Phase 2 study of dianhydrogalactitol (VAL-083) in patients with bevacizumab-naïve recurrent glioblastoma, MGMT-unmethylated

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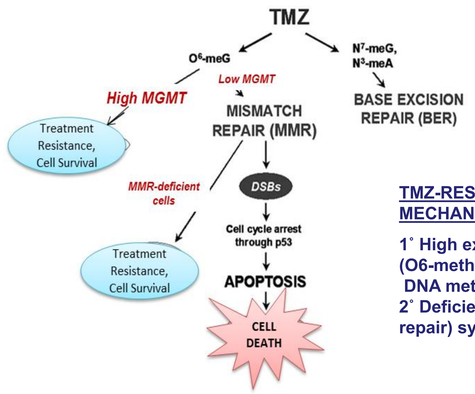
Glioblastoma (GBM) is the most common and aggressive primary brain cancer. Current standard of care includes surgery followed by concurrent therapy with radiation and temozolomide (TMZ) and maintenance TMZ. The vast majority of GBM patients experience recurrent/progressive disease within a year from initial diagnosis, and median survival after recurrence is 3-9 months. Effective therapies for recurrent GBM (rGBM) are lacking and these patients have a dismal prognosis, representing a significant unmet medical need. Unmethylated promoter status for O^6-methylguanine-DNA-methyltransferase (MGMT), a validated biomarker for TMZ-resistance, is strongly correlated with TMZ-resistance. Second-line treatment with the anti-angiogenic agent bevacizumab has not improved survival and 5-year survival is less than 3%.

VAL-083 overcomes MGMT-mediated chemoresistance

VAL-083 is a novel bi-functional DNA targeting agent that rapidly induces interstrand cross-links at N7-guanine, leading to DNA double-strand breaks (DSBs) and ultimately cell death. VAL-083's unique cytotoxic mechanism circumvents MGMT-mediated chemoresistance and maintains cytotoxic activity in cancer cells deficient in DNA mismatch repair (MMR). The N^7-targeting mechanism differs from temozolomide (TMZ) and nitrosoureas, enabling VAL-083 to overcome MGMT-mediated chemoresistance.



TMZ-RESISTANCE MECHANISMS

1˚ High expression of MGMT (O6-methylguanine DNA methyltransferase)
2˚ Deficient MMR (mismatch repair) system

FIGURE 1. Diagram showing the primary (MGMT) and secondary (MMR) mechanisms of TMZ-resistance

References

1. Zhai B, et al. Neuro-Oncology 19 (2017)
2. Hu, S.E et al. Cancer Res. 72 (2012)
3. Fouse S, et al. Neuro-Oncology 16 (2014)
4. Weathers et al. J Neurooncol;129(3): 487-94 (2016)

VAL-083 overcomes TMZ-resistance in both GBM cancer stem cells (CSCs) and non-CSCs, independent of MGMT.

VAL-083 is a potent inhibitor of GBM cultures, irrespective of MGMT and p53 status (Table 1). VAL-083 causes cell cycle arrest and loss of cell viability in TMZ-resistant cells with high MGMT expression. Furthermore, VAL-083 is is equally active against paired GBM cancer stem cells (CSCs) and non-CSCs (Figure 2).

TABLE 1. IC_{50} values of VAL-083, TMZ and lomustine in SF188, Med8a and adult T98G tumor cells. N=3[1,2]

Cell line		SF188	Med8a	T98G
p53 status		Mutant	Wild type	Mutant
MGMT expression		High	Low	High
IC_{50}	VAL-083	0.4 µM	1.6 µM	1.8 µM
	TMZ	>>100 µM	15.2 µM	>>100 µM
	lomustine	5.5 µM	6.8 µM	n/a

