Phase I/II Study of VAL-083 in Patients with Recurrent Malignant Glioma or Progressive-Secondary Brain Tumor

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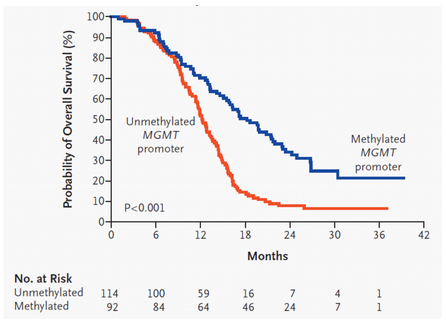
Background: VAL-083 is a first-in-class chemotherapeutic agent which was investigated for the treatment of primary brain tumors and other cancers starting in the late 1970s. In preclinical *in vivo* studies, VAL-083 demonstrated anti-tumor activity in a wide range of cancer cell lines, including sarcomas, melanomas, intracranial malignancies and lung cancer[1]. Human clinical studies have suggested that VAL-083 also has anti-tumor activity in various other cancers including glioblastoma multiforme (GBM). GBM continues to be major medical challenge today. Treatment advances are opposed by chemoresistance issues and difficulties in getting drugs across the blood brain barrier. VAL-083 is a highly water-soluble small molecule that readily crosses the blood brain barrier and accumulates in brain tissue. It has a distinct mechanism of action; bifunctional N^7 DNA alkylation, which is shown to be different from temozolomide (TMZ), Bevacizumab and BCNU[2,3]. Taken together, this suggests the opportunity to exploit activity of VAL-083 in GBM and secondary brain tumors demonstrating resistance to today's standard of care, and where poor clinical outcome remain a substantial unmet medical need.

The purpose of this Phase I/II study is to determine the safety and the maximum tolerated dose (MTD) of VAL-083 in patients with recurrent GBM. Progressive-secondary brain tumors were also examined in initial cohorts and may be further explored in future trials. Furthermore, the pharmacokinetic properties were explored and tumor responses to treatment were evaluated. **Methods**: Open-label, single-arm Phase I/II dose-escalation study in patients with histologically-confirmed initial diagnosis of malignant GBM or progressive-secondary brain tumor. The study utilizes a 3+3 dose-escalation design. Patients receive VAL-083 *i.v.* on days 1, 2, and 3 of a 21 day cycle. GBM patients have previously been treated with surgery and/or radiation, if appropriate, and must have failed both bevacizumab and temozolomide, unless contraindicated. Secondary brain tumor patients have failed standard brain radiotherapy with tumor progression after at least one line of systemic therapy. **Notes:** Due to prior chemotherapy and radiation therapy, patients with secondary brain tumors are likely more prone to myelosuppression and may have a different MTD. Therefore, after the third cohort, the trial will continue only with refractory GBM to determine MTD for advancement into future registration-directed trials. Progressive-secondary brain tumors resulting from solid-tumor brain metastases will be studied separately in a separate future trial. **ClinicalTrials.gov Identifier:** NCT01478178

Current situation: GBM is the most deadly form of human brain cancer, with a median survival for patients with recurrent GBM of 6 months.

High expression of MGMT (O6-methylguanine-DNA methyltransferase) is strongly correlated with chemoresistance to both first-line therapy TMZ and BCNU, and vastly reduces survival (Figure 1).



Source: Hegi ME et al. N Engl J Med. 2005; 352(10):997-1003.

Figure 1: Correlation of MGMT promoter methylation with overall survival for patients with GBM

Conclusions:

- **Treatment of relapsed GBM remains a significant unmet medical need**
- **VAL-083 has MGMT-independent activity in GBM cell lines SF188, U251 and T98G**
- **VAL-083 therapy is well tolerated to date; no drug-related serious AEs have been detected**
- **MTD has not been reached after completion of cohort 3 (5 mg/m²); cohort 4 (10 mg/m²) is ongoing**
- **A faster dose-escalation scheme has been implemented to allow the study to move rapidly toward a planned registration trial**
- **Pharmacokinetic analyses show dose-dependent increase in exposure with a short plasma 1-2 h half-life and a Cmax of <200 ng/mL at 10 mg/m² (see figure 4)**

VAL-083 is a bifunctional alkylating agent causing methylation of N^7-guanine and interstrand DNA crosslinks[3], which is believed to be distinct from the mechanisms of other alkylating agents (e.g. TMZ or BCNU). Absence of cross-resistance between VAL-083 and both TMZ and BCNU supports the potential efficacy of VAL-083 in the treatment of GBM patients failing these other agents. Historical clinical data further suggest comparable or enhanced survival and improved safety compared to TMZ and BCNU.

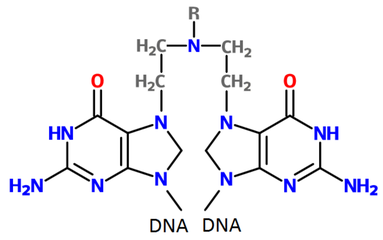


Figure 3. N7 guanine interstrand crosslinked DNA

Historical clinical data with VAL-083 support the potential for comparable or enhanced survival similar to standard chemotherapy with an improved safety profile in the treatment of GBM.

