No Survival Advantage to Using Bevacizumab as First-Line Therapy for Glioblastoma

Written by **Wayne Kuznar**

Data from a Phase 3 study indicate that the use of bevacizumab (BEV) in glioblastoma should not be extended to the first-line setting. Currently, BEV is approved by the United States Food and Drug Administration for the treatment of recurrent glioblastoma.

Findings from the double-blind, placebo-controlled, randomized trial entitled Temozolomide and Radiation Therapy With or Without Bevacizumab in Treating Patients With Newly Diagnosed Glioblastoma [RTOG 0825; NCT00884741; Gilbert MR et al. *J Clin Oncol* 2013 (suppl; abstr 1)] were announced by Mark R. Gilbert, MD, University of Texas MD Anderson Cancer Center, Houston, Texas, USA, on behalf of the participating cooperative groups: RTOG, NCCTG and ECOG.

The current standard of care for glioblastoma is surgical resection followed by chemoradiation with temozolomide (TMZ), but despite this treatment average survival remains <18 months. Angiogenesis is a hallmark feature of glioblastoma, and vascular endothelial growth factor (VEGF)-A is the most common angiogenic factor produced by glioblastoma tumors. Dr. Gilbert and colleagues therefore explored the utility of BEV, a humanized monoclonal antibody against VEGF-A with demonstrated activity in recurrent glioblastoma, as first-line therapy.

In the trial, 637 neurologically stable adults with newly diagnosed glioblastoma underwent 3 weeks of standard chemoradiation with daily TMZ. Patients were then randomized to complete chemoradiation with TMZ with either either placebo or BEV (10 mg/kg IV Q2W). Patients then continued with maintenance TMZ (Days 1 to 5 of a 28-day cycle) with either placebo or BEV Q2W through 6 to 12 cycles. All patients had undergone surgical resection before starting chemoradiation; ~60% in each arm had gross total resection. Nearly 80% of patients received intensity-modulated radiation therapy. At disease progression, the study treatment arm designation could be revealed, at which time patients were allowed to cross over or continue BEV. In the placebo arm, 40.7% of patients crossed over to BEV; 20.9% of patients in the BEV arm stayed on BEV after progression (Table 1). The coprimary endpoints were overall survival (OS) and progression-free survival (PFS).

Adverse events that were more common with BEV compared with placebo included hypertension (4.6% vs 1.0%), deep vein thrombosis/pulmonary embolism (9.9% vs 7.7%), wound healing issues (2.3.% vs 1.0%), gastrointestinal perforation (1.3% vs 0.7%), significant hemorrhage (1.3% vs 1.0%), and neutropenia (15.1% vs 7.3%).

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Table 1. Chemotherapy Received at Progression

Disposition at Progression	Placebo Arm (n=198)	BEV Arm (n=181)
Protocol-related salvage BEV given	85 (40.7%)	39 (20.9%)
Nonprotocol treatment given	21 (10.0%)	26 (13.9%)
No chemotherapy given	103 (29.3%)	122 (65.2%)

The median OS was 16.1 months in those randomized to placebo versus 15.7 months with randomization to BEV (HR, 1.13; p=0.21). The median PFS was longer by 3.4 months in the BEV group relative to the placebo group (10.7 vs 7.3 months; HR, 0.79; p=0.007), but this difference did not reach the prespecified 30% reduction in hazard of failure with a p value of 0.004 prescribed for the study. Methylation status of the *O-6 Methylguanine-DNA Methyltransferase (MGMT)* gene promoter was prognostic, with unmethylated status demonstrating significantly worse median OS and PFS. A subgroup analysis based on *MGMT* methylation status, a 9-gene expression signature,

and Clinical Prognostic Groups found no differences in outcomes between treatments by subgroup (Table 2).

