The Addition of Bevacizumab to Standard Radiation Therapy and Temozolomide

Followed by Bevacizumab, Temozolomide and Irinotecan for

Newly Diagnosed Glioblastoma

Running Title: Addition of Bevacizumab to Radiation Therapy & Temozolomide

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STATEMENT OF TRANSLATIONAL RELEVANCE

Bevacizumab and irinotecan are active against recurrent glioblastoma. This manuscript reports on the addition of bevacizumab to standard radiation therapy and daily temozolomide followed by temozolomide and the addition of bevacizumab and irinotecan. The current trial is a logical next step in the investigation of inhibitors of vascular endothelial growth factor for the treatment of glioblastoma by moving the bevacizumab/irinotecan to the newly diagnosed setting. The current trial reports on important safety and efficacy results. Both the progression-free and overall survival rates are prolonged compared to historical controls. Given the limitations of single institution phase II trials, the ongoing phase III randomized, placebo-controlled bevacizumab trials are essential to understand the role of bevacizumab for newly diagnosed glioblastoma.

ABSTRACT

Purpose

To determine if the addition of bevacizumab to radiation therapy and temozolomide, followed by bevacizumab, temozolomide and irinotecan for newly diagnosed glioblastoma patients is safe and effective.

Experimental Designs

Seventy five patients with newly diagnosed glioblastoma were enrolled on this phase II trial that investigated the addition of bevacizumab to standard radiation therapy and daily temozolomide followed by the addition of bevacizumab and irinotecan to adjuvant temozolomide. The bevacizumab was given at 10 mg/kg every 14 days beginning a minimum of 4 weeks post-
craniotomy. Two weeks after radiation therapy, the patients began 6-12 cycles of 5-day temozolomide with bevacizumab and irinotecan every 14 days. The primary endpoint was the proportion of patients alive 16 months after informed consent.

Results

The therapy had moderate toxicity. Three patients came off study during radiation therapy, one of whom had a grade 2 CNS hemorrhage. Seventy patients started the post-radiation therapy, and 16 (23%) terminated this adjuvant therapy early due to toxicity. The median overall survival was 21.2 months (95% CI 17.2-25.4), and 65% of the patients were alive at 16 months (95% CI: 53.4%, 74.9%). The median progression-free survival was 14.2 months (95% CI 12-16).

Conclusion

The addition of bevacizumab to standard radiation therapy and temozolomide followed by bevacizumab, irinotecan and temozolomide for the treatment of newly diagnosed glioblastoma has moderate toxicity and may improve efficacy compared with historical controls. The results from phase III trials are required before the role of bevacizumab for newly diagnosed glioblastoma is established.
INTRODUCTION

Glioblastoma is a devastating malignancy, with deleterious consequences on patients’ quality of life and a poor survival rate. There are approximately 14,000 new cases of glioblastoma diagnosed in the United States annually. (1) The prognosis remains poor, with a median survival of 12-18 months.(2-4) The addition of temozolomide to radiation therapy has improved the survival and has become the standard of care for newly-diagnosed glioblastoma.(4) For patients who underwent a surgical resection, the median survival for patients treated with radiation therapy and daily temozolomide followed by six months of adjuvant temozolomide was 15.8 months.(4) Importantly, the five-year survival was improved with the addition of temozolomide, with 9.8% of patients alive in the combination chemo-radiation therapy group compared 1.9% in the radiation therapy group.(5)

Further advances in the survival of patients with glioblastoma must exploit tumor biology. The tumor microenvironment is quite aberrant in glioblastoma, with high interstitial pressure, low pH, and hypoxia, all of which favor tumor development, as well as resistance to chemotherapy and radiation therapy.(6) One of the primary mediators of the tumor microenvironment is vascular endothelial growth factor (VEGF).(7, 8) Glioblastomas have the highest levels of VEGF among malignancies.(9) In addition, VEGF levels appear to be prognostic, with higher levels portending a poor prognosis.(10)

