- Weighted kappa statistic 0.31 indicating fair agreement overall

Comparison of site and central best response (Table 2):

- For 54 of 89 patients (61%) there was agreement for best response
- For 35 (39%) there was disagreement
- Weighted kappa statistic 0.31 indicating fair agreement overall

Table 2: Comparison of site and central best response assessments (kappa = weighted analysis)

<table>
<thead>
<tr>
<th>Site review</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>CR</td>
<td>PR</td>
<td>SD</td>
<td>PD</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Conclusions
- This study reinforces that off trial, clinical status together with radiology is an important determinant of whether a therapy is effective for an individual
Appendix 8: CABARET biomarker study poster (COGNO Annual Meeting 2016)

Introduction
The CABARET clinical trial, a randomized phase II study of Carboplatin and Bevacizumab in recurrent glioblastoma patients provided the tissues of clinical specimens to trial data.

Key questions cloud the value of Bevacizumab for recurrent glioblastoma:
1. Why is benefit from Bevacizumab seen only in some patients?
2. How do we predict these patients?

We used the CABARET dataset as a discovery cohort to identify the molecular phenotype (candidate molecular signature) of patients who responded to Bevacizumab.

We tested tissue n=56 for the expression level of 19 pre-selected proteins using immunohistochemistry (IHC).

Results
Biomarker Frequencies

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-MET</td>
<td>30/56</td>
</tr>
<tr>
<td>HIF2</td>
<td>40/56</td>
</tr>
<tr>
<td>CD34</td>
<td>20/56</td>
</tr>
<tr>
<td>CD45</td>
<td>30/56</td>
</tr>
<tr>
<td>CD8</td>
<td>40/56</td>
</tr>
<tr>
<td>S-100</td>
<td>20/56</td>
</tr>
<tr>
<td>LEF1</td>
<td>30/56</td>
</tr>
<tr>
<td>ANG</td>
<td>40/56</td>
</tr>
<tr>
<td>PDGFRB</td>
<td>20/56</td>
</tr>
</tbody>
</table>

Overall survival by Biomarker status

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-MET</td>
<td>90%</td>
</tr>
<tr>
<td>HIF2</td>
<td>80%</td>
</tr>
<tr>
<td>CD34</td>
<td>70%</td>
</tr>
<tr>
<td>CD45</td>
<td>60%</td>
</tr>
<tr>
<td>CD8</td>
<td>50%</td>
</tr>
<tr>
<td>S-100</td>
<td>40%</td>
</tr>
<tr>
<td>LEF1</td>
<td>30%</td>
</tr>
<tr>
<td>ANG</td>
<td>20%</td>
</tr>
<tr>
<td>PDGFRB</td>
<td>10%</td>
</tr>
</tbody>
</table>

High levels of C-MET and HIF2 in the tumour (pre-treatment) were associated with better overall survival when adjusted for age and MGMT methylation. Both C-MET and HIF2 are induced by hypoxia.

C-MET acts as a negative feedback inhibitor of MET receptor tyrosine kinase (RTK).

We would like to thank all of the staff and divisions at COGNO for supporting a biomarker project. Thank you to Roche and Cancer Council NSW for financial support.
Appendix 9: Signed supervisor declarations
Declaration for a thesis with publication

PhD and MPhil students may include a primary research publication in their thesis in lieu of a chapter if:

- The student contributed greater than 50% of the content in the publication and is the "primary author", i.e. the student was responsible primarily for the planning, execution and preparation of the work for publication.
- It has been peer-reviewed and accepted for publication.
- The student has approval to include the publication in their thesis from their Advisory Committee.
- It is a primary publication that reports on original research conducted by the student during their enrolment.
- The initial draft of the work was written by the student and any subsequent editing in response to co-authors and editors reviews was performed by the student.
- The publication is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in the thesis.

Students must submit this form, along with Co-author authorisation forms completed by each co-author, when the thesis is submitted to the Thesis Examination System: [https://tes.app.unimelb.edu.au/](https://tes.app.unimelb.edu.au/). If you are including multiple publications in your thesis, you will need to complete a separate form for each publication. Further information on this policy is available at: [gradresearch.unimelb.edu.au/preparing-my-thesis/thesis-with-publication](http://gradresearch.unimelb.edu.au/preparing-my-thesis/thesis-with-publication)

### A. PUBLICATION DETAILS (to be completed by the student)

<table>
<thead>
<tr>
<th>Full title</th>
<th>Health-related quality of life outcomes from CABARET: a randomized phase 2 trial of carboplatin and bevacizumab in recurrent glioblastoma.</th>
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</thead>
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<tr>
<td>Authors</td>
<td>Field KM, King MT, Simes J, Espinoza D, Barnes EH, Sawkins K, Rosenthal MA, Cher L, Hovey E, Wheeler H, Nowak AK.</td>
</tr>
<tr>
<td>Student’s contribution (%)</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Journal or book name</td>
<td>Journal of Neuro-Oncology</td>
</tr>
<tr>
<td>Volume/page numbers</td>
<td>J Neurooncol. 2017 May 22. doi: 10.1007/s11060-017-2479-8</td>
</tr>
<tr>
<td>Status</td>
<td>□ Accepted and in press</td>
</tr>
</tbody>
</table>

### B. STUDENT’S DECLARATION

I declare that the publication above meets the requirements to be included in the thesis.

