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

Jeffrey A. Bacha[1], Michelle Martinez-Rivera[2], Guangan He[2], Xiaolei Xie[2], Ming Chen[3], Zahid H. Siddik[2], Guo Chengcheng[4], Chen Zhong-Ping[4], Lu Shun[5] and Dennis M. Brown[1]

[1]DelMar Pharmaceuticals, Inc., Vancouver, Canada and California, CA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Guangxi Wuzhou Pharmaceutical (Group) Co. Ltd, Guangxi, China; [4]Sun Yat-Sen University Cancer Center, Guangzhou, China; [5]Shanghai Chest Hospital, Shanghai Jiao Tong University,

BACKGROUND

Poor outcomes in cancer therapy due to chemo-resistance remain a significant unmet clinical challenge for many solid tumors. Onset of drug resistance is a major factor limiting the clinical utility of chemotherapy and, therefore, new agents that circumvent resistance are needed.

VAL-083 is a bifunctional alkylating agent which primarily mediates cytotoxic guanine interstrand N^7 DNA cross-links (see Fig 1), separating it from other widely used DNA alkylating chemotherapeutics such as temozolomide, nitrosoureas and platinum-based agents.[1,2] VAL-083 readily crosses the blood-brain barrier and has been demonstrated to accumulate preferentially in tumor tissue. VAL-083 exhibited activity against a range of tumor types, including GBM, lung cancer, ovarian cancer and medulloblastoma, in historical clinical studies sponsored by the US National Cancer Institute.

GBM: VAL-083 is currently undergoing clinical studies for refractory glioblastoma multiforme (GBM) in the United States and has received orphan drug designation in Europe and the U.S. for the treatment of malignant gliomas. We have demonstrated that VAL-083 overcomes temozolomide (TMZ)-resistance associated with O^6-methylguanine-DNA methyltransferase (MGMT) expression *in vitro*. We have further shown that VAL-083 is highly effective against GBM cancer stem cells (CSC) and non-CSC and that it acts as a radiosensitizer in GBM cell lines, *in vitro*. VAL-083 significantly increased median survival in an orthotopic *in vivo* model using adult GBM cell line U251. Taken together our results suggest that VAL-083 may provide an alternative to TMZ in the treatment of GBM that has become TMZ-resistant or is expected to be TMZ-resistant based on the MGMT profile.

NSCLC: VAL-083 demonstrated clinical activity against non-small cell lung cancer (NSCLC) in historical trials sponsored by the US National Cancer Institute.[3,4] VAL-083 is approved for the treatment of lung cancer in the Peoples Republic of China (PRC, Approval No. Guayo Zhunzi H45021133), but its clinical use has been limited by lack of modern data. We have recently shown that VAL-083 is less dependent than cisplatin on wild-type p53 for cytotoxic activity and that there is a lack of significant cross-resistance between VAL-083 and cisplatin. In addition, we have shown that VAL-083 was substantially more potent in comparison to cisplatin in TKI-resistant NSCLC models *in vitro*, and that the combination of VAL-083 with cisplatin or oxaliplatin in NSCLC models H460, A549 and H1975 demonstrated significant super-additivity ($p<0.05$) and synergy (CI < 1). *In vivo*, combination treatments of VAL-083 with cisplatin in NSCLC produced superior tumor growth delays and survival benefits to cisplatin alone. These results support our hypothesis that the subtle differences between the N^7 targeting mechanisms of VAL-083 and platinum agents are clinically relevant and provide support for the utility of VAL-083 in treatment-resistant NSCLC.

Ovarian cancer: VAL-083 has demonstrated activity against ovarian cancer in historical clinical studies sponsored by the US National Cancer Institute.[5] VAL-083 is active in both cisplatin-sensitive (A2780) and cisplatin-resistant (2780CP-16, OVCAR-10, Hey and OVCA-433) ovarian cancer cell lines. This indicates a distinct mode of action compared to cisplatin. Supported by recent results showing synergy of VAL-083 in combination with cisplatin in NSCLC, these results suggest VAL-083 as a treatment alternative for ovarian cancer patients with p53 mutations or cisplatin resistance.

Childhood brain tumors: VAL-083 has demonstrated clinical activity against medulloblastoma (MB) and high grade gliomas (HGG) in historical NCI-sponsored clinical studies, including paediatric trials.[6] We have recently shown that VAL-083 has strong activity against GBM cells, paediatric and adult, as well as GBM stem cells (CSCs), independent of their MGMT status, *in vitro*. VAL-083 also demonstrated activity against MB cell lines, including chemo-resistant sonic hedgehog (SHH) cell lines with p53 mutations.

