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

Abstract # 2093

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Introduction & Background

Tumors of the brain are among the most challenging malignancies to treat. Median survival for patients with recurrent disease is approximately 6 months for glioblastoma multiforme (GBM). Central Nervous System (CNS) metastases have evolved as a major contributor to cancer mortality based on improvements in systemic therapies that cannot reach tumors spreading to the brain.

VAL-083 is a first-in-class bi-functional N^7 DNA-alkylating agent that readily crosses the blood-brain barrier and accumulates in brain tissue. VAL-083 has been granted orphan drug status by FDA and EMA for the treatment of gliomas.

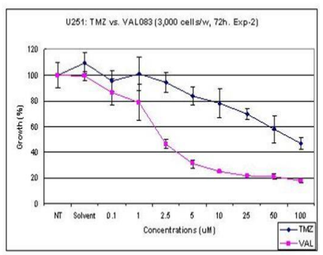
Historical clinical data with VAL-083 support the potential for comparable or enhanced survival similar to standard chemotherapy with an improved safety profile in the treatment of GBM.

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
NADR	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

Expression of O_6-methylguanine methyltransferase (MGMT) has been linked to poor patient outcome in GBM patients treated with temozolomide (TMZ). VAL-083 cytotoxic activity is independent of the MGMT associated chemotherapeutic resistance *in vitro* (figure 1) and thus has potential to be effective in TMZ-resistant GBM.

U251 cell line
Adult GBM

MGMT negative
TMZ sensitive



T98G
Adult GBM

MGMT positive
TMZ resistant

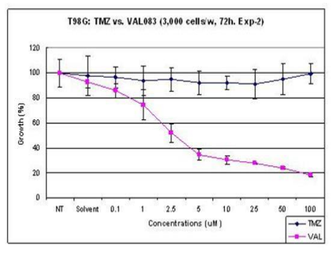


Figure 1. *Activity of dianhydrogalactitol (VAL-083) and temozolomide (TMZ) in MGMT negative human GBM cell line U251 and MGMT positive human GBM cell lineT98G (Dunn S et al., AACR 2012).*

Methodology

An open-label, single arm Phase I/II dose-escalation study designed to evaluate the safety, tolerability, pharmacokinetics and anti-tumor activity of VAL-083 in patients with i) histologically confirmed initial diagnosis of primary WHO Grade IV malignant GBM, now recurrent, or ii) progressive secondary brain tumor, having failed standard brain radiotherapy, and with brain tumor progression after at least one line of systemic therapy. The study utilizes a 3 + 3 dose escalation design, until the MTD or the maximum specified dose is reached. Patients receive VAL-083 intravenously at the assigned dose on days 1, 2, and 3 of each 21-day treatment cycle. In Phase II, additional patients will be treated at the MTD (or other selected optimum Phase II dose) to measure tumor responses. All patients enrolled have previously been treated with surgery and/or radiation, if appropriate, and must have failed both bevacizumab and TMZ, unless contraindicated. ClinicalTrials.gov Identifier: NCT01478178

Results

- VAL-083 therapy is well tolerated in GBM and secondary progressive brain tumor patients with no drug-related SAEs (see table 1) at doses studied to date.
- Maximum tolerated dose has not been reached after completion of cohort 3. (cohort 1 = 1.5mg/m^2; cohort 2 = 3.0mg/m^2; cohort 3 = 5.0mg/m^2). Continued dose escalation is planned.
- A proportion of GBM (2/8) and secondary-progressive brain cancer (1/6) patients having failed prior therapy show stable disease or tumor regression in response to VAL-083 treatment at the doses tested to date, in spite of doses in cohorts 1-3 being well below those used in historical clinical studies (see table 1).
- Cohort 3 was expanded to gather additional data on CNS metastatic patients at the 5mg/m^2 dose level
- There is one partial response, maintained over 15 cycles (see table 1).
- PK analysis shows dose-dependent increase in exposure with a short 1-2 h half-life and a Cmax of <100 ng/mL (see figure 2).

