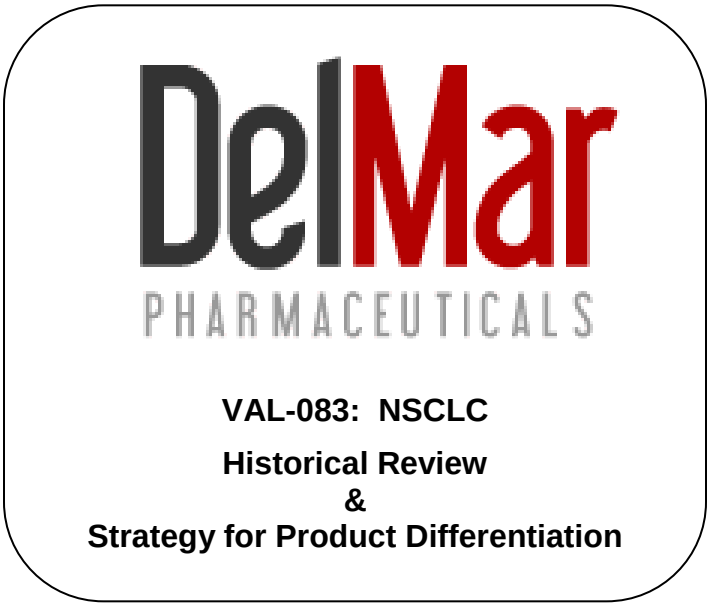


VAL-083: NSCLC

Historical Review
&
Strategy for Product Differentiation

Contents

1. EXECUTIVE SUMMARY

- **The prognosis for non-small cell lung cancer patients remains poor: Even with today's standard-of-care, patients diagnosed with stage IV NSCLC have a median overall survival of just 4 months and 1- and 5-year survival of less than 16% and 2%, respectively.**
- **Platinum based chemotherapy shows benefit in some patients; however, median progression free survival is less than six months in many published studies;**
- **Tyrosine Kinase Inhibitors (TKIs) have become standard-of-care and improved outcomes for EGFR-mutant NSCLC; however, the development of TKI resistance is an evolving and major unmet medical need, particularly in patients of East Asian descent who exhibit more frequent resistance to TKIs;**
- **VAL-083 is a well-characterized small-molecule chemotherapeutic agent that has demonstrated human clinical activity against a variety of malignancies including CNS, solid tumor and hematologic cancers and is effective at nanomolar concentrations against a variety hematological and lung cancer cell lines *in vitro*;**
- **VAL-083 has been studied extensively in the United States as evidenced by more than 40 NCI sponsored clinical studies. VAL-083 is approved in China for the treatment of chronic myelogenous leukemia (CML) & lung cancer;**
- **VAL-083 has been shown to work in concert with radiation or other chemotherapies and has been demonstrated to lack cross-resistance with other chemotherapies used in NSCLC;**
- **VAL-083 as a single agent has demonstrated both complete response (CR) and partial response (PR) in advanced lung cancer and significantly extended median survival in combination regimens in historical NCI-sponsored clinical trials;**
- **VAL-083 is well tolerated with a favorable safety profile in comparison to other cytotoxic agents with the only reported dose limiting toxicity of myelosuppression, which reverses spontaneously following treatment; and**
- **DelMar believes that VAL-083's unique mechanism of action and favorable safety profile positions VAL-083 as a potential therapeutic option for NSCLC patients failing standard-of-care, particularly in China where it is already approved.**

2. Introduction

Lung cancer is a leading cause of cancer-related mortality around the world and remains a significant unmet need despite advances in therapy. In general, prognosis for lung cancer patients remains poor, with 5-year relative survival less than 14% among males and less than 18% among females in most countries.

Non–small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases in the United States and approximately 90% of lung cancer cases diagnosed in China. The World Health Organization (WHO) predicts that the incidence of NSCLC in China may exceed 1 million cases per year by 2025.

When feasible, surgical resection remains the single most consistent and successful option for cure; however, close to 70% of patients with lung cancer present with locally advanced or metastatic disease at the time of diagnosis. The median overall survival time for patients with stage IV NSCLC is 4 months, while 1- and 5-year survival is less than 16% and 2%, respectively. Additionally, the incidence of brain metastases is high in patients with NSCLC, with a poor prognosis.

Platinum-based chemotherapy remains standard-of-care for non-resectable NSCLC, in addition to radiation for stage III or IV lung cancer. Some patients exhibiting EGFR-mutation may receive tyrosine kinase (TKI) therapy, often following failure of platinum based chemotherapy.

Tyrosine Kinase Inhibitors (TKIs) targeting the epidermal growth factor receptor (EGFR) have had a major impact on the treatment of non-small cell lung cancer (NSCLC) in patients with EGFR mutations. TKI therapy has resulted in vastly improved outcomes for these patients; however, resistance to TKIs has emerged as a significant unmet medical need. Recent evidence proposes unique mechanisms of TKI-resistance in patients of East Asian descent who experience significantly inferior responses to TKIs.

Patients with refractory or resistant NSCLC have limited therapeutic options.

VAL-083 *(dianhydrogalactitol)* is a first-in-class alkylating agent with a novel cytotoxic mechanism distinct from other alkylating agents used in the treatment of lung cancer.

In historical studies sponsored by the United States National Cancer Institute (NCI), VAL-083 exhibited clinical activity against a range of tumor types including CNS tumors, solid tumors, and hematologic malignancies.