Bevacizumab is a humanized monoclonal antibody to VEGF. Bevacizumab is an active treatment for recurrent glioblastoma.(11-13) In a randomized phase 2 trial of bevacizumab or bevacizumab with irinotecan, both groups demonstrated a higher response rate and six month progression-free survival than historical controls.(11) The original recurrent glioblastoma studies that investigated bevacizumab were in combination with irinotecan, so irinotecan was
added to the adjuvant bevacizumab and temozolomide in this study to maximize efficacy. Also, the phase II randomized study of bevacizumab or bevacizumab and irinotecan in recurrent glioblastoma patients reported higher response rates and 6 month progression free survivals with the combination. The current trial was designed to incorporate an anti-VEGF therapy into the treatment for newly diagnosed glioblastoma patients. In addition, irinotecan was added to adjuvant temozolomide with the goal of synergizing a topoisomerase 1 inhibitor with an alkylating agent.

METHODS

Patients: Seventy-five newly diagnosed glioblastoma patients were enrolled in the trial and had received no therapy for their tumor besides surgical resection. Patients had a Karnofsky performance status \( \geq 60\% \), and were \( \geq 18 \) years of age. Patients enrolled a minimum of two weeks but not > six weeks from their last surgical procedure. Eligibility required adequate hematologic and organ function. Patients had uridine glucuronosyl transferase (UGT) genotyping. Patients with \( \geq \) grade 2 CNS hemorrhage on their baseline MRI were excluded. All patients gave their informed consent and the protocol was approved by the Duke Institutional Review Board.

TREATMENT

Surgery – The protocol did not mandate the type of surgery however patients who underwent only biopsy were enrolled in a separate trial for unresectable patients. Patients were evaluated following craniotomy and were required to have fully recovered from their last surgical procedure.
Radiation Therapy – Patients received radiation therapy according to standard Radiation Therapy Oncology Group guidelines for a glioblastoma beginning 2-6 weeks after their craniotomy. The primary field was treated to 50.4 Gy in 1.8 Gy daily fractions followed by a boost of 9 Gy, also at 1.8 Gy daily fractions. The total dose was 59.4 Gy delivered over 33 fractions. The details about the radiation and toxicity have been reported.(14)

Temozolomide during Radiation Therapy – Patients took daily temozolomide at 75 mg/m²/day throughout the course of radiation therapy. Temozolomide was taken one hour prior to the radiation therapy. Patients had a CBC weekly and serum chemistries every other week during radiation therapy. Temozolomide was held if the patient developed ≥ grade 3 thrombocytopenia, ≥ grade 4 neutropenia, or ≥ grade 4 non-hematologic toxicity caused by temozolomide. Temozolomide was restarted at 50 mg/m²/day when the ANC ≥ 1,500, platelet count ≥ 125,000, SGOT and total bilirubin < 1.5 times the upper limits of normal, and the serum creatinine ≤ 1.5 mg/dl. If the patient had recurrent toxicity as specified above at 50 mg/m²/day, temozolomide was held for the duration of radiation therapy.

Bevacizumab – Bevacizumab was administered every 14 days at a dose of 10 mg/kg, beginning a minimum of 28 days after the craniotomy and was given during the radiation therapy. Bevacizumab was held for any ≥ grade 3 bevacizumab-related adverse events until the toxicity resolved to ≤ grade 1. Bevacizumab was discontinued for ≥ grade 2 pulmonary or CNS hemorrhage, or any grade 4 bevacizumab-related adverse event.
Adjuvant temozolomide, bevacizumab, and irinotecan – Two weeks following the completion of radiation therapy, the patient underwent re-evaluation including an MRI of the brain. As long as there was no evidence of tumor progression and all treatment related toxicities had resolved to ≤ grade 1, the patient proceeded with 6-12 months of adjuvant temozolomide, bevacizumab and irinotecan. Temozolomide was dosed at 200 mg/m²/day, day one through five of each 28 day cycle. Bevacizumab was dosed at 10 mg/kg every 14 days. Irinotecan was dosed every 14 days at 125 mg/m² for patients not on an enzyme inducing antiepileptic drug (EIAED). Irinotecan was dosed at 340 mg/m² for patients on an EIAED. Patients homozygous for the UGT 6/6 alleles or heterozygous for the 6/7 alleles received full dose irinotecan. Patients homozygous for the UGT 7/7 alleles received reduced dose irinotecan, those not on EIAEDs received 75 mg/m² and patients on EIAEDs received 275 mg/ m² every two weeks. Each cycle was 28 days.

