**ROLE OF BEVACIZUMAB IN NEWLY DIAGNOSED GLIOBLASTOMA**

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**TRIAL SUMMARY:** Benefits and risks of adding bevacizumab upfront to standard chemoradiation


Chemoradiation (CRT) with temozolomide (TMZ/CRT+TMZ) is the standard of care for newly diagnosed glioblastoma (GBM). This phase III trial, conducted by the Radiation Therapy Oncology Group (RTOG), North Central Cancer Treatment Group (NCCTG) and Eastern Cooperative Oncology Group (ECOG), evaluated whether adding bevacizumab (Bev) to standard CRT improves overall survival (OS) or progression-free survival (PFS) in this patient population.

Neurologically stable patients older than 18 years with Karnofsky performance score (KPS) ≥60 and >1cm³ tumour tissue block were randomized to standard CRT plus placebo (Arm 1) or standard CRT plus intravenous Bev 10 mg/kg every 2 weeks (Arm 2). Experimental treatment began at week 4 of radiation and then through 6 to 12 cycles of maintenance chemotherapy. Primary endpoints were OS and PFS, with significance levels of 0.023 and 0.002, respectively. At progression, treatment was unblinded and patients were allowed to cross over or continue Bev. Symptom, quality of life (QOL) and neurocognitive (NCF) testing was performed in most patients. Secondary analyses evaluated impact of methylguanine-methyltransferase enzyme (MGMT) methylation (meth) and prognostic 9-gene signature status.

Out of 978 registered patients, 637 were randomized. Inadequate tissue (n=105) and blood on imaging (n=40) were key reasons for nonrandomization. No difference was found between Arm 1 and Arm 2 for OS (median 16.1 vs 15.7 months; p=0.11). PFS was extended for Arm 2 (10.7 months vs 7.3 months in Arm 1; p=0.004). Patients with MGMT meth had superior OS (23.2 vs 14.3 months; p<0.001) and PFS (14.1 vs 8.2 months; p<0.001). Neither the 9-gene signature nor MGMT predicted selective benefit for Bev treatment, but best-prognosis patients (MGMT meth, favourable 9-gene) had a worse survival trend with Bev (15.7 vs 25 months; p=0.08). To date, 128 patients were unblinded on Arm 1 (salvage Bev in 86) and 87 patients on Arm 2 (continued Bev in 39). Increased grade ≥3 toxicity was seen with Bev, mostly neutropenia, hypertension and deep vein thrombi/pulmonary embolism (DVT/PE).

The authors concluded that the addition of Bev did not improve OS for newly diagnosed GBM patients; while it did improve PFS, this did not reach the significance criterion. MGMT and 9-gene profile did not identify selective benefit, but risk subset results suggested strongly against the upfront use of Bev in the best-prognosis patients. Full interpretation of the PFS results incorporating symptom burden, QOL and NCF is ongoing.

**COMMENTARY:** Glioblastoma is an aggressive, World Health Organization (WHO) grade IV primary brain tumour with a median OS of approximately 15 months with contemporary multimodality treatments. The current standard for newly diagnosed glioblastoma involves maximal safe surgical resection followed by concurrent chemoradiation (60 Gy in 30 fractions) with 75 mg/m² daily oral temozolomide for 6 weeks and then 6 to 12 months of adjuvant/maintenance temozolomide, 150–200 mg/m² for 5 days every 28 days (CRT + TMZ). As glioblastomas overexpress vascular endothelial growth factor A (VEGF-A) and demonstrate a high degree of vascularity, there is biologic rationale in evaluating antiangiogenic strategies in the management of glioblastomas. Bevacizumab, a monoclonal antibody against VEGF-A, has shown promise in recurrent and newly diagnosed glioblastoma based on early-phase clinical trials.

At the Society for Neuro-Oncology meeting in 2012 (SNO 2012), results from the phase III AVAglio trial (n = 921; mainly conducted in Europe) evaluating the addition of bevacizumab to standard of care with CRT + TMZ were presented; they demonstrated a PFS benefit of 4.4 months with bevacizumab (10.6 vs 6.2 months; HR 0.64, 95% CI 0.55–0.74; p<0.0001). Updated OS data from AVAglio presented at ASCO 2013, however, did not demonstrate a significant difference with added bevacizumab (16.8 vs 16.7 months; HR 0.88, 95% CI 0.76–1.02; p=0.0987).

At ASCO 2013, results from the Radiation Therapy Oncology Group (RTOG) 0825 trial, a second phase III trial evaluating the role of bevacizumab in newly diagnosed glioblastoma, were presented. This multicentre, double-blind, placebo-controlled trial randomized 637 patients following surgery in a 1:1 fashion to standard CRT + TMZ plus placebo (n=317; Arm 1) vs standard CRT + TMZ plus bevacizumab (n=320; Arm 2) given intravenously at 10 mg/kg every 2 weeks, starting at week 4 of CRT and...
through 6 to 12 cycles of maintenance chemotherapy. Inclusion criteria included age ≥18 years, KPS ≥70, stable neurologic status, central pathology confirmation with >1 cm³ of tumour tissue available and supratentorial location. The co-primary endpoints were OS and PFS, with secondary and tertiary endpoints of toxicity, neurocognitive function, health-related QOL and longitudinal measures of symptom burden. Secondary analyses included assessment of MGMT methylation status and a prognostic 9-gene signature. Treatment crossover was allowed at time of disease progression.