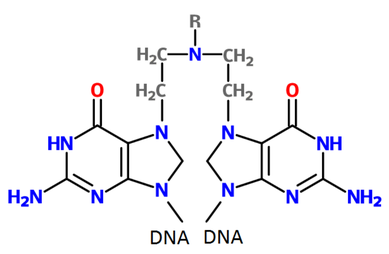


Figure 1. N7 guanine interstrand cross-linked DNA

VAL-083 Mechanism of Action

- **Interstrand cross-links at guanine N7**
- **Double-strand DNA breaks**
- **Apoptosis & Cell Death**

ABSTRACT # A0078

VAL-083 target indication	Historical clinical data	Present unmet medical need	VAL-083 solution	VAL-083 status
GBM	Eagan *et al.,* 1982[8]	TMZ-resistance due to MGMT expression[7]	Independent of MGMT	Phase II (ClinicalTrials.gov Identifier NCT01478178)
Lung cancer	Haas *et al.,* 1981[3] Eagan *et al.,* 1982[4]	Platinum resistance; TKI-resistance; Brain metastases	Overcomes cisplatin resistance; overcomes TKI-resistance; Crosses BBB	Approved in PRC; additional post-market clinical trials planned
Ovarian cancer	Slavik, *et al*. 1982[5]	Platinum resistance	Overcomes cisplatin resistance	Preclinical
Childhood brain tumors	Finklestein, *et al.* 1985[6]	SHH recurrence with p53 mutations	Independent of p53 status	Preclinical

Table 1: Overview of VAL-083 target indications and proposed solutions for unmet medical needs

Figure 2. VAL-083 was better than TMZ at inhibiting tumor cell growth in adult and paediatric GBM cells. This occurred in an MGMT-independent manner.

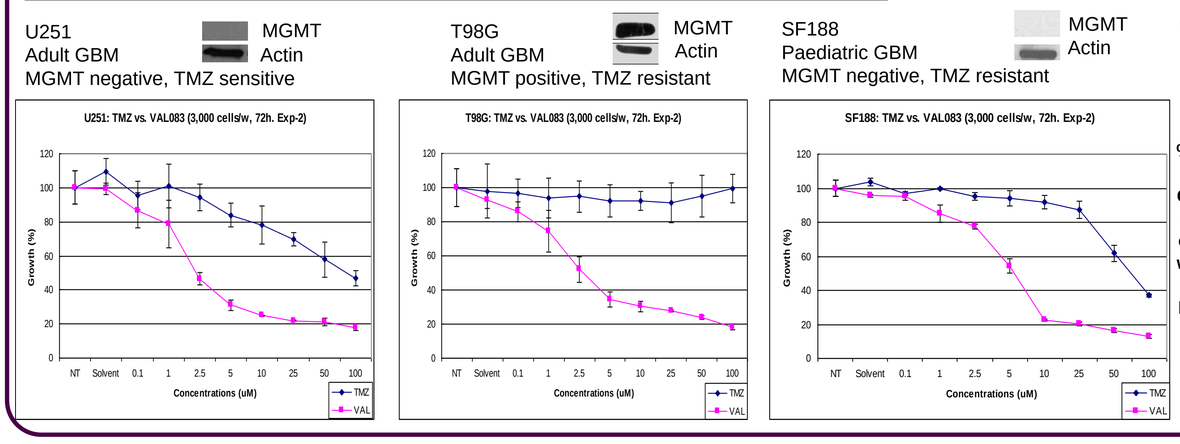


Figure 3. VAL-083 inhibited cell growth of MB cell lines with SHH characteristics, including p53mut Daoy and UW228 cells

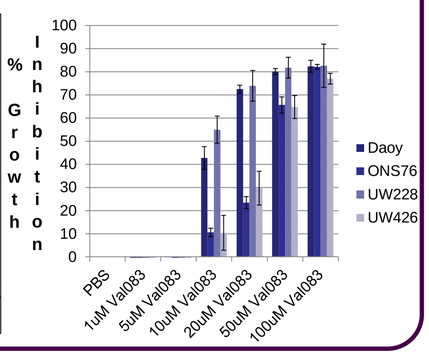


Figure 4. VAL-083 in combination with cisplatin (A,C,E) or oxaliplatin (B,D,F) had synergistic cell kill effect on H460 cells (A,B), A549 cells (C,D) and H1975 cells (E,F).