Subsequent cycles were started when patients met retreatment criteria including an ANC ≥ 1000 cells/µl, platelet count > 100,000/µl, SGOT and bilirubin < 1.5 X normal and a serum creatinine of ≤ 1.5 mg/dl, and resolution of all treatment related toxicities to < grade 1.

**Evaluation Procedures**

Patients had a CBC with differential weekly, complete metabolic panel and blood pressure check every two weeks, and a urinalysis with a protein to creatinine ratio every four weeks. Every eight weeks, they also underwent a physical exam, MRI of the brain, and toxicity assessment. MRI scans were evaluated using standard response assessment in neuro-oncology (RANO) criteria,(15) such that every image in each series was evaluated. In addition to MRI assessments, clinical status, corticosteroid dose, and Karnofsky performance status were determined at each evaluation. Study investigators used the constellation of clinical findings and MRIs to determine
progression. The RANO criteria define progression as clinical deterioration not attributable to concurrent medications or conditions, as well as increase in the post-contrast or T2/FLAIR non-enhancing lesions.

**Treatment Duration**

The protocol was originally written for six 28 day cycles of adjuvant therapy. After the protocol was begun, some patients requested continuing for a total of 12 cycles. The protocol was amended so the patients had the choice of continuing their adjuvant therapy to complete a full twelve cycles or to stop at six cycles.

**Statistics**

Efficacy assessments for the study regimen were based upon assessment from the time of consent to participate on the trial, and the analysis was intent to treat. The primary endpoint and basis for sample size calculation was the proportion of patients alive 16 months after protocol enrollment based upon a median survival of 15.8 months for resected patients treated with standard treatment. (4) If the true proportion of survivors was 45% or less, then the study treatment regimen would not be considered worthy of further development without modification. However, if the true proportion of survivors was 60% or greater, then there would be interest in further evaluating the study regimen. The Kaplan-Meier estimator was used to describe the survival and progression-free survival of patients treated with the combination chemotherapy treatment.

The effect of various patient specific prognostic factors on overall and progression-free survival was examined using a series of Cox models each with a single predictor. Hazard ratios and
associated Wald chi-square test results are reported. One of the patient specific prognostic factors was the recursive partitioning analysis (RPA) class, developed and verified by the RTOG.(16)

A landmark analysis was performed to compare survival outcomes between study patients who received 6 cycles of temozolomide/bevacizumab/irinotecan and those who received more than 6 cycles. For this analysis, overall and progression free survival was computed from the time of the 6th cycle for all patients who completed at least six cycles without evidence of progression.

RESULTS

Patient Characteristics

The initial 75 patients enrolled in the trial are included in this survival analysis, with the data cutoff May 13, 2010. All patients had a minimum follow-up of 18 months. Patients enrolled between April 15, 2007 and September 4, 2008. Patient characteristics are listed in Table 1.

Overall Survival

The primary end point of the trial was the proportion of patients alive 16 months after consenting to the clinical trial for their newly diagnosed glioblastoma. The median follow-up was 23.1 mos (95% CI 21.7-26.1). The median time from signing consent to starting therapy was 7 days. Sixty-five percent (95% CI 53.4-74.9) of the patients were alive 16 months after signing informed consent. The median overall survival was 21.2 months (95% CI 17.2-25.4). The one year survival was 78.7% (95% CI 67.6-86.3) and the two year survival was 44.9% (95% CI 32.7-56.5). Figure 1 is the Kaplan-Meier overall and progression-free survival curves.
Progression-free Survival

The median progression-free survival was 14.2 months (95% CI 12-16). The one year progression-free survival was 62.7% (95% CI 50.7-72.5), and the two year progression-free survival was 13.3% (95% CI 6.1-23.3).