Student’s name: Kathryn Field  
Student’s signature: [Signature]

Date (dd/mm/yy): 04/01/17

### C. PRINCIPAL SUPERVISOR’S DECLARATION

I declare that:

- the information above is accurate.
- The advisory committee has met and agreed to the inclusion of this publication in the student's thesis.
- All of the co-authors of the publication have reviewed the above information and have agreed to its veracity.
- "Co-Author Authorisation" forms for each co-author are attached.

Supervisor’s name: Mark Rosenthal  
Supervisor’s signature: [Signature]

Date (dd/mm/yy): 04/09/17
PhD and MPhil students may include a primary research publication in their thesis in lieu of a chapter if:

- The student contributed greater than 50% of the content in the publication and is the “primary author”, i.e. the student was responsible primarily for the planning, execution and preparation of the work for publication
- It has been peer-reviewed and accepted for publication
- The student has approval to include the publication in their thesis from their Advisory Committee
- It is a primary publication that reports on original research conducted by the student during their enrolment
- The initial draft of the work was written by the student and any subsequent editing in response to co-authors and editors reviews was performed by the student
- The publication is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in the thesis

Students must submit this form, along with Co-author authorisation forms completed by each co-author, when the thesis is submitted to the Thesis Examination System: https://tes.app.unimelb.edu.au/. If you are including multiple publications in your thesis you will need to complete a separate form for each publication. Further information on this policy is available at: gradresearch.unimelb.edu.au/preparing-my-thesis/thesis-with-publication

## A. PUBLICATION DETAILS (to be completed by the student)

### Full title
Continuing or ceasing bevacizumab beyond progression in recurrent glioblastoma: an exploratory randomized phase 2 trial

### Authors

### Student’s contribution (%)
>50%

### Journal or book name
Neuro-Oncology Practice

### Volume/page numbers
Neurooncol Pract npw025. DOI:https://doi.org/10.1093/nop/npw025

### Status
- [ ] Accepted and in press
- [x] Published
- Date accepted/ published 25/5/2017

## B. STUDENT’S DECLARATION

I declare that the publication above meets the requirements to be included in the thesis

### Student’s name
Kathryn Field

### Student’s signature

### Date (dd/mm/yy)
04/09/17

## C. PRINCIPAL SUPERVISOR’S DECLARATION

I declare that:
- the information above is accurate
- The advisory committee has met and agreed to the inclusion of this publication in the student’s thesis
- All of the co-authors of the publication have reviewed the above information and have agreed to its veracity
- “Co-Author Authorisation” forms for each co-author are attached.

### Supervisor’s name
Mark Rosenthal

### Supervisor’s signature

### Date (dd/mm/yy)
04/09/17
Declaration for a thesis with publication

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- The student contributed greater than 50% of the content in the publication and is the “primary author”, i.e. the student was responsible primarily for the planning, execution and preparation of the work for publication
- It has been peer-reviewed and accepted for publication
- The student has approval to include the publication in their thesis from their Advisory Committee
- It is a primary publication that reports on original research conducted by the student during their enrolment
- The initial draft of the work was written by the student and any subsequent editing in response to co-authors and editors reviews was performed by the student
- The publication is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in the thesis

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A. PUBLICATION DETAILS (to be completed by the student)

| Full title | Randomized phase 2 study of carboplatin and bevacizumab in recurrent glioblastoma. |
| Authors | Field, Simes, Nowak, Cher, Wheeler, Hovey, Brown, Barnes, Sawkins, Livingstone, Frielich, Phal, Fitt, Rosenthal |
| Student’s contribution (%) | >50% |
| Journal or book name | Neuro-Oncology |
| Status | □ Accepted and In press  □ Published  Date accepted/published 30/6/2015 |

B. STUDENT’S DECLARATION

I declare that the publication above meets the requirements to be included in the thesis

Student’s name: Kathryn Field

Student’s signature: [Signature]

Date (dd/mm/yyyy): 04/09/17

C. PRINCIPAL SUPERVISOR’S DECLARATION

I declare that:

- the information above is accurate
- The advisory committee has met and agreed to the inclusion of this publication in the student’s thesis
- All of the co-authors of the publication have reviewed the above information and have agreed to its veracity
- “Co-Author Authorisation” forms for each co-author are attached.

