Accrual goal = 146 patients.

*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.

†If the patient's most recent recurrence occurs while on immunotherapy, this must be judged as true recurrence using iRANO criteria.

‡Baseline scan may be done prior to registration per Section 9.2.

§Bevacizumab (or biosimilar agent) may be combined with other chemotherapies, immunotherapies, or Optune®.

ǁS1 DSC-MRI can be completed 12–25 days after initial dose of bevacizumab and before second dose of bevacizumab (or biosimilar agent) is given.

¶All patients will be followed for up to 5 years or 1 year after the last patient in enrolled, whichever occurs first.

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.
**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 or its biosimilars can be utilized as a biomarker for treatment response in patients with recurrent glioblastoma multiforme (GBM).

**Study Objectives**

**Primary Objective**
- Determine whether binary change (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) in recurrent GBM patients receiving bevacizumab or its biosimilars for the first time

**Secondary Objectives**
- Determine whether the baseline S0 normalized rCBV measure alone is associated with OS
- Determine whether change in normalized rCBV within enhancing tumor as a continuous variable is associated with OS
- Determine whether change in normalized rCBV within enhancing tumor as a continuous variable is associated with OS when adjusting for change in enhancing tumor volume and other potential confounders
- Determine whether baseline cerebral blood flow (CBF) or change in CBF are associated with OS
- Determine the association between standardized rCBV and OS

**Exploratory Objective**
- To determine whether baseline normalized rCBV or change in normalized rCBV are associated with progression-free survival (PFS)
- Determine whether baseline CBF or change in CBF are associated with PFS
- Determine the association between standardized rCBV and PFS

- Measure the repeatability of normalized rCBV and standardized rCBV at baseline (pre-bevacizumab or biosimilar)
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 or its biosimilars, either as a single therapy or in conjunction with other chemotherapeutic or immunotherapy 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. If the patient’s most recent recurrence occurs while on immunotherapy, this must be judged as a true recurrence (iRANO)

• This must be the first therapy containing bevacizumab or its biosimilars administered to the patient

• 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 concomitant standard radiation/temozolomide therapy (adjuvant temozolimide is allowable). 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 administration of bevacizumab or its biosimilars with respect to any recent surgeries; postsurgical scans must confirm presence of measurable residual disease

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

- Ability to tolerate brain MRI scans with Gadavist/Gadovist (gadabutrol)
- Scheduled to receive a treatment regimen containing bevacizumab or its biosimilars (e.g., alone or in combination with other chemotherapies/immunotherapies); may also be receiving treatment with Optune®

Main Exclusion Criteria

- 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)
- Weight incompatible with the MRI scanner limits, or MR incompatible implants/devices or metallic foreign bodies
- History of untreatable claustrophobia
- Pregnancy or breastfeeding