Overall Survival from the Time of Progression

Following documented tumor progression, the median overall survival was five months (95% CI 2.1-7.8), with a range of one month to 27+ months. Patients were treated with a number of different regimens at the time of progression, the majority included bevacizumab.

Toxicity During Combined Radiation Therapy Daily Temozolomide and Bevacizumab

The addition of bevacizumab to radiation therapy and daily temozolomide had minimal toxicity. Seventy-two of the 75 patients (96%) completed the radiation therapy, while three patients terminated protocol-prescribed radiation treatment early for different reasons – one patient had a grade 2 CNS hemorrhage; one patient had pancytopenia; and the third patient had a symptomatic pulmonary embolus. All three patients subsequently completed their radiation therapy off protocol. In addition to the three patients who came off study during their radiation therapy, three patients had their daily temozolomide held for hematologic toxicity including two patients with grade 4 thrombocytopenia, and one patient with grade 4 neutropenia. Temozolomide was restarted at a reduced dose for these patients and they were able to complete planned radiation therapy including co-administration of temozolomide for >75% of planned days. The mean number of doses of bevacizumab during radiation therapy was three, with a range of 1-4. In addition to the three patients who came off of study during the radiation therapy, the two patients
with grade 4 thrombocytopenia had their bevacizumab held and another patient had one dose of bevacizumab held to repair a stitch abscess. Two patients had tumor progression following radiation therapy, so never started the adjuvant chemotherapy and bevacizumab.

**Toxicity during the adjuvant temozolomide, bevacizumab, and irinotecan**

Patients received between 6 and 12 cycles of temozolomide, bevacizumab and irinotecan on study. Six patients (8%) developed grade 4 thrombocytopenia and an additional four patients (5%) developed grade 4 neutropenia. There were two toxic deaths, one from neutropenic sepsis and one from a pulmonary embolism. In addition, sixteen of the 70 patients (23%) that started adjuvant temozolomide, bevacizumab and irinotecan terminated protocol treatment for toxicity, including one bowel perforation, likely attributable to the bevacizumab. The grade 4 hematologic toxicities and reasons the patients came off study during the adjuvant chemotherapy are listed in Table 2.

**Prognostic Factors**

We investigated a number of patient specific prognostic factors to determine if they predicted progression-free or overall survival. An analysis of tumor specific prognostic factors, such as MGMT promoter methylation status, is underway and the results will be reported separately. The list of prognostic factors examined in the analysis included age (as a continuous variable), age group (≥50 vs <50), anti-epileptic drug (EIAED vs non-EIAED), anti-epileptic drug (EIAED vs none), anti-epileptic drug (non-EIAED vs none), anti-epileptic drug (EIAED vs non-EIAED/none), steroid (dexamethasone vs none), steroid dose (daily total), UGT1A1 genotype (homozygous 7/7 vs homozygous 6/6 or heterozygous 6/7), KPS (continuous), KPS group (<90
vs ≥90) RPA class (4 vs 3), resection type (subtotal vs gross total), time from surgery to XRT (weeks), and time from surgery to XRT (<4 vs ≥ 4 weeks). Greater age, subtotal resection, and RPA class 4 were significant predictors of poorer overall survival. Dexamethasone usage was a significant predictor of poorer progression-free survival, with the effect of uncategorized age, poorer KPS, and subtotal resection trending towards statistical significance. Table 3 lists the clinical characteristics associated with overall and progression-free survival.

**Six cycles versus 12 cycles**

A landmark analysis was done to determine if there were any differences in overall survival or progression-free survival between patients who completed 6 cycles versus those patients that received more than 6 cycles. There were no differences between the two groups.

