Report on study number 2007-002142-37 (Sponsor's protocol code number SURGE 01-07)

SUNITINIB (SUTENT, SU11248) in Patients with Recurrent or Progressive Glioblastoma multiforme. An Academic Prospective Single-arm Phase II Clinical Trial including Translational Research Studies

Purpose: The aim of this prospective multicenter phase II clinical trial was to evaluate the antitumor activity of a continuous once-daily dosing regimen of sunitinib in patients with first recurrence of supratentorial primary GBM.

Methods: At study enrollment, all participants were treated with sunitinib 37.5 mg in a continuous once-daily dosing regimen. The dosage was titrated up to 50 mg per day or down to 25 mg per day or 12.5 mg per day in steps of 12.5 mg depending on toxicity after the first 2 treatment weeks. Dose escalation to 50 mg per day was considered for participants who experienced no or mild (grade ≤1) nonhematologic adverse events (AEs) or mild to moderate (grade ≤2) hematologic AEs. Participants who experienced grade 3 or 4 AEs stopped treatment until the AE severity decreased to grade ≤1 for nonhematologic AEs or grade ≤2 for hematologic AEs. Participants with a treatment interruption over 3 weeks were discontinued from the study. Treatment was otherwise continued until tumor progression. All participants were clinically monitored by physical and neurological examinations, laboratory testing, and quality-of-life assessments, which were performed at baseline, weeks 1 and 2, and every 2 weeks thereafter until tumor progression. Cardiac function assessment and MRI scans were carried out every 8 weeks until tumor progression.

Randomization and study groups: Forty participants with a first recurrence of a histologically proven primary GBM were enrolled between October 2007 and April 2009. The maximum follow-up period was 5 years (October 2007 to October 2012).

Inclusion and exclusion criteria: Eligible for the study were patients with a first recurrence of a histologically proven supratentorial GBM diagnosed by MRI according to Macdonald criteria or by histological confirmation following re-resection.

Study endpoints: The primary study endpoint was a 6-month progression-free survival (PFS6) rate, defined as the percentage of participants who remained alive and progression free at 6 months after treatment initiation. Secondary study endpoints included objective response assessment, median progression-free survival (PFS), median overall survival (OS),12-month OS rate, safety and toxicity, quality-of-life assessment, and translational molecular studies on the sunitinib target molecules in tumor and vascular endothelial cells by immunohistochemistry.

Statistical analysis: The statistical significance of differences in values between the groups was calculated with the Mann-Whitney U test (MWU test). Associations of categorical parameters were tested using the chi square test. PFS and OS curves were summarized by the Kaplan-Meier method. The univariate and multivariate Cox proportional hazards model (forward stepwise procedure, 95% confidence interval [CI]) were used to assess the relationship between outcome and time-to-event endpoints or molecular parameters. Quality-of-life data analysis was based on mixed linear models comprising scores as dependent variables and time since baseline as fixed effect.

Results: The median PFS for the study population was 2.2 months (range, 0.5–41.4; 95% CI, 1.8–3.3). After 8 weeks on sunitinib, no radiographic responses (CR, PR) were detected; the best response was stable disease. Responders on sunitinib, predefined by a PFS ≥6 months on treatment (n = 5, 12.5%), showed a longer median PFS of 16.0 months (6.4, 7.3, 16.0, 17.0, 41.4 mo; 95% CI, 6.4–41.4) compared with sunitinib nonresponders with a median PFS of 1.8 months (range, 1.0–4.3; 95% CI, 1.6–2.3). Median OS for the study population was 9.2 months (range, 1.7 to 49.2; 95% CI, 6.6–11.9); the 12-month OS rate was 27.5% (95% CI, 13.5%–41.5%]. Sunitinib responders showed a median OS of 46.9 months (range, 21.2–49.2; 95% CI, 11.9–49.2) compared with sunitinib nonresponders with a median OS of 8.1 months (range, 1.7 to 18.4; 95% CI, 5.4–10.1). Two participants (5%) from the sunitinib responder subgroup were still alive after a follow-up period of 60 months.

Conclusions: In summary, continuous daily sunitinib demonstrated minimal activity in participants with primary GBM at first recurrence, but substantial toxicity when given at higher doses. High vascular c-KIT expression may define a subgroup of patients with a benefit from sunitinib treatment by achieving prolonged PFS, which requires further confirmatory translational studies.