VAL-083 demonstrated promise in the treatment of NSCLC both as a single-agent and in combination regimens in NCI-sponsored clinical trials. DelMar believes that the unique mechanism of action of VAL-083, in combination with newly developed data positions the drug as a valuable therapy for NSCLC patients who have failed other therapeutic interventions, including TKIs and platinum based therapies.

VAL-083 is approved in China for the treatment of chronic myelogenous leukemia (CML) and lung cancer *(Approval No. Guoyao Zhunzi H45021133; manufactured by Guangxi Wuzhou Pharmaceutical (Group) Co. Ltd.)* Currently, DelMar Pharmaceuticals, Inc. is investigating this product in Phase I/II clinical trials in the United Stated as a potential treatment for refractory glioblastoma multiforme (*clinicaltrials.gov identifier: NCT01478178*). VAL-083 has been granted orphan drug status in the United States and European Union.

DelMar Pharmaceuticals and Guangxi Wuzhou Pharmaceuticals are collaborating to develop new clinical data to support the expanded use of VAL-083 for the treatment of NSCLC under its current approval in China.

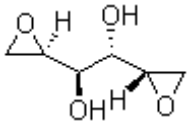
In addition, DelMar Pharmaceuticals plans to pursue global development of the drug as a treatment for NSCLC.

3. VAL-083 Background

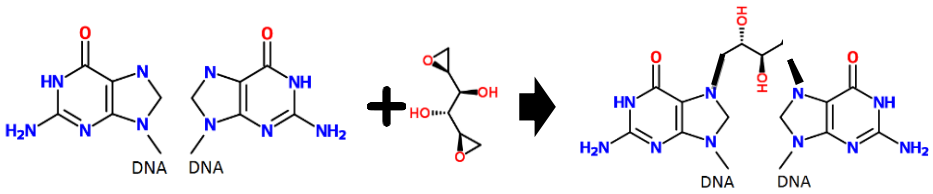
VAL-083 is DelMar Pharmaceuticals' development identifier given to 1,2:5,6-dianhydrogalactitol (dianhydrodulcitol, DAG, NSC-132313), a chemotherapeutic agent that was investigated at the National Cancer Institute in the United States for the treatment of cancer in human clinical trials starting in the late 1970s. NCI-sponsored clinical studies suggest promising anti-tumor activity in with VAL-083 in the treatment of hematologic malignancies and a range of solid and CNS tumors. Antitumor activity was observed *in vivo* following both i.v. and oral administration.

Research was eventually not pursued in the United States due to an increased focus by the NCI on targeted biologic therapies during the early 1990s. VAL-083 was subsequently approved in China for the treatment of chronic myeloid leukemia and lung cancer.[1]

VAL-083 is a structurally unique bi-functional alkylating agent mediating interstrand DNA crosslinks targeting N7 of guanine. The functional groups and cytotoxic mechanism associated with VAL-083 differ from other alkylating chemotherapeutic agents, such as the platinum-based compounds, nitrosureas or temozolomide.

Molecular Structure	
Molecular Formula	$C_6H_{10}O_4$
Molecular Weight	146.14
CAS Registry Number	23261-20-3

The principal mechanism of action is attributed to alkylation via the epoxide groups, which form cross-links at the N-7 position of guanine leading to double-strand DNA breaks.[2] The prevalence of CpG islands in DNA, particularly within the promoters of genes, provides substantial regions of where guanine residues are in close proximity for targeting by VAL-083 cross-links.



VAL-083 exhibits a favorable safety profile. Dose limiting toxicity in humans is myelosuppression, which has been shown to reverse spontaneously following treatment. Alopecia is not associated with VAL-083 therapy; gastrointestinal toxicity is limited and no significant target organ damage has been reported in the literature.[3]

VAL-083 has demonstrated efficacy in cyclophosphamide, BCNU and phenylanine mustard resistant cell lines and no evidence of cross-resistance has been encountered in published clinical studies. DelMar

[1]Chinese Product Label for VAL-083
[2]Institoris et al. In vivo study on alkylation site in dna by the bifunctional dianhydrogalactitol, Chem.-BioL Interactions, 35 (1981) 207--216
[3]Vogel et al. Phase I trial of DAG administered IV in a weekly schedule. Cancer Treat Rep. 1976 Jul; 60(7):895-901. PMID: 795538

Pharmaceuticals has demonstrated that VAL-083 anti-cancer activity is independent of prominent repair and resistance mechanisms such as O6-methylguanine methyltransferase (MGMT)[4], and that the drug is active against platinum-resistant cell lines *in vitro* and *in vivo.* Further, the combination of VAL-083 + cisplatin demonstrates synergistic characteristics.

VAL-083 crosses the blood-brain barrier and accumulates in tumor tissue, suggesting VAL-083 may be a therapeutic option for patients with brain metastasis.

VAL-083 is approved for treatment of lung cancer in China and has documented activity against NSCLC in historical NCI-sponsored clinical trials conducted in the United States as a stand-alone therapy or in combination with other chemotherapeutic agents. Published results from China and therapeutic label claims are consistent with data developed through NCI-sponsored research.

