Accrual goal = 165 patients.

Patients will be treated with standard-dose bevacizumab, either alone or in combination with other chemotherapies but not immunotherapies.

*Requirements for recurrent GBM: a) any progression in a patient who has not previously received a bevacizumab-containing regimen, b) imaging upon which local site decision is made must be recent (within 28 d of registration) and demonstrate progressive contrast enhancement (> 25% increase from nadir in contrast-enhancing volume or new measurable contrast-enhancing lesion remote from the primary site) with measurable enhancement defined as 2 perpendicular in-plane diameters of at least 10 mm and at least 10 mm in the third orthogonal direction.

†S1 DSC-MRI can be completed 12-25 days after initial dose of bevacizumab and before second dose of bevacizumab is given.

‡All patients will be followed for a minimum of 1 year and up to 5 years every 3 months. Follow-up on all patients will continue until the last patient’s 1-year follow-up is completed.

DSC = dynamic susceptibility contrast; GBM = glioblastoma multiforme; MRI = magnetic resonance image; RANO = Response Assessment in Neuro-Oncology; S0 = baseline scan; S1 = postdose 1 treatment scan.

Baseline DSC-MRI (S0 scan) → Initial dose of bevacizumab → S1 DSC-MRI† → 2nd dose of bevacizumab → Follow-up

Study Schema
Overall EAF151 Study Objective
Examine whether the assessment of relative cerebral blood volume (rCBV), measured by dynamic susceptibility contrast (DSC) MRI, prior to the second administered dose of bevacizumab can be utilized as a biomarker for treatment response in patients with recurrent glioblastoma multiforme (GBM).

Study Objectives

Primary Objective
• Determine whether binary changes (increase vs decrease) in normalized rCBV within enhancing tumor, from baseline scan (S0) to postdose 1 treatment scan (S1), is associated with overall survival (OS)

Secondary Objectives
• Determine whether the baseline S0 normalized rCBV measure alone is associated with OS
• Determine whether binary changes (increase vs decrease) in normalized rCBV within enhancing tumor, from baseline (S0) to postdose 1 treatment scan (S1), is associated with progression-free survival (PFS)
• Determine whether changes in normalized rCBV as a continuous variable within enhancing tumor, from baseline (S0) to postdose 1 treatment scan (S1), is associated with OS or PFS
• Determine the association between normalized rCBV and OS when adjusting for the changes in enhancing tumor volume
• Determine whether baseline cerebral blood flow (CBF) or changes in CBF are associated with OS or PFS
• Determine the association between standardized rCBV and PFS or OS

Exploratory Objective
• Measure the repeatability of normalized CBV and standardized CBV at baseline (pre-bevacizumab)
Eligibility Criteria*

Main Inclusion Criteria

• ≥ 18 years of age with histologically proven intracranial glioblastoma or gliosarcoma at initial surgery. Patients will be eligible if the original histology was low-grade glioma and a subsequent diagnosis of glioblastoma or gliosarcoma is made (high-grade transformation)

• Karnofsky performance status ≥ 60

• For patients with intratumoral hemorrhage (acute, subacute, or chronic) as seen on hemosiderin-sensitive (gradient-echo) MRI there must be at least 10 × 10 × 10 mm “measurable enhancement” not obscured or distorted by magnetic susceptibility blooming artifact

• Progression of disease assessed by local site using Response Assessment in Neuro-Oncology (RANO) criteria, with plan to administer bevacizumab, either as a single therapy or in conjunction with other chemotherapeutic regimens in order to treat tumor progression/recurrence per treating physician. Patients receiving bevacizumab primarily for reduction of edema (ie, alleviation of symptoms) rather than for tumor treatment are excluded

• Must be first bevacizumab-containing therapy

• Progressive enhancement (> 25% increase in contrast-enhancing volume compared to nadir or a new measurable lesion) on MRI within 28 days of registration and ≥ 42 days since completion of standard radiation/temozolomide therapy. Measurable enhancement is defined as 2 perpendicular in-plane diameters of at least 10 mm and at least 10 mm in the third orthogonal direction

• Cleared for bevacizumab administration with respect to any recent surgeries; postsurgical scans must confirm presence of measurable residual disease

• Ability to tolerate brain MRI scans with dynamic intravenous gadolinium-based contrast agent injections

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.
Main Inclusion Criteria (Cont)

- Weight compatible with limits imposed by the MRI scanner table
- Scheduled to receive treatment with a bevacizumab-containing chemotherapy; may also be receiving treatment with Optune®

Main Exclusion Criteria

- Planned treatment with immunotherapies (vaccines, checkpoint inhibitors, T cells)
- Known allergy-like reaction to gadolinium or moderate or severe allergic reactions to one or more allergens, as defined by the American College of Radiology (ACR)
- Pregnancy or breastfeeding