Table 1: *Prior therapy, Serious Adverse Events (SAE), Dose-limiting toxicities (DLT) and tumor response of the 14 patients evaluated to date.*

Tumor Type	n	Prior Therapy	DLT	SAE	Tumor Response
GBM	8	Surgery/XRT/TMZ/ BEV	None	None (n=6) Not related to study drug (n=2)*	Overall = 25% PR (1); SD (1)
CNS met	6**	Standard of care***	None	None (n=5) Not related to study drug (n=1)	Overall = 17% SD (1)

Three events in two patient
****Breast adenocarcinoma (2); small cell lung carcinoma (3); melanoma (1)***
*****Whole-brain radiotherapy and stereotactic radiosurgery when appropriate, plus at least one line of systemic therapy***

Summary Inclusion Criteria:

- Patients must be greater than or equal to 18 years old.
- Histologically confirmed initial diagnosis of primary WHO Grade IV malignant glioma (glioblastoma), now recurrent, or progressive secondary brain tumor, has failed standard brain radiotherapy, and has brain tumor progression after at least one line of systemic therapy.
- If GBM, previously treated for GBM with surgery and/or radiation, if appropriate, and must have failed both bevacizumab (Avastin®) and temozolomide (Temodar®), unless either or both are contraindicated.
- Must have a predicted life expectancy of at least 12 weeks.

Summary Exclusion Criteria:

- Current history of neoplasm other than the entry diagnosis. Patients with previous cancers treated and cured with local therapy alone may be considered with approval of the Medical Monitor.
- Evidence of leptomeningeal spread of disease.
- Prior treatment with prolifeprospan 20 with carmustine wafer (Gliadel® wafer) within 60 days prior to first treatment (Day 0).
- Prior intracerebral agents.
- Evidence of recent hemorrhage on baseline MRI of the brain.
- Concomitant medications that are strong inhibitors of cytochrome P450 and CYP3A up to 14 days before Cycle 1, Day 1 (pimozide, diltiazem, erythromycin, clarithromycin, and quinidine, and amiodarone up to 90 days before)

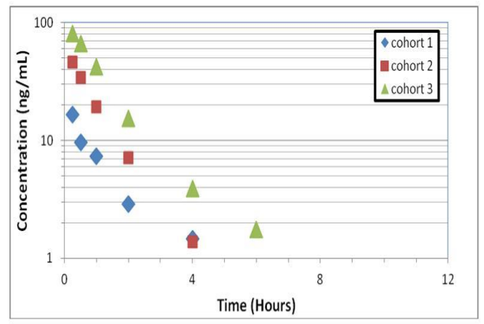
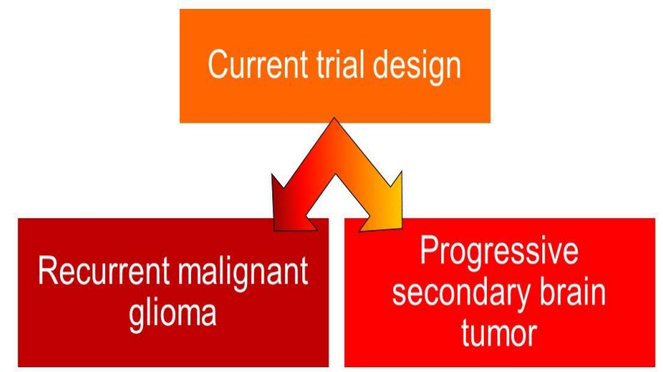


Figure 2: *Plasma concentration-time profiles of VAL-083 showing dose-dependent systemic exposure (Mean of 3 subjects per cohort).*

Future directions

- Continue dose-escalation to determine an optimal and safe treatment regimen for registration studies of VAL-083.
- Characterize responses relative to MGMT status in GBM patients.
- Due to prior chemotherapy and radiation therapy, patients with secondary brain tumors are likely more prone to myelosuppression and may have a different MTD than patients with GBM. Therefore, the trial will be split into i) GBM and ii) progressive secondary brain tumors, so that the MTD and impact of MGMT-driven chemoresistance can be assessed in GBM, while separately exploring the potential for treating solid-tumor brain metastases.



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