At a median followup of 20.5 months, RTOG 0825 did not demonstrate any difference in OS between the 2 arms, with median OS of 16.1 months in Arm 1 vs 15.7 months in Arm 2 (HR 1.13, 95% CI 0.93–1.37; p=0.21). Although an improvement in PFS was observed with the addition of bevacizumab (10.7 vs 7.3 months), this did not meet prespecified criteria for statistical significance (HR 0.79, 95% CI 0.66–0.94; p=0.007) vs prespecified PFS significance level of p<0.002. Prestratified molecular subgroup analyses with MGMT methylation status and a 9-gene signature did not identify a group of patients who benefited from the addition of bevacizumab, and a trend toward worsened survival was observed for patients with MGMT promoter methylation and favourable 9-gene signature. Secondary outcomes showed increased toxicities in the bevacizumab arm, including hypertension (4.6% vs 1.0%), neutropenia (15.1% vs 7.3%), DVT/PE (9.9% vs 7.7%), wound issues (2.3% vs 1.0%), GI perforation (1.3% vs 0.7%) and significant hemorrhage (1.3% vs 1.0%), whereas tertiary outcomes showed worsened neurocognitive function (p=0.038) and overall symptom interference with daily activities (p 0.001).²¹,²²

Despite promising early trial data, the large phase III RTOG 0825 and AVAglio trials have failed to demonstrate an OS benefit from adding bevacizumab to standard of care in patients with newly diagnosed glioblastoma. These findings reinforce the importance of conducting well-designed phase III clinical trials prior to implementing novel agents in clinical practice. The lack of OS benefit observed may reflect treatment crossover at time of disease progression (~31% in AVAglio, not yet fully reported in RTOG 0825), tumour heterogeneity, a relative lack of VEGF dependency at time of treatment initiation (vs at recurrence) and suboptimal drug delivery. Although similar PFS benefits were seen in RTOG 0825 and AVAglio, this finding was not statistically significant in RTOG 0825.

In contrast to the AVAglio trial, which showed improved health-related QOL in the bevacizumab arm (including prolonged KPS scores, reduced steroid usage, delayed time to definitive deterioration, and improved physical functioning, social functioning, motor dysfunction and communication deficit using the European Organization for Research and Treatment of Cancer [EORTC] QLQ-C30 and BN20 tools),²⁰ patient-reported outcomes from RTOG 0825 demonstrated adverse QOL outcomes during the progression-free period with bevacizumab. These discordant findings likely reflect differences in trial design, including QOL assessment and statistical techniques, lack of neurocognitive assessment in AVAglio, voluntary participation of QOL measurements in RTOG 0825 vs mandatory participation in AVAglio, and exclusion of biopsy-only patients in RTOG 0825. A combined analysis of patient-level data may provide further insight in relevant QOL outcomes.

Importantly, there are currently no predictive biomarkers associated with bevacizumab use. In RTOG 0825, subgroup analyses with MGMT promoter methylation status and a 9-gene signature did not predict benefit with bevacizumab, and in fact, an adverse survival trend was seen in the best-prognosis patients with MGMT promoter methylation and a favourable 9-gene signature. Intriguingly, an additional subgroup analysis of RTOG 0825 identified a potential predictive biomarker associated with benefit from bevacizumab, consisting of a molecular signature of over 40 genes.⁴

The clinical applicability of this signature will require further prospective validation. Additionally, future studies should seek to clarify whether specific molecular subtypes of glioblastoma are associated with different treatment outcomes with antiangiogenic therapies.⁵

Given the lack of OS benefit reported in both RTOG 0825 and AVAglio, current evidence does not support the addition of bevacizumab to standard of care in patients with newly diagnosed glioblastoma. Whether PFS represents an appropriate surrogate endpoint in glioblastoma is a matter of debate, especially given the conflicting QOL data to date. Presently in the Canadian context, the costs of bevacizumab are likely to outweigh the potential benefits. Future research should be aimed at identifying predictive biomarkers of antiangiogenic therapies, including bevacizumab, and clarifying their role within different molecular subtypes of glioblastoma. Currently, the use of bevacizumab in glioblastoma should be reserved for selected patients in the recurrent setting.

**IN BRIEF**

**Already known**
- Bevacizumab has shown promise in the setting of recurrent and newly diagnosed glioblastoma based on early-phase clinical trials.

**What this study showed**
- The addition of bevacizumab to standard of care in newly diagnosed glioblastoma did not improve overall survival, and patient-reported outcomes showed adverse qualify-of-life measures.

**Next steps**
- Further research will need to identify predictive biomarkers associated with bevacizumab use. Subgroup analysis of RTOG 0825 identified a molecular signature of over 40 genes that requires prospective validation.
Disclosure
Dr. Tsang reports no conflict of interest relevant to this article.

References