ABSTRACT #TPS2082

Glioblastoma (GBM) is the most common and aggressive primary brain cancer. Current standard of care includes surgery, radiation and treatment with temozolomide (TMZ), however nearly all tumors recur and the prognosis for recurrent GBM is dismal. Most GBM tumors have unmethylated promoter status for O6-methylguanine-DNA-methyltransferase (MGMT); a validated biomarker for TMZ-resistance. Second-line treatment with anti-angiogenic agent bevacizumab has not improved overall survival (OS) and 5-year survival is less than 3%. Dihydroorotagalactitol (VAL-083) is a bi-functional alkylating agent targeting N7-Guanine and inducing interstrand DNA cross-links, double-strand breaks and cell death in GBM cell lines and GBM cancer stem cells, independent of MGMT status in vitro. VAL-083 readily crosses the blood-brain barrier and accumulates in brain tumor tissue. VAL-083 targets N7 of guanine and has demonstrated MGMT-independent cytotoxicity in multiple GBM cell lines and cancer stem cells and is able to overcome temozolomide resistance in vitro demonstrating a distinct mechanism of action.

Dihydroorotagalactitol (VAL-083) is a bi-functional DNA targeting agent with a distinct mechanism of-action differentiating it from other chemotherapeutic agents used in the treatment of GBM and other CNS tumors. VAL-083 readily crosses the blood-brain barrier and accumulates in brain tumor tissue. VAL-083 targets N7 of guanine and has demonstrated MGMT-independent cytotoxicity in multiple GBM cell lines and cancer stem cells and is able to overcome temozolomide resistance in vitro demonstrating a distinct mechanism of action.

BACKGROUND

VAL-083 activity against colorectal cancer cell lines was independent of MMR: Cytotoxicity of VAL-083 measured in two pairs of isogenic human colorectal cancer cell lines. MMR-proficient cell lines: HCT116-PS-MHL1 and LoVo-PS-MHS2, were established by lentiviral infection. MMR-deficient cell lines: LoVo-PS100092 (MSH2-deficient cell line) and LoVo-PS100058 (MSH2-deficient cell line). N=3

CONCLUSIONS & NEXT STEPS

VAL-083 is a "first-in-class" DNA targeting agent with demonstrated activity against GBM in historical-NCI sponsored clinical trials.

VAL-083’s unique cytotoxic mechanism maintains activity against GBM cell lines and cancer stem cells independent of MGMT methylation and MMR in vitro.

A dosing regimen of 40 mg/m²/day VAL-083 administered on days 1,2,3 of a 21-day cycle was well-tolerated and data supports the potential to offer a clinically meaningful survival benefit in bevacizumab failed GBM patients

Taken together, these data support the potential of VAL-083 to offer a new treatment option for GBM patients whose tumors exhibit features correlated with resistance to currently available therapies.

Three additional clinical trials with VAL-083 are planned or enrolling

1. Phase 3 Study in Temozolomide-Avastin Recurrent GBM (“STAR-3”): A pivotal, randomized, controlled trial of VAL-083 in patients with recurrent GBM who have failed temozolomide/radiation therapy and bevacizumab

Study design

- Approximately 180 patients with historically confirmed recurrent GBM who have failed both standard radiation + chemotherapy and bevacizumab will be randomized in a 2:1 fashion to receive either VAL-083 or commonly used salvage chemotherapy.
- The proposed study is projected to be enrolled at approximately 25 centers in the United States.
- The proposed primary endpoint is overall survival (OS).
- The estimated length of the proposed study is less than 2 years from initiation.
- STATUS: Study start-up activities underway in the United States

2. Open label, single-arm, biomarker-driven Phase 2 trial in MGMT- unmethylated, bevacizumab-naive, recurrent GBM is currently enrolling at MD Anderson Cancer Center

Study design

- 48 patients will be enrolled to determine if treatment of MGMT- unmethylated recurrent GBM with VAL-083 improves overall survival (OS), compared to historical control.
- The lomustine arm of the recently published EORTC26101 trial will serve as the reference control
- STATUS: Currently enrolling at the University of Texas MD Anderson Cancer Center

3. Open label, single-arm, biomarker-driven, Phase 2 trial of VAL-083 and radiation therapy in newly diagnosed MGMT- Unmethylated GBM

Study design

- Up to 30 patients with newly diagnosed GBM with unmethylated-MGMT will be treated with VAL-083 and compared to historical control; the results will support a global randomized Phase II/III clinical trial evaluating VAL-083 efficacy in newly diagnosed GBM patients with unmethylated-MGMT.
- Progression free survival (PFS) will serve as the primary endpoint to assess VAL-083 treatment activity.
- STATUS: Study start-up activities underway at Sun Yat Sen University Cancer Center (Guangzhou, China)

REFERENCES

5. Tataranni et al. Neuro Oncol 2006; 8:43-57