4. Lung Cancer

Epidemiology

Lung cancer is characterized as small cell and non-small cell lung cancer (NSLSC). NSCLC is the most common type of lung cancer. There are three common forms of NSCLC: *adenocarcinomas* are often found in an outer area of the lung; *squamous cell carcinomas* are usually found in the center of the lung next to an air tube (bronchus); and *large cell carcinomas*, which can occur in any part of the lung and tend to grow and spread faster than adenocarcinoma.

Smoking is the most important risk factor in the development of lung cancer. Emphasizing the well-established causal relationship, it has been found that smokers have a 15- to 30-fold increase of developing lung cancer compared with nonsmokers. Additionally, high levels of air pollution have been implicated as a significant cause of lung cancer.

Smoking patterns in the Chinese population likely influence the incidence of lung cancer in China. According to The Nationwide Nutrition and Health Survey (2002), China has the world's largest smoking population. China consumes about third of the cigarettes produced globally, due to a combination of its huge population and the high prevalence of smoking among Chinese males.

The World Health Organization reports that the incidence of lung cancer in China is 34 per 100,000 population; however, some estimates are much higher exceeding 120 per 100,000 population for males aged 55-60 in urban areas. According to an exhaustive survey conducted by the Chinese Ministry of Health and the Ministry of Science and Technology, smoking, poor diet, water pollution and environmental problems have caused the nation's cancer death rate to rise 80 percent in the past 30 years. Cancer is now accountable for 25 percent of all urban deaths and 21 percent of all rural deaths in China. Based on these trends, the World Health Organization projects that the incidence of lung cancer in China is expected to exceed one million new cases per year by 2025. Anecdotally it has been stated that NSCLC represents 90% - 95% of lung cancers in China.

Lung cancer is a leading source of brain metastases; patients with non-small-cell lung carcinoma (NSCLC) develop CNS metastases in about 20–40% of cases. Brain metastases are usually associated with poor outcome, and treatment is palliative in most cases. Standard treatment options include symptomatic therapy with corticosteroids and whole-brain radiotherapy (WBRT), which lead to a median

[4]Dunn et al. VAL083, a novel N7 alkylating agent, surpasses temozolomide activity and inhibits cancer stem cells providing a new potential treatment option for glioblastoma multiforme. American Association of Cancer Research 2012 Annual Meeting. Permanent Abstract No. 811

survival of 3–6 months. Novel therapies with demonstrated efficacy and low toxicity are needed for NSCLC-related CNS metastases.

Standard of Care in the Treatment of NSCLC

Treatment paradigms for NSCLC vary globally, with commonality for recommending TKI therapy for patients whose cancer exhibit epidermal growth factor receptor (EGFR) mutations. Patients exhibiting EGFR mutations have shown an impressive 60% initial response rate to TKIs which exceeds the response rate for conventional chemotherapy.

Comparison of NSCLC Standard of Care across USA/EU/China

Jurisdiction	First Line NSCLC Therapy	Second Line NSCLC Therapy
NCCN (USA) *2012*	• Bevacizumab (Avastin™) + chemotherapy • Cisplatin/pemetrexed • Cetuximab/Vinorelbine/Cisplatin	• Docetaxel or pemetrexed or erlotinib or platinum doublet +/- bevacizumab for performance status (PS) 0-2, and Erlotinib (Tarceva™) for PS 3-4
EMSO (Europe)	• Platinum based combination chemotherapy with vinorelbine, gemcitabine, taxanes, irinotecan and pemetrexed • Erlotinib (Tarceva™) or Gefitinib (Iressa™) for EGFR mutations • Anti-angiogenesis agents optional	• Docetaxel, pemetrexed, Gefitinib (Iressa™), recommended for PS 0-2, and Erlotinib (Tarceva™) for PS 3-4
CACA (China)	• Platinum-based 2-drug combination • TKI for EGFR mutations	• Docetaxel, pemetrexed, and TKI for EGFR mutations *Note: TKI's gefitinib (Iressa™) and erlotinib (Tarceva™) have been approved and launched in the China market for the treatment of NSCLC.*

Standard of care in China for newly diagnosed NSCLC is platinum-based combination therapy. In a large comparative clinical trial, 1112 patients with advanced NSCLC were treated at the Chinese Academy of Medical Science and Cancer Hospital. The study examined outcomes among four different third-generation chemotherapy (paclitaxel, gemcitabine, vinorelbine or docetaxel) plus platinum doublets. There was no difference among the doublets in terms of progression free survival (PFS) or overall response.[5] As the first-line treatment of advanced NSCLC, carboplatin doublets were superior to cisplatin doublets, with PFS times of (3.65 ± 0.20) and (3.05 ± 0.14) months, respectively (P = 0.014).

Second line therapy for NSCLC in China consists of docetaxel (Taxotere®) or pemetrexed (Alimta®), both are delivered in intravenous formulations. In general, docetaxel is used in the treatment of squamous cell

[5]Zhonghua Yi etal. Efficacy analysis of third-generation plus platinum doublets in the first-line chemotherapy of advanced non-small cell lung cancer. Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 2012 Jun 12;92(22):1527-31 (article in Chinese)

NSCLC and pemetrexed is preferred in the treatment of recurrent adenocarcinoma. Median survival for patients with recurrent NSCLC is less than 28 weeks.

NSCLC patients exhibiting EGFR mutations have shown an impressive 60% initial response rate to tyrosine kinase inhibitors (TKIs), which significantly exceeds the response rate for conventional chemotherapy in this patient population. Published results from past clinical trials demonstrated that patients that do not harbor any EGFR mutations do not respond as favorably to TKIs as those with confirmed EGFR mutations.