Supervisor’s name: Mark Rosenthal

Supervisor’s signature: [Signature]

Date (dd/mm/yyyy): 04/09/17
Declaration for a thesis with publication

PhD and MPhil students may include a primary research publication in their thesis in lieu of a chapter if:

- The student contributed greater than 50% of the content in the publication and is the “primary author”, i.e. the student was responsible primarily for the planning, execution and preparation of the work for publication.
- It has been peer-reviewed and accepted for publication.
- The student has approval to include the publication in their thesis from their Advisory Committee.
- It is a primary publication that reports on original research conducted by the student during their enrolment.
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<tr>
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<th>The role of early magnetic resonance imaging in predicting survival on bevacizumab for recurrent glioblastoma: Results from a prospective clinical trial (CABARET).</th>
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<tbody>
<tr>
<td>Authors</td>
<td>Field KM, Phal PM, Fitt G, Goh C, Nowak AK, Rosenthal MA, Simes J, Barnes EH, Sawkins K, Cher LM, Hovey EJ, Wheeler II.</td>
</tr>
<tr>
<td>Student’s contribution (%)</td>
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</tr>
</tbody>
</table>

B. STUDENT’S DECLARATION

I declare that the publication above meets the requirements to be included in the thesis.

Student’s name | Student’s signature | Date (dd/mm/yyyy)

Kathryn Field | [Signature] | 04/09/17

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Supervisor’s name | Supervisor’s signature | Date (dd/mm/yyyy)

[Signature] | 04/09/17
Appendix 10: Signed co-author declarations – Main paper
Co-author authorisation form

All co-authors must complete this form. By signing below co-authors agree to the listed publication being included in the student’s thesis and that the student contributed greater than 50% of the content of the publication and is the “primary author” ie. the student was responsible primarily for the planning, execution and preparation of the work for publication.

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| Student’s contribution (%) | >50% |
| Journal or book name | Neuro-Oncology |
| Status | ☒ Published | Date accepted/published 30/6/2015 |

---

B. CO-AUTHOR’S DECLARATION (to be completed by the collaborator)

I authorise the inclusion of this publication in the student’s thesis and certify that:

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Co-author’s name | Co-author’s signature | Date (dd/mm/yy) |
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<tr>
<td>JOHN SIMES</td>
<td>[Signature]</td>
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</table>
Co-author authorisation form

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<tbody>
<tr>
<td>Mark Rosenthal</td>
<td></td>
<td>17/08/17</td>
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</table>
Co-author authorisation form

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Co-author’s name: Wheeler

Co-author’s signature: [Signature]

Date (dd/mm/yy): 15/08/2015
Co-author authorisation form

All co-authors must complete this form. By signing below co-authors agree to the listed publication being included in the student’s thesis and that the student contributed greater than 50% of the content of the publication and is the “primary author” ie. the student was responsible primarily for the planning, execution and preparation of the work for publication.

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<tr>
<td>Dr Elizabeth Hovey</td>
<td>[Signature]</td>
<td>19/08/17</td>
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<table>
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<tr>
<td>Dr Lawrence Cher</td>
<td></td>
<td>31.7.17</td>
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<table>
<thead>
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The University of Melbourne  
CRICOS Provider Number: 00116K  
Last Updated 17 August 2015
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<table>
<thead>
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<th>Co-author’s name</th>
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<tbody>
<tr>
<td>Elizabeth Barnes</td>
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Co-author authorisation form

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<table>
<thead>
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<tr>
<td>Associate Professor Pramit Phal</td>
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The University of Melbourne
CRICOS Provider Number: 00116K

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>50%

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Volume/page numbers

Status
☑ Published

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Co-author's name

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| Full title | Randomized phase 2 study of carboplatin and bevacizumab in recurrent glioblastoma. |
| Authors | Field, Simes, Nowak, Cher, Wheeler, Hovey, Brown, Barnes, Sawkins, Livingstone, Freilich, Phal, Fitt, Rosenthal |
| Student’s contribution (%) | >50% |
| Journal or book name | Neuro-Oncology |
| Status | □ Accepted and in-press  □ Published  Date accepted/published 30/6/2015 |