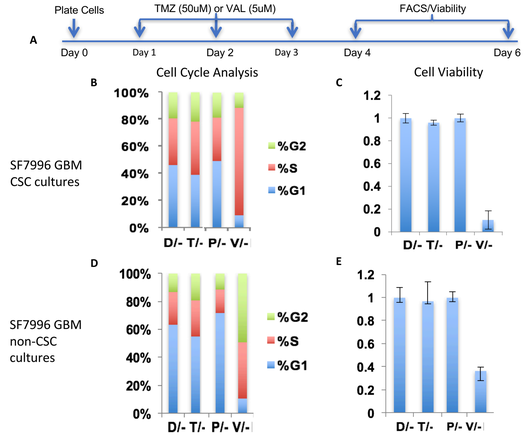


FIGURE 2. *(A) TMZ (50uM) or VAL-083 (5uM) were added to primary CSC and non-CSC cultures at various doses. Cell cycle analysis at day 4 (B, D) and cell viability analysis at day 6 (C,E) post treatment for the paired CSC (B,C) and non-CSC (D,E) GBM SF7996 culture. (D = DMSO, T= TMZ, P=PBS, V=VAL-083)[3]*

VAL-083 ACTIVITY IS INDEPENDENT OF MISMATCH REPAIR (MMR), THE SECONDARY TMZ-RESISTANCE MECHANISM

VAL-083 cytotoxic activity is independent of cancer cell's Mismatch Repair (MRR) status, suggesting that VAL-083 can overcome the secondary TMZ-resistance mechanism (Figure 3).

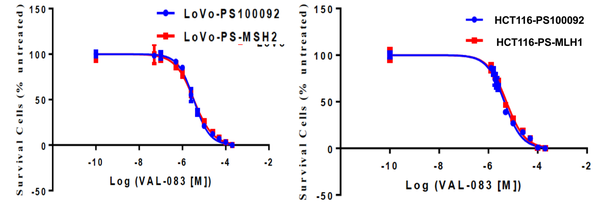
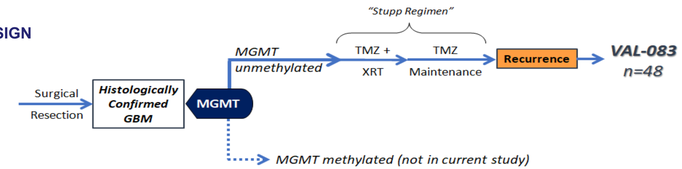


FIGURE 3. *Cytotoxicity of VAL-083 in isogenic human colorectal cancer cel lines using the crystal violet assay. MMR-proficient cell lines, HCT116-PS-MLH1 and LoVo-PS-MSH2, were established by lentiviral infection. HCT116-PS100092 is the MLH1-deficient cell line, HCT116-PS-MLH1 is the MLH1-proficient cell line; LoVo-PS100092 is the MSH2-deficient cell line, and LoVo-PS-MSH2 is the MSH2-proficient cell line. N=3[1]*

An open label, single-arm, biomarker-driven, Phase 2 study of VAL-083 in patients with MGMT-unmethylated, bevacizumab-naïve recurrent GBM

(Clinicaltrials.gov Identifier: NCT02717962).

STUDY DESIGN



- Up to 48 patients with bevacizumab-naïve recurrent GBM with unmethylated-MGMT will be enrolled to determine if VAL-083 treatment with improves overall survival (OS) compared to historical reference control.
  - Median OS in the MGMT-unmethylated lomustine of EORTC26101 trial (7.15 months) will serve as the reference control.[4]
- Subjects receive 40mg/m^2 VAL-083 on days 1,2,3 of a 21 day cycle.
- Primary endpoint: Median OS will serve as the primary endpoint.
- Secondary endpoints: Progression free survival (PFS), safety evaluations and symptom burden evaluation using MDASI-BT.

STUDY STATUS *(31-Mar/2018)*

- Currently enrolling at UT MD Anderson Cancer Center.
- 22 of a planned 48 patients have been enrolled.
- 7/22 (32%) have exhibited stable disease as best response.
- Similar to prior experience, myelosuppression has been the most common adverse event observed; no drug related SAEs (≥G4) have been observed in any study patients to date.

View trial details (http://clinicaltrials.gov):