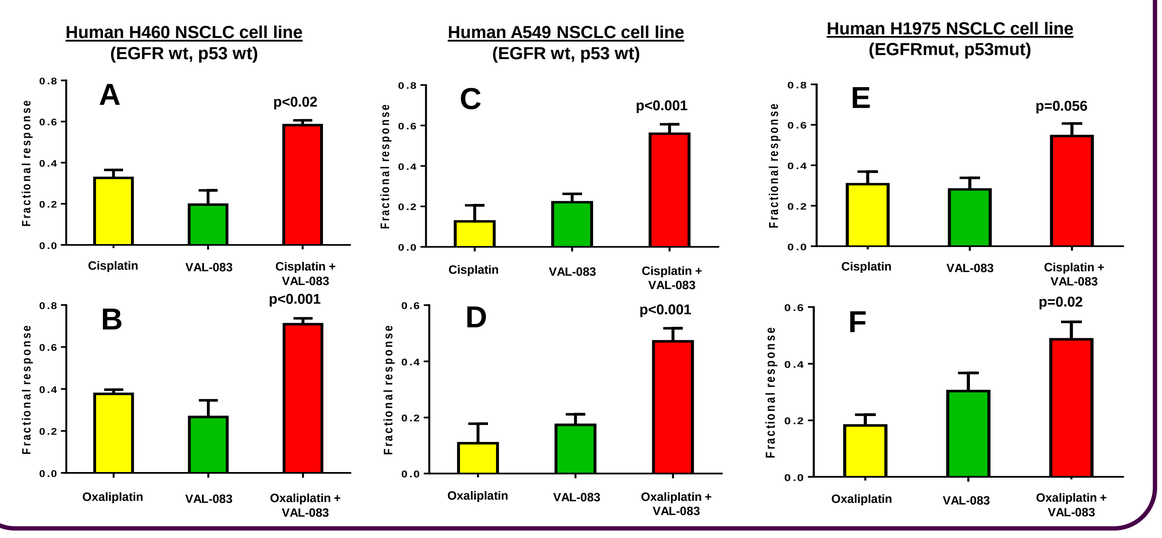
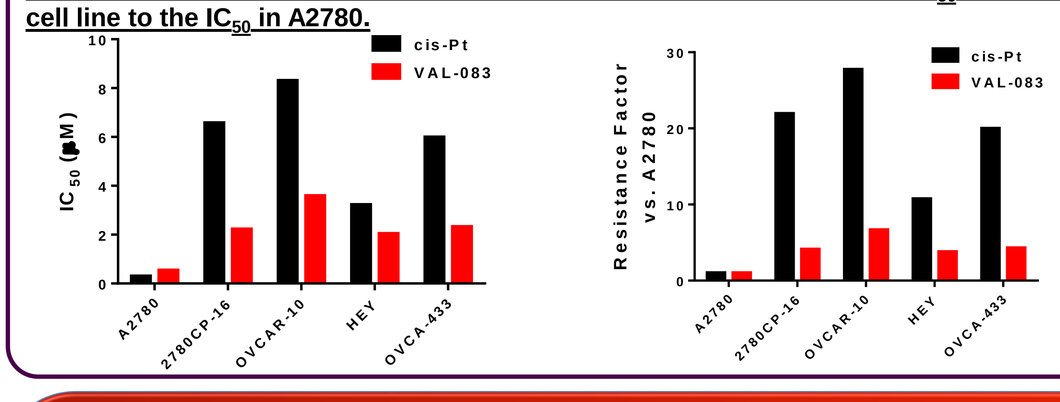


Figure 5. Cytotoxicity (A) and resistance factors (B) of cisplatin and VAL-083 in wild-type p53 ovarian cancer cell lines. Resistance Factor is calculated as the ratio of IC_{50} in the resistant cell line to the IC_{50} in A2780.



NEXT STEPS:

Additional clinical trials of VAL-083 in NSCLC and newly diagnosed GBM are planned. Favorable results would support expanded clinical use of VAL-083 under its current approval in People's Republic of China and will serve as the basis for global development of VAL-083 as an important chemotherapeutic agent in the treatment of cancer where resistance to alkylation-based chemotherapy remains an unmet medical need in the modern treatment of cancer.

CONCLUSIONS:

- ***Historical clinical activity combined with new understanding of mechanism supports the potential of VAL-083 as a possible solution for major unmet needs in the treatment of a variety of cancers***
  - ✓ **VAL-083 activity is independent of MGMT and overcomes TMZ-resistance in GBM cell lines**
  - ✓ **VAL-083 overcomes cisplatin-resistance in ovarian cancer cell lines**
  - ✓ **VAL-083 overcomes TKI-resistance in NSCLC cell lines, including H1975 with T790M mutation in EGFR**
  - ✓ **VAL-083 overcomes cisplatin-resistance in NSCLC cell lines**
  - ✓ **VAL-083 displays synergy and super-additivity with both cisplatin and oxaliplatin in NSCLC cell lines, including TKI-resistant cells**
  - ✓ **VAL-083 activity is less dependent on p53 status than cisplatin in NSCLC cell lines**
  - ✓ **VAL-083 has strong activity against paediatric brain tumors *in vitro* including HGG, GBM CSCs and p53 mutated SHH medulloblastoma**

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