The frequency of EGFR mutations in NSCLC patients of European descent is approximately 10%, but has been observed at much higher rates among Asians. Findings from the PIONEER study (2012) suggest that the pattern of EGFR mutation among Asians was unique and different from that of Caucasian NSCLC populations. The PIONEER study analyzed the EGFR mutation status in 1,450 NSCLC patients from seven Asian countries. The overall frequency of EGFR mutation in this unselected Asian population with advanced lung adenocarcinoma was high, with 51.4 percent of patients testing positive for mutations.

The TKIs gefitinib (Iressa®) and erlotinib (Tarceva®) are approved as standard-of-care in China for NSCLC patients with EGFR mutations; however, as few as 10% of eligible patients are able to receive TKI therapy due to the high cost of treatment or limited prevalence of testing technology.

For NSCLC patients who do receive TKI therapy, the development of TKI resistance is common and acquired resistance becomes a major clinical problem. Nearly all NSCLC patients who attained disease control on TKI eventually become resistant.[6,7]

It has also been reported that cigarette smoke may directly induce resistance to TKIs.[8] This factor could further exacerbate therapeutic resistance in populations such as China where smoking is highly prevalent. In addition, the same East-Asian specific genotype recently correlated with primary resistance to TKI therapy in CML has also been shown to correlate with erlotinib (Tarceva™) resistance in EGFR mutated NSLSC.

A significantly higher rate of incomplete cytogenetic responses to TKIs been reported among individuals in East Asia compared to individuals in Europe and North America.[9] Recently, a deletion polymorphism that results in the generation of isoforms with TKI resistance was identified. Interestingly, this genotype is found only in individuals of East Asian descent. The Asian-unique TKI resistant isoforms have a co-deletion in the in the BIM gene such that these individuals lack a crucial BH3 domain.

BIM, a pro-apoptotic protein, has been established to be an important mediator of signaling pathways that induce cell death.[10] BIM is involved in TKI-induced apoptosis in sensitive EGFR mutant cells and imatinib-induced apoptosis of BCR-ABL leukemic cells.[11,12] For example, BIM up-regulation is required for TKIs to induce apoptosis in kinase-driven cancers, including CML and NSCLC.

[6]Charpidou et al. EGFR mutations in non-small cell lung cancer--clinical implications. In Vivo. 2008 Jul-Aug;22(4):529-36.
[7]Mok et al. To overcome T790M associated EGFR TKI resistance by addition of mono-clonal antibodies against HER-1 and/or HER-2 receptors: P2-046 Journal of Thoracic Oncology 2007 2(8):508
[8]Filosto et al. Cigarette Smoke Induces Aberrant EGF Receptor Activation That Mediates Lung Cancer Development and Resistance to Tyrosine Kinase Inhibitors. Molecular Cancer Therapeutics. Advanced On-line publication. February 2012.
[9]ibid ref. 17
[10]Hubner et al. Multisite Phosphorylation Regulates BIM Stability and Apoptotic Activity. Molecular Cell 30(2008), 415–425
[11]Costa et al. BIM Mediates EGFR Tyrosine Kinase Inhibitor Induced Apoptosis in Lung Cancers with Oncogenic EGFR Mutations PLOS MedV4:10(2007):1669-80
[12]Kuroda et al. (2006) Bim and Bad mediate imatinib-induced killing of Bcr/Ablþ leukemic cells, and resistance due to their loss is overcome by a BH3 mimetic. Proc Natl Acad Sci U S A 103: 14907–14912

All active isoforms of the BIM gene contain a BH3 domain that can bind to and inactivate members of the anti-apoptotic BCL2 family of proteins. BH3 region of BIM is essential for interaction with pro-survival Bcl-2 family members and for most of its ability to promote apoptosis.[13]

The BIM deletion polymorphism in the BIM gene results in the generation of BIM isoforms that lack the crucial BH3 domain. Such individuals are resistant to TKIs even in the absence of kinase-domain mutations. This Asian-unique polymorphism has a profound effect on the TKI sensitivity of CML and EGFR NSCLC cells *in vitro*. Further, it has been demonstrated that individuals with the polymorphism have markedly inferior responses to TKI than do individuals without the polymorphism. The polymorphism correlated specifically with clinical resistance to imatinib in CML as well as a shorter progression-free survival (PFS) with EGFR TKI therapy in NSCLC.[14]

5. VAL-083 in NSCLC: Pre-clinical data

Pre-clinical and clinical studies sponsored by the NCI suggest that VAL-083 may have activity against a range of tumor types and was the most active of 177 chemotherapeutic agents in mouse tumor models studied by researchers at the Mayo Clinic.[15,16]

The Chinese literature supports a wide range of activities with VAL-083 demonstrating effective against S180 (*murine sarcoma*), S37 (*murine sarcoma*), U14 (*murine cervical squamous cell carcinoma*), HepS (*murine hepatocellular carcinoma*), HepA (*murine hepatocellular carcinoma*), EAC (*murine esophageal adenocarcinoma*), W256 (*rat breast carcinoma*) and L1210 (*murine lymphocytic leukemia*) *in vivo*, of which W256 and L1210 showed the greatest sensitivity.

