Primary Objectives
1. To evaluate the safety and tolerability of sonodynamic therapy (SDT) in rGBM subjects.
2. To determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of MR-Guided Focused Ultrasound (MRgFUS) energy in combination with SONALA-001 (sonodynamic therapy) in subjects with rGBM.
3. To determine the recommended phase 2 schedule of SDT in subjects with rGBM.
4. To determine the 6 month progression-free survival rate of subjects who receive SDT.

Secondary Objectives Include
1. Preliminary efficacy assessments, including objective response rate (ORR; RAPNO), progression-free survival (PFS), duration of response (DOR), and overall survival (OS).
2. The pharmacokinetics (PK) of aminolevulinic acid (ALA) and Protoporphyrin IX (PpIX) following intravenous dosing with SONALA-001.

Enrollment
Approximately 44 subjects with rGBM will be enrolled at 15 sites.

Currently Recruiting:
- Ivy Brain Tumor Center, Phoenix, AZ – Principal Investigator: Nader Sanai, MD
- NYU Langone Health, New York, NY – PI: Dimitris Placantonakis, MD, PhD
- Cleveland Clinic, Cleveland, OH – PI: Matthew Grabowski, MD
- Mayo Clinic, Rochester, MN – PI: Terence C. Burns, MD, PhD
- UCSF, San Francisco, CA – PI: Nicholas A. Butowski, MD

Investigational Drug Product
- SONALA-001 (10 mg/kg, intravenous ALA)

Key Inclusion Criteria (See clinicaltrials.gov listing for full inclusion criteria)
1. Must be 18 years or older at screening visit.
2. Histologically proven GBM (as defined in 2021 WHO Classification of Tumors of the Central Nervous System; Louis, Perry et al. 2021) that has recurred or progressed and for which resection is not indicated.
3. Tumor must be located in the supratentorial or cerebellar region. Tumors with infratentorial locations require consultation with the Sponsor/Medical Monitor to confirm suitability for treatment.
4. Previous treatment with standard of care radiotherapy (RT) and temozolomide (temozolomide required only if tumor has at least partial methylation of the O6-methylguanine-DNA methyltransferase promoter). Temozolomide should be administered concurrent with RT and adjutantly for newly diagnosed disease unless intolerant or ineligible for treatment.
5. No recurrence within 4 weeks of completion of RT, defined from the imaging assessment immediately after completion of RT.
6. Up to two prior systemic treatments for recurrent or progressing disease.
7. Karnofsky Performance Status ≥ 70 assessed within 14 days of C1D1.
8. Adequate baseline organ function, as defined in the body of the protocol.

Key Exclusion Criteria (See clinicaltrials.gov listing for full exclusion criteria)
1. Tumor in the brainstem (not including fluid-attenuated inversion recover [FLAIR] changes), or a diagnosis of gliomatosis cerebri (highly infiltrative T2 hyperintense tumor with ill-defined margins encompassing at least three lobes of the brain). Tumors with infratentorial locations require consultation with the Sponsor/Medical Monitor to confirm suitability for treatment.
2. Prior systemic anticancer treatment (e.g., chemotherapy, biologic therapy [i.e., small molecular inhibitors], monoclonal antibodies, investigational agents) within 21 days or 5 half-lives (whichever is shorter), prior to Cycle 1 Day 1 (C1D1) or per below:
   a. Nitrosoureas or bevacizumab within two weeks prior to C1D1;
   b. If a subject is receiving an anti-PD-1 or anti-PD-L1 antibody on a shorter frequency (i.e., every two weeks), then the subject is eligible if last dose within 2 weeks prior to C1D1.
3. Prior therapy such as interstitial brachytherapy, Gliadel® Wafers (carmustine implants), laser interstitial thermal therapy (LiTT), or Optune therapy, within 4 weeks prior to C1D1 or as long as there are any ongoing treatment related Grade ≥ 2 CTCAEs or intolerable side effects.
4. Radiation therapy within 4 weeks prior to C1D1.
5. Diagnosis of porphyria.
6. Hypersensitivity to porphyrins.
7. Known history of allergy to gadolinium contrast agents.