Phase II study of mipsagargin (G-202), a PSMA-activated prodrug targeting the tumor endothelium, in adult patients with recurrent or progressive glioblastoma

David Piccioni[1], Tiffany Juarez[1], Bradley Brown[1], Lara Rose[1], Victoria Allgood[2], Santosh Kesari[1,3];
[1]UC San Diego Moores Cancer Center, La Jolla, CA; [2]Genspera, Inc., San Antonio, TX, [3]John Wayne Cancer Institute, Santa Monica, CA.

Purpose

The purpose of this study is to evaluate the efficacy of G-202, a PSMA-activated prodrug, in recurrent or progressive glioblastoma

Background

- Glioblastoma is the most common primary malignant brain tumor, and response rates for recurrent disease are poor
- PSMA (Prostate-Specific Membrane Antigen) is a transmembrane glycoprotein glutamate carboxypeptidase type II, originally identified in malignant prostate tissue
- More recently, PSMA has been identified in the endothelium of many solid tumors, but not in the endothelium of normal tissues, making it an attractive target for antineoplastic therapy
- The tumor endothelium of glioblastoma exhibits strong expression of PSMA (Figure 1)
- Mipsagargin (G-202) is a thapsigargin prodrug (12ADT) consisting of a cytotoxic analog of thapsigargin coupled to a masking peptide (Figure 2)
- 12ADT is a natural product toxin that has been shown to kill a broad spectrum of cancer cell lines by blocking the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA), leading to apoptosis
- PSMA cleaves the thapsigargin analog from its masking peptide at the tumor endothelium, confining the release of the cytotoxin to the tumor vasculature
- G-202 is dosed IV on 3 consecutive days every 28 day cycle

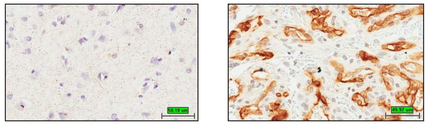

Figure 1. PSMA-positive vasculature in glioblastoma (Right) but not in the vasculature of normal brain (Left)

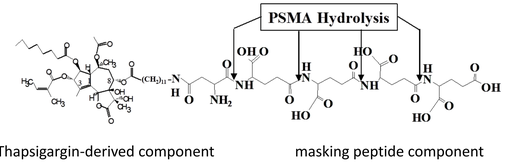

Figure 2. Structure of G-202. The thapsigargin-derived prodrug (12ADT) is cleaved from the masking peptide by the PSMA enzyme in the tumor endothelium (arrows)

Study Design

- Two stage, single-arm, open label single-institution phase II clinical trial of G-202 in recurrent or progressive glioblastoma
- Accrual goal of 34 efficacy-evaluable patients, defined as those that receive two cycles of drug followed by disease assessment
- Up to 3 prior recurrences allowed
- Primary endpoint: 6 month PFS
- Secondary endpoints include safety, efficacy, effects of G-202 on quantitative blood flow metrics, CSF and blood pharmacokinetics, and molecular response correlates
- Two regimens were evaluated: 40 mg/m^2 on days 1,2, and 3 of a 28 day cycle, and 40 mg/m^2 on day 1, and 66.8 mg/m^2 on days 2 and 3. Based on tolerability the lower dosing regimen was selected for further evaluation

Results

- A two stage design was performed. Two out of the first eleven efficacy-evaluable patients were needed to have at least stable disease to move to stage two. One patient had stable disease and one patient had a partial response (Figure 3, Figure 4). The study was then expanded to a goal of 34 efficacy-evaluable patients. A third patient had stable disease at 2 months.
- PSMA staining of the 3 responders has demonstrated > 2+ positivity by IHC
- To date, 19 patients have been enrolled and dosed with at least one cycle and are safety-evaluable. Four patients were not efficacy-evaluable. Four additional patients have been recently started on study and have not reached the first disease assessment at 8 weeks.