DelMar believes VAL-083's unique bi-functional alkylating mechanism of action makes it a valuable drug of choice in NSCLC patients who are or become resistant to standard-of-care. Unpublished *in vitro* and *in vivo* data demonstrates synergy with platinum therapy suggesting that VAL-083 could potentially play a meaningful role as a component of front-line platinum doublet therapy. In addition, VAL-083 readily crosses the blood brain barrier suggesting a therapeutic opportunity for NSCLC with brain metastasis.

The activity of VAL-083 against a range of NSLSC cell lines has been extensively studied *in vitro* and *in vivo* by the NCI and exhibits cell-kill activity at low nanomolar concentrations.

Summary of NCI in vitro data in NSCLC

NSCLC Line		**IC50 (nM)**
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

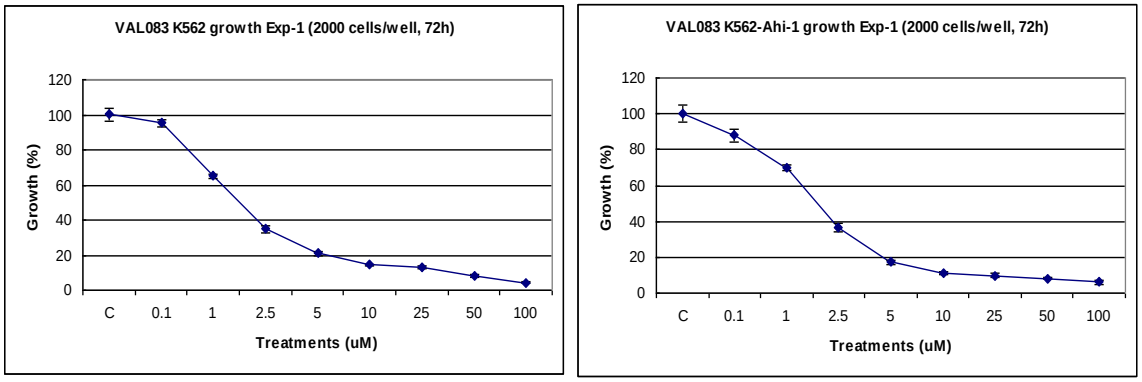
[13]O'Connor et al. Bim: a novel member of the Bcl-2 family that promotes apoptosis. The EMBO Journal Vol.17 No.2 pp.384–395, 1998
[14]King, et al. A common *BIM* deletion polymorphism mediates intrinsic resistance and inferior responses to tyrosine kinase inhibitors in cancer. Nature Medicine Advanced Online Publication. 18Mar/2012
[15]Nemeth et al. Pharmacologic and antitumor effects of 1,2:5,6-dianhydrogalactitol (NSC-132313). Cancer Chemother Rep. 1972:56:593-602.
[16]Eagan et al. Dianhydrogalactitol and Radiation Therapy Treatment of Supratentorial Glioma. JAMA 1979:241(19):2046-2050.

VAL-083 is approved by the Chinese State Food and Drug Administration (SFDA) for the treatment of CML and lung cancer in China. As previously noted, use of the drug in the modern era has been limited. The direct translation of the label: *"VAL-083 can rapidly shrink the size of lung tumors"*, requires further exploration in the modern treatment paradigm.

DelMar Pharma believes that the unique bi-functional mechanism of VAL-083 offers a potential promising new treatment option for NSCLC patients failing other therapies, including platinum-based chemotherapy regimens and modern targeted therapies such as TKIs. Given that the drug is already approved for lung cancer in China, DelMar believes that a unique opportunity to reposition the drug in the Chinese market to benefit NSCLC patients with unmet medical needs due to drug resistance.

To date, DelMar has established initial *in vitro* data in available cell lines demonstrating that VAL-083 maintains cytotoxic activity independent of mutations resulting in total resistance to TKIs.

TKI Sensitive **TKI Resistant**



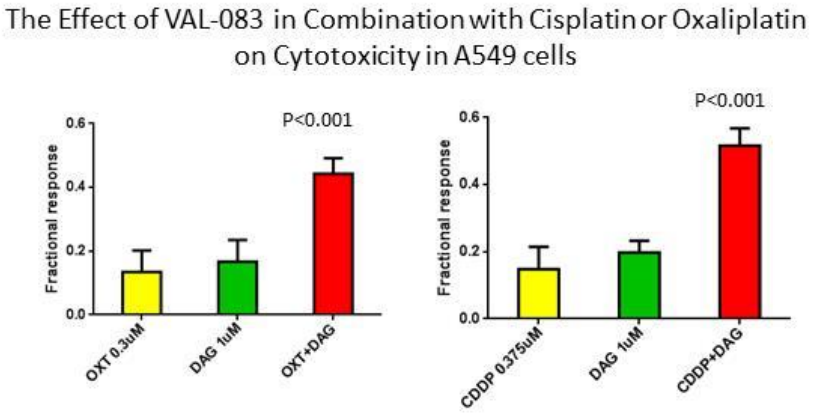
The activity of VAL-083 appears to be comparative or superior to cisplatin or oxaliplatin *in vitro.* Studies investigating the signaling pathways affected by each compound are ongoing and preliminary data suggests that the mechanism of VAL-083 is distinct from platinum-based therapies.

