The unique mechanism of action of VAL-083 may provide a new treatment option for some chemo-resistant cancers

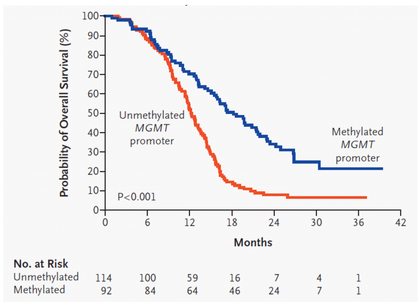
Anne Steino[1] Jeffrey A. Bacha[1], William J. Garner[1], Sarath Kanekal[1], Zahid H.Siddik[2], Dennis Brown[1]

[1]Del Mar Pharmaceuticals (BC) Ltd., British Columbia, Canada;
[2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

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), non-small cell lung cancer (NSCLC) and chronic myelogenous leukemia (CML). GBM, NSCLC and CML continue to be major medical challenges today. Treatment of all three types of cancer is challenged by chemoresistance issues, and in the case of GBM, 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. It has a distinct mechanism of action; bifunctional alkylation, which is shown to be different from, and in some cases superior to, the mechanisms of e.g. cisplatin, nitrogen mustards and temozolomide (TMZ)[2,3]. Taken together, this suggests the opportunity to exploit activity of VAL-083 in tumors demonstrating resistance to today's standard of care, and where poor clinical outcome remain a substantial unmeet medical need.

GBM

Current situation: GBM is the most deadly form of human cancer, with a median survival of less than 15 months with all available treatments.
High expression of MGMT (O6-methylguanine-DNA methyltransferase) is highly correlated with chemo-resistance to first-line therapy TMZ 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

VAL-083 was better than TMZ for inhibiting tumor growth in GBM cell lines, and the activity of VAL-083 was independent of MGMT.

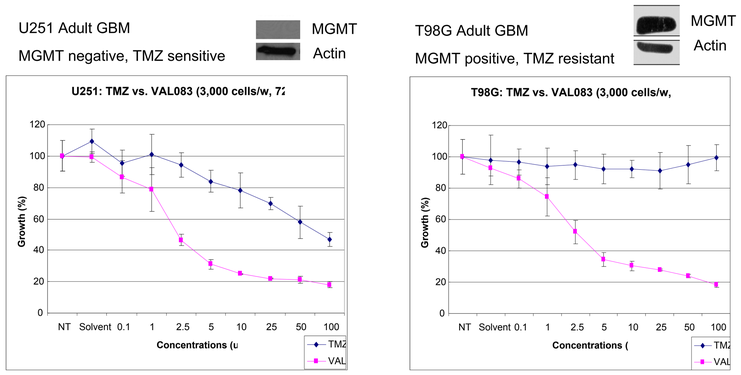


Figure 2. VAL-083 activity against U251 and T98G GBM cells (Dr. Dunn, S.E.).

Next steps
Demonstrated activity in tumors with high MGMT expression support utility of VAL-083 in refractory and newly diagnosed GBM VAL-083 is currently in phase I/II clinical trial in recurrent GBM with promising initial results. ClinicalTrials.gov Identifier NCT01478178.

NSCLC

Current situation: Patients with recurrent NSCLC have a median survival of less than 28 weeks. Development of chemoresistance to standard platinum doublet therapy is high, and the prognosis for NSCLC remains poor. Even with today's standard of care, patients diagnosed with stage IV NSCLC have a median survival of just 4 months, and a 5-year survival of less than 2%.

VAL-083: VAL-083 has been shown to have activity in various lung cancer cells (Table 1) and is approved for the treatment of lung cancer in China.

NSCLC cell line		IC50
A549	Adenocarcinoma	-3.9
EKVX	Adenocarcinoma	-3.9
HOP-62	Adenocarcinoma	-4.4
HOP-92	Large cell	-4.0
NCI-H226	Squamous cell	-3.9
NCI-H23	Adenocarcinoma	-4.0
NCI-H322M	Adenocarcinoma	-4.0
NCI-H460	Large cell	-4.1
NCI-H522	Adenocarcinoma	-4.1

Table 1: Summary of NCI in vitro data in NSCLC

VAL-083 creates interstrand crosslinks at the N7 guanine on DNA, which is believed to be distinct from platinum-based chemotherapy.

VAL-083 was superior to cisplatin in tumor growth delay in an in vivo model, and combination of the two, resulted in a better than additive effect (Table 2).

Treatment	Dose (mg/kg)	Days to 4x Median	Tumor delay (Days)
Untreated	-	6.29	0.00
Cisplatin	4	7.75	1.45
VAL-083	10	11.45	5.16
VAL-083 + cisplatin	10/4	14.94	8.65

Table 2: Tumor growth delay study using RIF-1 cell-line in C3H mice. IP injection of cisplatin or VAL-083.

Next steps
Preclinical studies of VAL-083 activity in cisplatin-refractory or cisplatin-resistant NSCLC and as a component of platinum doublet therapy in newly diagnosed NSCLC.

CML

Current situation: Tyrosine Kinase Inhibitor (TKI) therapy has greatly improved clinical outcome for many patients. However, development of TKI-resistance has emerged as an unmet clinical need, particularly in persons of Asian descent (due to BIM co-deletion genotype).

VAL-083: VAL-083 has in vitro activity in both TKI-sensitive and TKI-resistant CML cell lines (Figure 3)

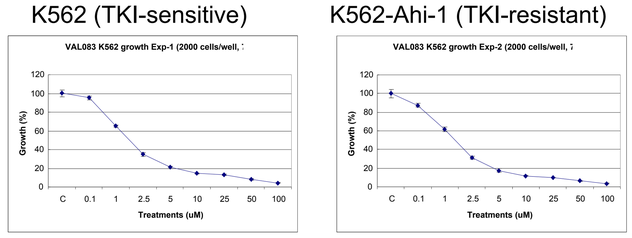


Figure 3: VAL-083 activity in TKI-sensitive (K562) and TKI-resistant (K562-Ahi-1) CML cells (Dr. Dunn, S.E.).

VAL-083 is approved for treatment of CML in China and has proven activity in clinical trials (Table 3).

Reference	Drug Dose and Regimen	Reported Results
Lin Bao Jue, Tao Rui Fang 1979 (n=5)	not reported	Overall: 100% CR 4/5 PR 1/5
Huang Zhung Qien Wu Mao E.1980 (n=12)	IV q.d. for 7 days in a 14-day cycle at 50 mg/day	Overall: 91.6% CR 7/12 PR 4/12 MR 1/12
Huang and Wu 1982 (n=21)	IV q.d. for 7 days in a 14-day cycle at dose of 25-50 mg/ day	Overall: 93.3% CR 4/21 PR 14/21 MR 3/21

Table 3: VAL-083 has clinical efficacy against CML

Next steps
Potential for alternative therapy in TKI resistant CML and for patients that are irresponsive or intolerant to TKIs.
Preclinical studies of VAL-083 activity in TKI-resistant CML.
Preclinical and clinical studies of VAL-083 activity in hydroxyurea-resistant CML and as a component of combination therapy with hydroxyurea in newly diagnosed CML or refractory CML.

Conclusions: Mechanism of action, historical data and newly developed data suggests potential of VAL-083 to address significant unmet clinical needs in a number of cancer types, including GBM, NSCLC and CML. Continued research into mechanism and therapeutic positioning is being undertaken. Validation of clinical utility through ongoing and new clinical research in USA and China.

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