**BACKGROUND**

VAL-083 is a bi-functional DNA targeting agent that readily crosses the blood-brain barrier and has shown activity against GBM in prior NCI-sponsored clinical trials. A Phase III clinical trial studying VAL-083 in recurrent GBM, after TMZ and bevacizumab failure, suggested the potential of VAL-083 to offer a clinically meaningful survival benefit. The mechanism-of-action of VAL-083 differs from other chemotherapeutic agents, including TMZ and nitrosoureas, inducing interstrand cross-links at guanine-N7 causing DNA double-strand breaks and cancer cell death.

**CURRENT VAL-083 GBM CLINICAL TRIALS (SEE ABSTR. #90.57)**

1. **Enrolling:** Open label single-arm, biomarker-driven. Phase 2 study of VAL-083 in patients with MGMT-unmethylated, bevacizumab-naive recurrent glioblastoma
2. **Planned (2017):** Pivotal, randomized multi-center Phase 3 study in bevacizumab-nailed GBM.
3. **Planned (2017):** Open label single-arm, biomarker-driven. Phase 2 study of VAL-083 and radiation therapy patients with in newly diagnosed MGMT-unmethylated GBM.

**MGGT-INDEPENDENCE**

VAL-083 cytotoxic activity is independent of MGMT-mediated temozolomide-resistance.

**VAL-083 DISPLAYS SYNERGY WITH TEMOZOLOMIDE AND TOPOISOMERASE INHIBITORS**

The distinct mechanism-of-action of VAL-083 makes it a valuable partner for combination therapies with agents already used in the treatment of GBM and other CNS tumors.

- **VAL-083 demonstrated synergy with temozolomide in GBM cancer stem cells completely eliminating cancer stem cells spheres after 2 passages (Figure 5).**
- **As VAL-083 induce cell cycle arrest in S- followed by G2/M-phase, we predicted synergy with agents that require cancer cells to be in S/G2-phase for maximum effect, including topoisomerase inhibitors. As expected, VAL-083 demonstrated synergy with etoposide (topoisomerase II inhibitor) and camptothecin (topoisomerase I inhibitor) (Table 2).**

**REFERENCES**

1. Zhang et al, AACR meeting 2017, Abstr #431
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4. Fossie S, et al, SNCO annual meeting 2014, Abstract #E7-16
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8. Zhang et al, EMA meeting 2016, Abstr #436

**TABLE 2. VAL-083 demonstrates synergy with etoposide (topoisomerase II inhibitor) and camptothecin (topoisomerase I inhibitor) in PC3 prostate and A549 NSCLC cancer cells. CI values for the cytotoxic effect (Fa) <1 shows synergy. N=4-5.**