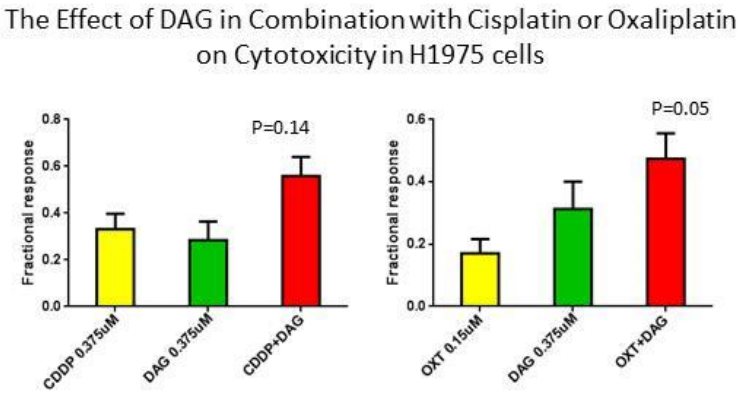
The *in vitro* activity of VAL-083 in combination with cisplatin or oxaliplatin was tested in NSCLC cell-lines **A549** and **H1975.**

A549 cells express wild-type EGFR and K-ras mutation. A549 cells were resistant to TKI inhibitors in tissue culture; however, A549 tumors growing *in vivo* have been observed to be moderately sensitive to treatment with TKIs.

H1975 cells express mutated EGFR with L858R and T790M resistance mutation and are generally resistant to treatment with TKIs.

Cells were treated with VAL-083 (DAG in the figure below) and cisplatin or oxaliplatin, simultaneously, using IC10-30 concentrations of the individual agents, and cytotoxicity was monitored on day 5 with the colorimetric MTT assay. P-values were calculated by Student's t-test analysis of experimental values vs. predicted additive values for the treatment combinations.





These results suggest that VAL-083 in combination with either cisplatin or oxaliplatin has a more than additive or super-additive cytotoxic effect on both TKI-resistant (H1975) and TKI-sensitive (A549) NSCLC cells and support the potential for synergistic benefit for a combination of VAL-083 and platinum-based therapies.[17]

Similar results were observed in a standard *in vivo* model of anti-cancer activity, in which mice were treated with a single IP injection of either cisplatin or VAL-083 on an equimolar basis. In addition, the combination of VAL-083 followed immediately by cisplatin was evaluated. VAL-083 was superior to cisplatin in tumor growth delay and the combination of VAL-083 + cisplatin produced a more than additive effect in tumor growth delay.

[17]Steino et al. The unique mechanism of action of VAL-083 may provide a new treatment option for chemo-resistant non-small cell lung cancer. Abstract #A65 AACR New Horizons in Cancer Research 2014.

mouse fibrosarcoma model (RIF-1 cell-line in C3H mice)			
Treatment	**Dose (mg/kg)**	**Days to 4 x Median tumor size**	**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

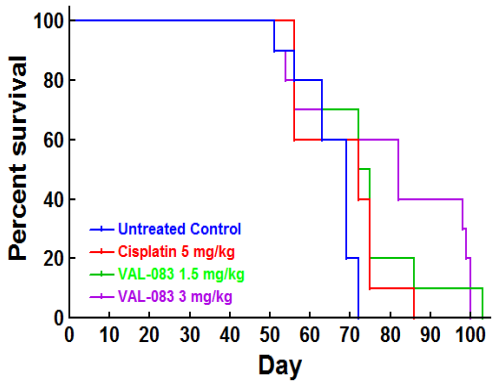
VAL-083 was also compared to cisplatin in xenograft models of Rag2 mice bearing subcutaneous human lung adenocarcinoma xenograft tumors of either A549 or H1975 origin. VAL-083 in three different doses was given i.p. 3 times/week for 3 weeks, and the *in vivo* efficacy of VAL-083 in controlling tumor growth compared to cisplatin (5 mg/kg). Saline was used as control.

Disease progression was evaluated by tumor volume, clinical observations and body weight measurements. Although both A549 and H1975 cell lines are similarly resistant to TKIs in tissue culture, A549 cells display moderate *in vivo* sensitivity to EGFR TKIs when grown as xenografts, whereas H1975 cells do not.[18]

A549 (TKI-resistant / EGFR-WT): A significant survival benefit was observed with VAL-083 at 3mg/kg as shown below. A log-rank statistical test (Mantel-Cox) was performed, indicating a significant difference between the survival curves (p-value = 0.0446). A tumour growth delay of 26 days was observed in animals treated with 3 mg/kg VAL-083 compared to untreated controls, versus positive control, 5 mg/kg Cisplatin, which resulted in a tumour growth delay of 4 days compared to untreated controls. Mean tumor volume on day 68 was significantly reduced in animals treated with 3 mg/kg VAL-083 (p=0.001) compared to untreated control.