**DISCUSSION**

The prognosis for newly diagnosed glioblastoma remains poor with median overall survival in the 12-18 month range. (2-4) The phase III EORTC/NCIC study demonstrated that the addition of temozolomide to standard radiation therapy followed by adjuvant temozolomide improved median overall survival of newly diagnosed glioblastoma patients by 2.5 months to 14.6 months, compared to 12.1 months with radiation therapy alone. (4) This phase III trial established a new standard of care for newly diagnosed glioblastoma patients using radiation therapy plus concomitant and adjuvant temozolomide. However, the prognosis remains relatively poor, with less than 10% of patients alive at five years with the combination therapy. (5) VEGF is a critical determinant of glioblastoma biology. (6, 15) Glioblastoma tumors have the highest levels of VEGF compared to other tumor types, and the more VEGF, the worse the prognosis. (9, 10) Bevacizumab, a humanized monoclonal antibody to VEGF, has demonstrated activity in
The current phase 2 trial reports the addition of bevacizumab to standard radiation therapy and temozolomide followed by adjuvant temozolomide, bevacizumab and irinotecan for newly diagnosed glioblastoma. Overall, the regimen was tolerable with moderate toxicity and there is a suggestion of an improvement in both progression-free survival and overall survival compared to historical controls.

At the time the current trial was designed, the most robust data was the EORTC/NCIC phase III study. The current trial was developed to compare with the temozolomide plus radiation therapy arm, and only included those patients that underwent surgical resection because every patient in the current trial underwent surgical resection. The goal of the trial was to provide safety and efficacy data to justify a phase III trial. The primary endpoint was the percentage of patients alive sixteen months from the time of study enrollment, with a goal of 60% overall survival. The current trial resulted in 65% overall survival at 16 months, compared to 50% among patients treated on the EORTC/NCIC study with concurrent temozolomide and radiotherapy after resection.(4) Furthermore, median overall survival on our study was 21.2 months. Our survival data are similar to those reported in a phase 2 study from UCLA that added bevacizumab to standard radiation therapy and temozolomide followed by temozolomide and bevacizumab.(17) The UCLA trial reported a median overall survival of 19.6 months. The authors compared the data to a non-randomized, concurrently treated group that did not receive bevacizumab as part of their initial therapy. Selection bias and treatment at the time of progression make the comparison difficult to interpret. In addition, the UCLA study reported survival from the date of diagnosis, not the date of enrollment. Both the EORTC/NCIC and our study reported survival from the date of enrollment, which was a median one month after diagnosis. The rationales for including
irinotecan in the adjuvant therapy were to synergize a topoisomerase 1 inhibitor with an alkylating agent and to inhibit hypoxia inducing factor-1 alpha (HIF-1 α). There is some data that topoisomerase 1 inhibitors inhibit HIF-1 α.(18, 19) It is impossible to determine the role of irinotecan in the results, if selection bias or irinotecan contributed to the approximate 2.5 month improvement in overall survival in our study vs the UCLA study.

However, our study results should be interpreted with caution for several reasons. First, the care for glioblastoma patients has evolved over the past decade, with a steady improvement in the overall survival, compared to historical controls.(20) Three recent single agent phase II studies from the New Approaches to Brain Tumor Therapy CNS consortium (NABTT) reported a median overall survival of approximately 18-20 months.(20, 21) Importantly, these three studies also measured overall survival from the date of diagnosis rather than the date of study enrollment. Second, results of single-institution studies frequently report encouraging results that are not confirmed in phase 3 trials due to several factors, including selection bias. Finally, further follow-up is required for maturation of our study data.

There is a theoretical risk of including anti-VEGF therapy in the treatment of newly diagnosed glioblastoma patients. In the absence of VEGF, tumors may co-opt normal vessels, which may result in a more invasive phenotype and less concentrated mass of tumors.(22-24) There are pre-clinical reports that the inclusion of anti-VEGF therapy into the therapy of malignant gliomas may produce a more invasive phenotype.(23) This raises the concern that the inclusion of bevacizumab in the therapy for newly diagnosed patients will result in an improvement in the progression free survival, but no improvement in the overall survival. However, the two phase 2 trials to date that included bevacizumab in the treatment of newly diagnosed glioblastoma patients (our study and that cited in reference 17) suggest that overall survival may be improved.
The current trial of the addition of bevacizumab to radiation therapy and temozolomide followed by temozolomide, bevacizumab, and irinotecan reports important safety data about the inclusion of bevacizumab in the treatment of newly diagnosed glioblastoma, and also reports a suggestion of improvement in the progression free survival. It is critical to complete the two large phase III placebo-controlled trials investigating the inclusion of bevacizumab in the treatment of newly diagnosed glioblastoma patients, as well as, understanding VEGF resistance to further improve the survival in glioblastoma.
REFERENCES

