Angiopoietins may play a role in mediating resistance to anti-VEGF therapy in glioblastoma (GBM). AMG 386 is a novel Fc fusion protein that sequesters angiopoietins Ang1 and Ang2. This is a phase II, double-blinded, placebo-controlled trial examining the efficacy of bevacizumab (Bev) 10 mg/kg every 2 weeks + AMG 386 15 mg/kg every week compared to Bev + placebo in Bev-naïve patients with recurrent GBM. The initial 6-patient lead-in cohort examined the safety of combining Bev + AMG 386. No more than 1 of the 6 eligible patients in the safety cohort experienced a DLT, and therefore the study proceeded. Patients ≥ 18 yrs with KPS ≥ 70 and GBM or variant in first or second relapse were randomized to Bev + placebo or Bev + AMG 386. The primary endpoint was 6-month progression-free survival (PFS6). Secondary endpoints included safety, radiographic response, progression free survival, and overall survival. 114 eligible patients were needed to yield an 85% statistical power to detect a projected absolute difference of 19% on PFS6 rate (AMG 386 arm vs. placebo arm: 55% vs. 36%) at a one-sided significance level of 0.15, based on a two-sample test on proportion. For the analysis on the primary endpoint, MRI or CT scans obtained at baseline, best response, and progression or 6 months after treatment started (if not progressed within 6 months) were collected for each patient for central radiology review. RANO response criteria were used for all efficacy determinations. Accrual on study was completed in 9/2014. Updated results for all 114 eligible patients will be presented. This project was supported by grants U10CA21661, U10CA180868, U10CA180822, U10CA37422, and UG1CA189867 from the National Cancer Institute (NCI) and Amgen.