Table 2. Outcomes by Subgroup

Subgroup	Analysis Endpoint	Placebo Median (mos)	BEV Median (mos)	HR 95% CI	p Value
All patients	OS PFS	16.1 7.3	15.7 10.7	1.13 (0.93–1.30) 0.79 (0.66–0.94)	0.21 0.007
***MGMT*/Molecular Profile**					
MGMT meth, favorable molecular profile	OS PFS	25.0 13.5	16.7 13.0	2.25 (0.90–5.63) 1.39 (0.67–2.89)	0.08 0.38
MGMT meth, unfavorable molecular profile	OS PFS	25.3 8.4	21.1 16.9	1.24 (0.73–2.12) 0.63 (0.40–0.98)	0.43 0.04
MGMT unmeth, favorable molecular profile	OS PFS	14.6 7.3	13.9 10.1	1.02 (0.66–1.57) 0.72 (0.48–1.07)	0.94 0.10
MGMT unmeth, favorable unmolecular profile	OS PFS	14.6 5.4	14.0 9.8	1.13 (0.86–1.49) 0.86 (0.67–1.11)	0.36 0.25
RPA Class					
RPA Class III	OS PFS	19.8 9.5	20.6 14.9	0.98 (0.54–1.81) 0.74 (0.43–1.25)	0.48 0.13
RPA Class IV	OS PFS	15.6 7.3	15.7 10.8	1.14 (0.90–1.44) 0.78 (0.63–0.96)	0.14 0.01
RPA Class V	OS PFS	13.3 4.4	12.6 9.8	1.01 (0.66–1.56) 0.70 (0.46–1.06)	0.48 0.05

BEV=bevacizumab; meth=methylated; unmeth=unmethylated; OS=overall survival; PFS=progression-free survival; RPA=recursive partitioning analysis.

A prespecified analysis evaluated symptom burden, health-related quality of life and neurocognitive function in patients who were deemed to be progression-free. This study showed that patients on the BEV arm had a greater increase of patient-reported symptom burden and more decline of neurocognitive function and quality of life over time compared with patients in the placebo arm.

Preliminary molecular analysis from a subset of tumor tissues suggests that a molecular profile may be able to identify a subgroup of patients that could benefit from BEV in the first-line setting. However, until a patient subgroup can be identified, the results of the study do not support the use of BEV in the first-line setting for glioblastoma.

Predictive Molecular Biomarkers: Enriching Clinical Trial Populations for Glioblastoma

Written by Brian Hoyle

The results of a correlative study in the Phase 3 Temozolomide and Radiation Therapy With or Without Bevacizumab in Treating Patients With Newly Diagnosed Glioblastoma trial [Radiation Therapy Oncology Group (RTOG) 0825; NCT00884741; Sulman EP et al. *J Clin Oncol* 2013 (suppl; abstr LBA2010)] examining the molecular predictors of outcome and response to bevacizumab (BEV) added to standard chemoradiation for patients with newly diagnosed gliobastoma were discussed by Erik P. Sulman, MD, PhD, University of Texas MD Anderson Cancer Center, Houston, Texas, USA.

The study aimed to identify patients likely to respond to BEV during initial treatment for glioblastoma using a gene biomarker detectable in formalin-fixed, paraffin-embedded (FFPE) tissue.

The study focused on the mesenchymal signature, a set of genes upregulated in glioblastomas that are associated with invasive, angiogenesis functions and poor patient survival [Colman H et al. *Neuro Oncol* 2010]. BEV was hypothesized to beneficially affect patients (ie, prolonged overall survival [OS] and progression-free survival [PFS]) whose tumors exhibit the mesenchymal gene signature. A multigene signature that approximates mesenchymal enrichment was used for patient stratification in the trial. This multigene signature did predict modest improvement in PFS and OS in newly diagnosed glioblastoma patients treated with BEV compared with patients treated with a standard regimen. However, patients with more mesenchymal tumors did worse, which was the opposite of what was anticipated.

This predictive response was consistent with a whole genome transcriptome analysis in a subset of 114 cases, which detected a subgroup of mesenchymal genes expressing tumors that, when compared with other molecular subtypes, correlated with worse survival of patients treated with BEV.

Because of the survival differences observed in mesenchymal-expressing tumors, real-time polymerase chain reaction assays of a set of mesenchymal genes that were validated for use with FFPE tissue were used to build a predictive model with an optimal set of genes in a training/validation approach. A subset of 234 patients (out of a total of 637 randomized in the trial) was used for the analysis. The resulting predictor of response to BEV for patients with newly diagnosed glioblastoma (PRoB-GBM) separated patients into BEV-responsive and unresponsive groups. In the training set, PRoB-GBM predicted BEV response for PFS ($p<0.0001$) and OS ($p<0.0001$). The validation set also showed favorable responders with a significant response for PFS ($p=0.0385$) and OS ($p=0.0014$). Patients in the control arm displayed no difference, indicating that the biomarker is predictive and not prognostic.

In the subgroup of 234 patients, use of PRoB-GBM predicted BEV responders. For PFS, the target group of patients predicted to benefit from BEV treatment did display enhanced PFS (13.2 months) as compared with 7.2