Table 1. Patient Characteristics

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<th>Characteristic</th>
<th>Total (n)</th>
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<tr>
<td>Total</td>
<td>75 patients</td>
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<tr>
<td>Male/Female</td>
<td>45/30</td>
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<tr>
<td>Median age</td>
<td>55.6 (range 19 – 78)</td>
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<td>Gross total resection/subtotal resection</td>
<td>40/35</td>
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<tr>
<td>Karnofsky Performance Status</td>
<td></td>
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<tr>
<td>70 to 80:</td>
<td>22</td>
</tr>
<tr>
<td>90 to 100:</td>
<td>53</td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td>Yes – 53 / No – 22</td>
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<td>Median dose of Dexamethasone</td>
<td>4 mg (0 to 40 mg)</td>
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<td>Antiepileptic drug</td>
<td>Yes – 63 / No – 12</td>
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<tr>
<td>Enzyme inducing antiepileptic drug vs. non-enzyme inducing antiepileptic drug</td>
<td>23/40</td>
</tr>
<tr>
<td>Median # days from craniotomy to initiation of radiation therapy</td>
<td>28 (17-55)</td>
</tr>
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Table 2. Toxicity during Temozolomide, Bevacizumab and Irinotecan

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Recurrent grade 4 thrombocytopenia</td>
<td>2 (2.9%)</td>
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<tr>
<td>DVT/PE</td>
<td>4 (5.7%)</td>
</tr>
<tr>
<td>GI toxicity</td>
<td></td>
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<tr>
<td>Bowel perforation</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Rectal abscess</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 (1.4%)</td>
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<tr>
<td>Fatigue w/decreased KPS</td>
<td>5 (7.1%)</td>
</tr>
<tr>
<td>PCP</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>1 (1.4%)</td>
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Table 3. Cox models predicting overall and progression-free survivals

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<thead>
<tr>
<th>Covariate</th>
<th>Overall survival</th>
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<th>Progression-free survival</th>
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<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>Wald Chi-square p</td>
<td>Hazard Ratio</td>
<td>Wald Chi-square p</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Age at consent (continuous)</td>
<td>1.05 (1.02, 1.08)</td>
<td>0.01</td>
<td>1.02 (1.04)</td>
<td>0.09</td>
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<td>Age group (≥50 vs. &lt;50)</td>
<td>2.06 (0.99, 4.29)</td>
<td>0.05</td>
<td>1.52 (0.84, 2.72)</td>
<td>0.16</td>
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<td>Steroid (dexamethasone vs. none)</td>
<td>1.63 (0.81, 3.3)</td>
<td>0.17</td>
<td>1.94 (1.08, 3.49)</td>
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<td>KPS (continuous)</td>
<td>0.96 (0.93, 1)</td>
<td>0.05</td>
<td>0.97 (0.94, 1)</td>
<td>0.06</td>
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<tr>
<td>RPA Class (4 vs. 3)</td>
<td>2.37 (1.06, 5.33)</td>
<td>0.04</td>
<td>1.73 (0.92, 3.27)</td>
<td>0.09</td>
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<tr>
<td>Resection type (Subtotal vs. Gross total)</td>
<td>2.02 (1.09, 3.72)</td>
<td>0.02</td>
<td>1.63 (0.98, 2.7)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Figure Legend:

**Figure 1.** Progression-free and overall survivals from time of consent.
The Addition of Bevacizumab to Standard Radiation Therapy and Temozolomide Followed by Bevacizumab, Temozolomide and Irinotecan for Newly Diagnosed Glioblastoma

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