Results

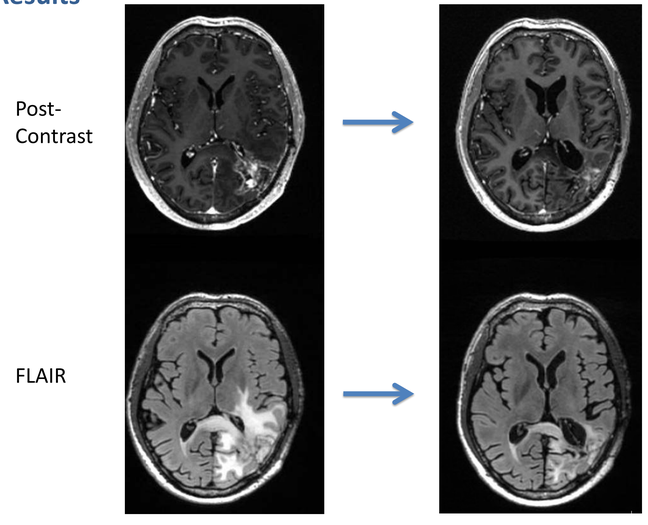

Figure 3. Patient 7. Imaging response at 8 months. Partial response. Pre-treatment images on the left. 8 month MRI on the right. Decrease in both contrast enhancement (top) and edema (bottom). Patient continues on trial.

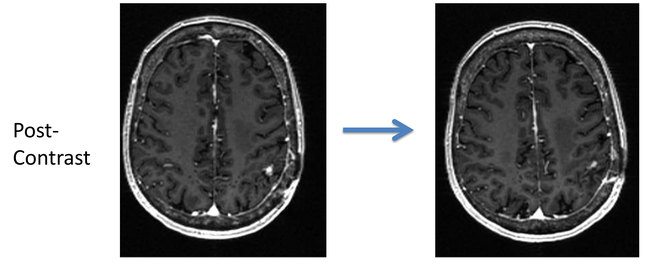

Figure 4. Patient 12. Imaging response at 2 months. Stable disease. Pre-treatment images on the left. 2 month MRI on the right. Patient had progression on imaging at 4 months.

Results

- The most common grade I AE attributable to the study drug was a transient increase in creatinine in 8 of 19 patients. The remaining grade 2 or greater AEs attributed to the study drug are listed in Table 1.

	Grade		
Adverse Effect	**2**	**3**	**4**
Nausea/Vomiting	1	1	1
Infusion Reaction			1
Fatigue	2		
Reflux	1		
Rash	2		
Hyperglycemia	1		
Increased ALT	1	1	
Increased Creatinine			1
Diarrhea			1

Table 1: Adverse Effects ≥ Grade 2, that are possibly, probably or definitely related to the study drug. 19 evaluable patients.

Conclusions

- Three of eleven patients demonstrated at least stable disease at the first disease assessment (2 SD, 1 PR), one of which has met the primary endpoint of 6 month PFS
- No dose-limiting toxicities have occurred. Preliminary evidence suggests that G-202 is well tolerated and my induce disease stabilization or treatment response
- PSMA staining of tumor tissue shows variability of expression but all 3 responders have >2+ staining. Biomarker evaluation is ongoing
- The study is currently open and actively enrolling

References

1. Nomura N, Pastorino S, Jiang P, Lambert G, Crawford JR, Gymnopoulos M, Piccioni D, Juarez T, Pingle SC, Makale M, Kesari S. Prostate specific membrane antigen (PSMA) expression in primary gliomas and breast cancer brain metastases. Cancer Cell Int. 2014;14(1):26
2. Andersen TB, Lopez CQ, Manczak T, Martinez K, Simonsen HT. Thapsigargin—from Thapsia L. to mipsagargin. Molecules. 2015; 20 (4):6113-27.
3. Wernicke AG, Edgar MA, Lavi E. Prostate-specific membrane antigen as a potential novel vascular target for treatment of glioblastoma multiforme. Arch Pathol Lab Med. 2011; 135; 1486-1489.