B. CO-AUTHOR’S DECLARATION (to be completed by the collaborator)

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<td>Anna K Nowak</td>
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Appendix 11: Signed co-author declarations – Part 2 paper
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| Student’s contribution (%) | >50% |
| Journal or book name | Neuro-Oncology Practice |
| Volume/page numbers | Neurooncol Pract npw025. DOI:https://doi.org/10.1093/nop/npw025 |
| Status | □ Accepted and In-press □ Published □ Date accepted/published 25/5/2017 |

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Co-author’s name | Co-author’s signature | Date (dd/mm/yyyy)
---|---|---
John Simes | [Signature] | 23/5/2017
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Co-author’s name: Helen White

Co-author’s signature: [Signature]

Date (dd/mm/yy): 18/08/17
Co-author authorisation form

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<td>Dr. Elizabeth Hovey</td>
<td>[Signature]</td>
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Full title  Continuing or ceasing bevacizumab beyond progression in recurrent glioblastoma: an exploratory randomized phase 2 trial


Student’s contribution (%)  >50%

Journal or book name  Neuro-Oncology Practice

Volume/page numbers  Neurooncol Pract npw025. DOI:https://doi.org/10.1093/nop/npw025

Status  □ Accepted and In-press  ☑ Published  Date accepted/published 25/5/2017

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Co-author’s name  Dr Lawrence Cher

Co-author’s signature

Date (dd/mm/yy)  31.7.17
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| Elizabeth Barnes | | |
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| Status | ✗ Published | Date accepted/published 25/5/2017 |

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I authorise the inclusion of this publication in the student’s thesis and certify that:

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- the student contributed greater than 50% of the content of the publication and is the “primary author” ie. the student was responsible primarily for the planning, execution and preparation of the work for publication.

Co-author’s name | Co-author’s signature | Date (dd/mm/yy)
---|---|---
Anna K Nowak | [Signature] | 1/8/17
Co-author authorisation form

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**Full title**
The role of early magnetic resonance imaging in predicting survival on bevacizumab for recurrent glioblastoma: Results from a prospective clinical trial (CABARET).

**Authors**

**Student’s contribution (%)**
>50%

**Journal or book name**
Cancer

**Volume/page numbers**

**Status**
☐ Accepted and In-press  ☑ Published  Date accepted/published 5/7/2017

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**Co-author’s declaration**

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**Co-author’s name**

CHRISTINE G-H

**Co-author’s signature**

[Signature]

**Date (dd/mm/yyyy)**

14/08/17
Appendix 12: Signed co-author declarations - HRQL paper
Co-author authorisation form

All co-authors must complete this form. By signing below co-authors agree to the listed publication being included in the student’s thesis and that the student contributed greater than 50% of the content of the publication and is the “primary author” ie. the student was responsible primarily for the planning, execution and preparation of the work for publication.

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| Student’s contribution (%) | >50% |
| Journal or book name | Neuro-Oncology Practice |
| Status | □ Accepted and In-press  □ Published  Date accepted/published 22/5/2017 |

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<tr>
<td>John Simes</td>
<td>[Signature]</td>
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| Co-author’s name | Co-author’s signature | Date (dd/mm/yy) |
| Mark Rosenthal | [Signature] | 14/08/17 |
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<td>Dr H. Wheeler</td>
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<td>Dr Lawrence Cher</td>
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| Co-author’s name | Co-author’s signature | Date (dd/mm/yy) |
| David Espinoza | ✍️ | 01/08/17 |
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<td>Elizabeth Barnes</td>
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<tr>
<td>Madeleine T King</td>
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<td>1 Aug 2017</td>
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| Co-author’s name | Co-author’s signature | Date (dd/mm/yy) |
| Anna K Nowak | [Signature] | 1/8/17 |
Appendix 13: Signed co-author declarations – early MRI paper
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Co-author’s name: John Simes

Co-author’s signature: [Signature]

Date (dd/mm/yy): 23/5/2017
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Authors

Student’s contribution (%) >50%

Journal or book name
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Volume/page numbers

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Co-author’s name
Dr IT Wheeler

Co-author’s signature

Date (dd/mm/yy)
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| Elizabeth Barnes | | |
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Co-author's name: GREGORY  FITT  
Co-author's signature: [signature]  Date (dd/mm/yy): 01-08-2017
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<td>[Signature]</td>
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| John Simes | [Signature] | 18/09/17 |
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Co-author’s name
Gregory Fitt

Co-author’s signature

Date (dd/mm/yy) 17-09-2017
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Co-author’s name: Anna Nowak
Co-author’s signature: [Signature]
Date (dd/mm/yy): 18/09/17
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Co-author’s name: A/Prof Pramit Phal

Co-author’s signature:

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Co-author’s name: Mark A Rosenthal
Co-author’s signature: [Signature]
Date (dd/mm/yy): 18/09/17

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Co-author’s name  
Kate Sawkins

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