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Adding bevacizumab to initital glioblastoma treatment doesn't improve overall survival

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Results of a randomized phase III clinical trial conducted by the Radiation Therapy Oncology Group determined that adding bevacizumab to initial treatment for glioblastoma did not improve patient overall survival or progression-free survival. Results appear in the Feb. 20, 2014, issue of the *New England Journal of Medicine*.

Glioblastoma (GBM) is the most common primary malignant adult brain tumor and, despite treatment advances in recent years, the average survival of patients enrolled in clinical trials is less than 16 months with few patients living beyond five years. GBM tumors are characterized by angiogenesis—the formation of new blood vessels that support tumor growth stimulated by the GBM-produced vascular endothelial growth factor A (VEGF-A). Bevacizumab is a monoclonal antibody that targets VEGF-A production to block the growth of tumor-derived blood vessels.

"Clinical trials evaluating the addition of bevacizumab to standard treatment for recurrent glioblastoma demonstrated clinical benefit and led to the drug's U.S. Food and Drug Administration approval for this indication," says Mark Gilbert, M.D., Radiation Therapy Oncology Group 0825 principal investigator and professor of neuro-oncology at The University of Texas MD Anderson Cancer Center in Houston. "Additionally, compelling preclinical data suggest that anti-angiogenic targeted therapies may normalize the tumor's rapidly forming and underdeveloped blood vessels, resulting in improved oxygen and chemotherapy delivery to the tumor and potentially enhanced radiotherapy (RT) and chemotherapy treatment," explains Gilbert. The

Radiation Therapy Oncology Group (RTOG) 0825 study tested this hypothesis.

Six hundred and twenty-one adult study participants included in the study's final analysis were enrolled in the multicenter trial and randomized into one of two study arms, with treating physicians blinded to treatment assignment. All participants were treated with standard-of-care (60 Gy RT and daily temozolomide chemotherapy). Bevacizumab (experimental arm) or a placebo (standard treatment arm) was administered starting at week 4 of RT and continued every 2 weeks until 1) disease progression, or 2) severe treatment-related toxicity, or 3) completion of adjuvant therapy. At the time of disease progression, the treatment arm was unblinded allowing for follow on treatment with or without bevacizumab.

The authors reported data at a median follow-up time of 20.5 months, which revealed no statistical difference in overall survival between the two study arms (median 16.1 months for the standard-treatment arm vs. 15.7 months for the bevacizumab arm). Although there was a difference in progression-free survival (PFS) (7.3 months for the placebo arm vs. 10.7 months for the bevacizumab arm), the pre-established level of benefit for PFS was not reached. "The relevant result is that the upfront use of bevacizumab is not indicated," says Gilbert. "It's important to emphasize that the question we sought to answer was whether administering bevacizumab as first-line treatment improved survival; the cross-over component allowed comparison of risk and benefit of early versus late treatment We now know by giving it late you delay the risk of toxicity, and that may be relevant."

Study participants were stratified equally across study arms by prognostic molecular markers of tumor O6-methylguanine–DNA methyltransferase (MGMT) methylation status and a tumor-based 9-gene assay. Investigators, however, did not find a subgroup of patients based

on the molecular marker analysis who survived longer from first-line bevacizumab administration. "We postulated that patients with worse prognosis, determined by their tumor markers, would do better if they received bevacizumab as first-line treatment because they may not survive to take advantage of, or do well enough to be considered for, second-line treatment, but we didn't find that result" says Gilbert.

Because bevacizumab is known to confound magnetic resonance imaging (MRI) examination results used to assess GBM tumor progression, RTOG 0825 investigators incorporated a "net clinical benefit" component in the trial design to determine if quality of life, symptom burden and neurocognitive function test results corroborate MRI-reported stable or improved disease status. More than 80 percent of study participants agreed to take part in the net clinical benefits component, which demonstrated a greater decline of cognitive function for patients in the bevacizumab arm compared with those in the placebo arm. "While we found a difference in progression-free survival in the bevacizumab arm, there was an overall increase in symptom burden and decline in neurocognitive function and some measures of quality of life over time comparing the patients receiving bevacizumab with those on placebo," says Gilbert.

"Study participants' consent allowing the collection of tumor tissue and blood samples, as well as imaging examination, longitudinal symptom, QOL, and neurocognitive function data provides RTOG investigators a rich archive of data to support ongoing investigations of potential molecular markers to identify subgroups of patients who may benefit from early bevacizumab," says study co-principal investigator Minesh Mehta, M.D., chair of the Radiation Therapy Oncology Group Brain Tumor Committee and a professor of radiation oncology at the University of Maryland School of Medicine.

"The RTOG 0825 results provide important insight about the use of anti-

angiogenic therapies with standard first-line treatment," says Walter J. Curran Jr., M.D., Radiation Therapy Oncology Group chairman, co-author and executive director of the Winship Cancer Center at Emory University in Atlanta. "The unprecedented collection of specimens and associated outcome data will provide significant future information as we investigate new treatment strategies for these patients within NRG Oncology. I thank our ECOG and NCCTG colleagues for their significant trial support."

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