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

months in the other patient group (p<0.0001). Similarly, OS was enhanced in the predicted target group (20.3 months) versus 10.4 months in the other group (p<0.0001).

The PRoB-GBM unfavorable group (ie, predicted to respond poorly to BEV) correlated with both the unfavorable (ie, more mesenchymal) multigene assay used to stratify patients in the trial as well as to the mesenchymal class identified by transcriptome analysis, suggesting that the predictive responder group was low in mesenchymal gene expression. In multivariate analyses, PRoB-GBM showed a strong interaction with treatment arm (placebo vs BEV) and, within the BEV arm only, was predictive of OS independent of prognostic factors including methylated or unmethylated *MGMT* gene, and RTOG Recursive Partitioning Analysis of Glioma class.

Within the trial, patients who experienced tumor recurrence (including those in the control arm) could be given salvage treatment with BEV. In these patients, PRoB-GBM was not predictive for salvage treatment, indicating that the PRoB-GBM biomarker may be useful only in the newly diagnosed setting.

Thus, the developed biomarkers represent a molecular diagnostic tool that can be used to identify patients for BEV treatment for newly diagnosed glioblastoma using FFPE tissue.

Antiangiogenesis Therapy With Bevacizumab Improves Survival in Metastatic or Relapsed Cervical Cancer

Written by **Wayne Kuznar**

Bevacizumab (BEV) is the first targeted agent that when added to standard chemotherapy improved overall survival (OS) in women with metastatic or relapsed cervical cancer. This finding from a randomized, open-label Phase 3 study represents the first instance in which a targeted therapy has significantly prolonged survival in this setting. Results were presented by Krishnansu S. Tewari, MD, University of California Irvine, Irvine, California, USA.

Acquired drug resistance to platinum-based therapies has rendered these treatments less effective for cervical cancer recurrence, leading to poor outcomes. Tumor neovascularization imparts an aggressive course in cervical cancer, prompting this investigation of an antiangiogenesis therapy targeting the vascular endothelial growth factor A (VEGF-A) in patients with relapsed or advanced disease.

The Paclitaxel and Cisplatin or Topotecan With or Without Bevacizumab in Treating Patients With Stage IVB, Recurrent, or Persistent Cervical Cancer study of the Gynecological Oncology Group [GOG 240; NCT00803062; Tewari KS et al. *J Clin Oncol* 2013 (suppl; abstr 3)] included 452 women with recurrent or metastatic cervical cancer who were randomized to 1 of 4 treatment arms using a 2x2 factorial design: 1) treatment with paclitaxel (PAC) 135 or 175 mg/m^2 intravenously (IV) plus cisplatin (CIS) 50 mg/m^2 IV; 2) PAC/CIS plus BEV 15 mg/kg IV; 3) PAC 175 mg/m^2 IV plus topotecan (TOPO) 0.75 mg/m^2 on Days 1 to 3; or 4) PAC/TOPO plus BEV 15 mg/kg IV. Patients were treated every 21 days until progression, unacceptable toxicity, or complete response. To be eligible, patients had to have measureable disease, a performance status of 0 to 1, and no prior chemotherapy for recurrent disease. The nonplatinum regimen selected was based on laboratory data indicating synergy between TOPO and microtubule-interfering agents and demonstrated activity in recurrent cervical cancer.

A preplanned interim analysis comparing the platinum doublet and the nonplatinum doublet on median OS showed no significant difference between the chemotherapy-alone groups (median OS, 15 months with PAC/CIS versus 12.5 months with PAC/TOPO; one-sided p=0.880).

Median progression-free survival was improved from a mean of 5.9 months with chemotherapy alone to 8.2 months with the addition of BEV. Similarly the response rate was significantly higher with BEV plus chemotherapy compared with chemotherapy alone (48% vs 36%; p=0.0078), with significantly more complete responses in patients treated with anti-VEGF therapy.

Median OS was 17.0 months in BEV-treated patients versus 13.3 months in the arms assigned to chemotherapy alone (HR, 0.71; p=0.0035). Median OS was superior with the addition of BEV to either chemotherapy regimen, although this difference achieved statistical significance when comparing BEV/CIS/PAC to CIS/PAC alone (17.5 vs 14.3 months, respectively; p=0.0348).

There were four fatal adverse events each with BEV and chemotherapy alone. No new side effects were identified with BEV. Gastrointestinal fistula grade ≥3, a recognized complication of BEV, occurred in 7 (3%) of BEV-treated patients and none of those on chemotherapy alone. Grade ≥2 hypertension was a complication in 54 patients (25%) of the BEV group and 4 (2%) of the group that received chemotherapy alone, but no patient withdrew from the study because of hypertension.

Health-related quality of life was measured by the Functional Assessment of Cancer Therapy–Cervical Cancer-Trial Outcome Index. The score on this index ranges from 0 to 116 points, with a clinically meaningful change being 4 to 5 points, said Dr. Tewari. Scores on this index were marginally lower, a maximum of 2.95 points and a mean of 1.2 points lower (p=0.3), in the BEV groups compared with