Results VAL-083 v. cisplatin in A549 model *in vivo*

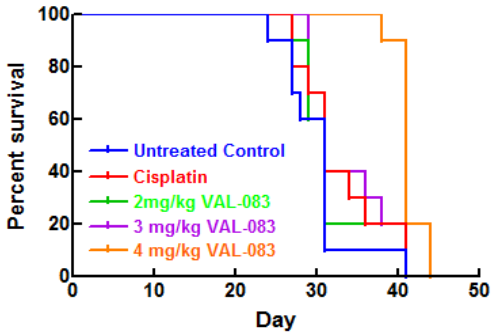
Treatment	**MTV* day 68**	**TCR* day 68**	**TGD* (Days)**	**TGI* (%)**	**P value**	**Median survival (days)**
Control	638	1	0	0	n/a	69
Cisplatin 5 mg/kg	460	0.72	4	29 %	0.059	72
VAL-083 1.5 mg/kg	440	0.69	9	32 %	0.069	73
VAL-083 3 mg/kg	303	0.47	26	55 %	0.001	82



[18]Naumov et al. Combined Vascular Endothelial Growth Factor Receptor and Epidermal Growth Factor Receptor (EGFR) Blockade Inhibits Tumor Growth in Xenograft Models of EGFR Inhibitor Resistance. Clin Cancer Res. May 15, 2009; 15(10): 3484–3494

H1975 (TKI-resistant/EGFR Mut): A significant survival benefit was observed with VAL-083 at 4mg/kg as shown in Figure 2 and Table 3. The median survival time for mice treated with 4 mg/kg VAL-083 was 41 days compared to 31 days for all other treatment and control groups. A log-rank statistical test (Mantel-Cox) was performed indicating p value of 0.0009 indicating a significant difference between the survival curves. Mean tumor volume on day 31 was significantly reduced in animals treated with 4 mg/kg VAL-083 compared to control (p=0.004).

Treatment	MTV* day 31	TCR* day 31	P value**	Median survival (days)
Control	459	1	n/a	31
Cisplatin 5 mg/kg	381	0.83	0.102	31
VAL-083 2 mg/kg	396	0.87	0.490	31
VAL-083 3 mg/kg	383	0.84	0.769	31
VAL-083 4 mg/kg	262	0.57	0.004	41



These results suggest that VAL-083 maintains activity where cisplatin fails to gain a statistically significant benefit, even in a TKI-resistant setting. Taken together, these preclinical data suggest that VAL-083 is superior to cisplatin in both TKI-sensitive and TKI-resistant tumor models, has synergistic effect in combination with cisplatin and oxaliplatin, and suggest clinical potential in TKI-resistant NSCLC. This data provides direction to clinical research aimed at influencing practice patterns under VAL-083's current label and support expanded global development.

6. VAL-083 in NSCLC: Clinical Data

VAL-083 was investigated in a number of clinical trials in the United States and Europe during the 1970s both as a stand-alone therapy and in combination with other chemotherapeutic regimens. All trials showed clinical activity in lung cancer patients; however, in general, combination treatment yielded superior outcomes.

Summary of NCI-Sponsored Single Agent Phase II Lung Cancer Clinical Trials with VAL-083

Reference	Enroll Eval.	Design Control	Drug Dose and Regimen	Diagnosis Inclusion	Activity
Haas et al., 1981	73 70	open-label single-arm	IV DAG 30 mg/m^2/day x 5 days re-treat monthly, if impaired renal function then 15 mg DAG	advanced lung cancer	1 CR 3 PRs
Eagan et al., 1977	99 96	prospective randomized open-label, two arms crossover with disease progression	DAG: IV 30 mg/m^2/day x 5 days, re-treat every 4-5 weeks CAP: IV C – 400 mg/m^2 IV; A - 40 mg/m^2 IV; P - 40 mg/m^2 IV; re-treat CAP every 4 weeks C – cyclophosphamide, A – adriamycin, P – cisplatin	advanced non-small cell lung cancer (only 2 with prior chemotherapy)	Regression DAG: 6/62 CAP: 26/69
Hass, et. al., 1976	37	Phase I, dose-escalation	IV DAG 30 mg/m^2/day x 5 days & 21mg/m2/day x 10 days	Phase I	5SD and 1PR/12 SCC (50%) 3SD and 1CR/16 Adeno (25%)

Hass et al reported increasing disease in a proportion of subjects in a Phase I study; however, the authors noted that most of these patients received submaximal doses. Partial and complete responses were observed in a higher dose cohort.

Eagan et al reported results of a Phase 2 study of heavily pre-treated subjects. Ninety nine (99) patients with advanced non-small cell lung cancer were enrolled and randomized to VAL-083 or triple therapy composed of C-cyclophosphamide, A-adriamycin and P-cisplatin. VAL-083 was given in a 5-day course at a dose of 30 mg/m2/day, with retreatment every 4-5 weeks. CAP was C 400 mg/m2, A 40 mg/m2, and P-40 mg/m2 every 4 weeks. Patients were crossed over to the other therapy following progression of disease. Of the 96 evaluable patients, VAL-083 monotherapy had a 12% overall response rate (4 of 31), whereas the CAP triple therapy regimen had a 38% overall regression rate (26 of 69). Leucopenia was more common with the CAP regimen, and thrombocytopenia was more common and severe with VAL-083. Nausea and vomiting were more frequent and severe with CAP, versus mild and infrequent with VAL-083.[19]

Haas et al reported results of a Phase 2 study of VAL-083 as monotherapy in patients with advanced lung cancer yielded responses in three of 33 patients with adenocarcinoma and in one of 11 patients with large cell anaplastic carcinoma. Toxic effects were myelosupression. Other observed toxicities were acceptable and were related to serum creatinine values.[20]

[19]Eagan et al. Platinum-Based Polychemotherapy Versus Dianhydrogalactitol in Advanced Non-Small Cell Lung Cancer. Cancer Treatment Reports Vol. 61, No. 7, October 1977

[20]Haas et al. Phase II evaluation of dianhydrogalactitol in lung cancer: a Southwest Oncology Group Study. Cancer Treat Rep. 1981 Jan-Feb;65(1-2):115-117

VAL-083 was also studied in combination with other standard chemotherapies of the era as a treatment for lung cancer.