GBM Chemotherapy	VAL-083 *Eagan (1979)*	Temozolomide *Stupp (2005)*	Carmustine (BCNU)
Median O.S. (*XRT+chemo*)	67 weeks	58 weeks	40-50 weeks
DLT	Hematologic	Hematologic	Hematologic
Nadir	18-21 days	21-28 days	21-35 days
Recovery	Within 7-8 days	Within 14 days	42-56 days
Other severe toxicities reported (>2%)	none	nausea, vomiting, fatigue, asthenia, neuropathy	pulmonary, nausea, vomiting, encephalopathy renal

VAL-083 was better than TMZ for inhibiting tumor growth in GBM cell lines SF188, U251, and T98G, and the activity of VAL-083 was independent of MGMT (Figure 2).

Table 1. TMZ resistance and MGMT status in GBM cell lines SF188 (pediatric), U251 (adult), and T98G (adult) (Dr. Dunn, S. E.)

GBM cell line	SF188	U251	T98G
TMZ resistance	++	+	+++
MGMT status	-	-	+

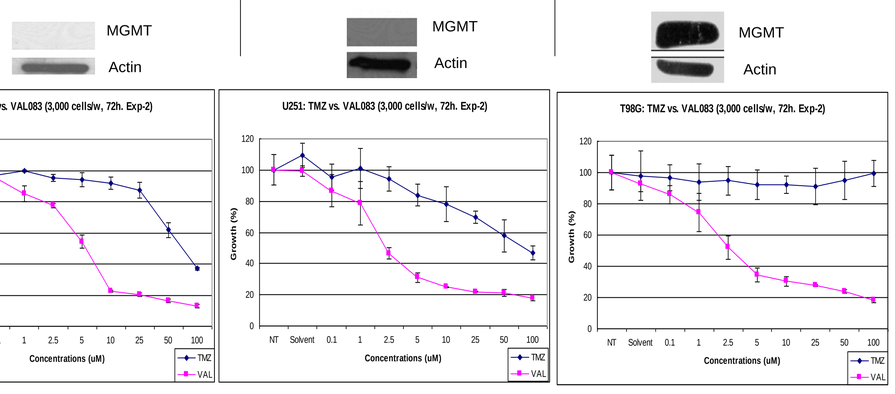


Figure 2. VAL-083 activity against GBM cell-lines SF188, U251 and T98G GBM cells (Dr. Dunn, S.E.).

Results and Observations to Date (study ongoing): Enrollment of cohorts 1 through 4 has been completed. No drug-related serious adverse events (SAEs) were detected, and maximum tolerated dose (MTD) not reached.

Enrollment of Cohort 5 (20mg/m2) is expected in December 2013, subject to completion of mandated safety observation period with Cohort 4 (10mg/m²). 18% of patients evaluated in Cohorts 1-3 exhibited stable disease or tumor-regression. Evaluation and clinical observations of Cohort 4 are ongoing. Following a safety review, a faster dose escalation scheme has been allowed by the FDA to move rapidly toward establishing the MTD for the new dosing regimen and a planned registration trial.

Dose Escalation Scheme mg/m²		Patients Treated	Status
Original	Revised		
1.5	1.5	3	Completed – No DLT
3.0	3.0	4*	Completed – No DLT
5.0	5.0	10*	Completed – No DLT
10.0	10.0	3	No DLT**
15.0			
20.0	20.0	3 planned	Enrollment planned Dec 2013
25.0			
30.0	30.0	3 planned	To be initiated subject to no DLT in 20mg/m² dose

***Cohorts 2 and 3 were expanded to allow for patient demand and to gather additional data on CNS metastases patients.**
****Observation period for final patient ongoing**

Pharmacokinetics: Pharmacokinetic analyses show dose-dependent systemic exposure with a short plasma 1-2 h half-life; average Cmax at the highest dose tested (10 mg/m²) is <200 ng/mL.

Pharmacokinetics VAL-083 in Brain Tumor Patients

Cohort	Dose mg/m²	Tmax h	Cmax ng/mL	AUC ng*h/mL	t-1/2* H
1	1.5	0.25	16.5	18.9	2.02
2	3	0.25	46.4	48.5	0.83
3	5	0.25	80.5	108.0	1.27
4	10	0.25	172.0	191.7	1.19

*Terminal half-life, lambda z. All values are mean of 2-4 patients.

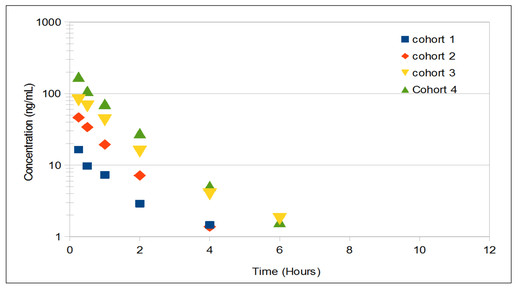


Figure 4: Plasma concentration-time profiles of VAL-083 showing dose-dependent systemic exposure

Acknowledgements: This research is funded by the National Research Council Canada (NRC) and the Industrial Research Assistance Program (IRAP)

References: 1. Nemeth L *et al*. Cancer Chemother Rep. 1972; 56:593-602. 2. Institóris E, Tamas J. Biochem J. 1980; 185, 659-666 3. Institóris E *et al*. Cancer Chemotherapy and Pharmacology. October (II) 1989; 24:5:311-13