Table 5.3: Summary of NCI-Sponsored Combination Phase II Lung Cancer Clinical Trials with VAL-083

Ref	Enroll Eval.	Design Control	Drug Dose and Regimen	Diagnosis Inclusion	Results
Eagan et al., 1980	44 41	randomized parallel two-arms	Two arms DA: DAG + Adriamycin DAP: DAG + Adriamycin + cisplatin:	advanced squamous cell lung cancer	Regression rate: DA 27%, DAP 53% Median survival: DA 126 days, DAP 185 days
Eagan et al., 1981b	40 37	Open-label single-arm	Three drug regimen: DAG, doxorubicin & cisplatin DAG: IV 25mg/m^2/day x 3 days Doxorubicin: IV 40mg/m^2 on day 1 only Cisplatin: IV 20mg/m^2/day x 3 days	advanced squamous cell lung cancer	Tumor regression 20/37 Median survival 229 days

Forty-one patients with advanced squamous cell lung cancer and no prior chemotherapy were entered in a prospectively randomized trial comparing VAL-083 plus Adriamycin (DA) versus DA plus cis-dichlorodiammineplatinum (II) (DAP). The DAP regimen was superior to the DA regimen in regression rate (53% v 27%), median regression duration (255 v 122 days), median time to tumor progression (approximately 175 v 58 days), and median survival time (185 v 126 days). Patients who were greater than 60 years old responded particularly well to the DAP regimen and accounted for most of the survival advantage. Nausea, vomiting, and myelosuppression were more frequent and severe with the DAP regimen. This study seems to indicate a role of cis-dichlorodiammineplatinum(II) in patients with advanced squamous cell lung cancer. The particular advantage noted for older patients needs further evaluation.[21]

Forty patients with advanced squamous lung cancer were treated with a combination of VAL-083, doxorubicin, and cisplatin in a clinical study. Overall 20 of 37 patients (54%) had tumor regressions with an overall median survival time of 229 days. Hematologic side-effects were significant with most patients experienced a 2-4 g/dL decrease in their hemoglobin. Leukopenia and thrombocytopenia occurred in 93% and 83% of patients, respectively. There were no drug-related deaths. All patients developed alopecia, and one patient had congestive heart failure; nausea and vomiting were moderate to severe in almost all patients.[22]

More recently, anecdotal evidence from a patient treated with VAL-083 at Guangxi Medical University demonstrated potential in refractory lung cancer. A regimen of 40mg/day x 5 days with 5 days rest between cycles was well tolerated by a 38 year old male with refractory lung cancer. The patient has received multiple cycles of treatment since December 2012 and appears to be receiving clinical benefit. The data is anecdotal, but worthy of further investigation.

[21]Eagan et al. A role of cis-dichlorodiammineplatinum(II) in squamous cell lung cancer. Cancer Treat Rep. 1980 Jan;64(1):87-91
[22]Eagan et al. Phase II study of the combination of dianhydrogalactitol, doxorubicin, and cisplatin (DAP) in patients with advanced squamous cell lung cancer. Cancer Treat Rep. 1981 May-Jun;65(5-6):517-9

7. Safety & Toxicity

VAL-083 appears to be a well-tolerated chemotherapeutic agent with definite antitumor activity in humans. An extensive clinical safety data base exists for VAL-083 in the United States and in China. A review of the Chinese literature and US Phase I and Phase II US data support the safety profile of VAL-083.

Toxicity in NCI-sponsored Phase I studies of patients with unresectable or metastatic cancer was mainly hematologic, with thrombocytopenia being somewhat more common than leukopenia.[23]

Additional noted toxicities include nephrotoxicity, fatigue, and alopecia, but these were not reported to be severe. No cumulative renal, hepatic, central nervous system, cardiac or pulmonary toxicity was observed. Toxicities in the combination studies were generally more frequent and severe, and more intense administration (weekly, rather than monthly) also increased toxicities. Any observed gastrointestinal toxicity included nausea and vomiting and was generally mild to moderate.

The main dose-limiting toxicity related to the administration of VAL-083 observed in the NCI-sponsored clinical studies overall was myelosuppression, both thrombocytopenia and leukopenia, with a higher frequency and severity of these toxicities observed in patients with significant prior therapies. .

Thrombocytopenia was generally reported as the dose-limiting factor. Recovery of platelet counts to the normal range occurred spontaneously following the course within a reasonable time frame allowing for multiple courses of treatment. General hematologic toxicities could likely be further managed by modern concomitant medications such as Neupogen™.

Summary of VAL-083 Safety Studies

Ref	Dose	Schedule	Dose Limiting Toxicity
Single-Agent Safety Studies			
Espana, 1978	150mg/m^2	Single dose	tolerated
Eagan, 1976 (n=50)	2-40 mg/m^2/d	x5 days every 5 weeks	Myelosuppression
Hass, 1976 (n=37)	2-31 mg/m^2/d	x5 or 10 days every 5 weeks	Myelosuppression
Vogel, 1976 (n=28)	2-80 mg/m^2/d	Once per week	Myelosuppression
Chinese product insert	25-40 mg/m^2/d	x5 days every 2 weeks	Myelosuppression
Combination Safety Studies			
Creagan, 1979 (n=8)	VAL-083: 60-70 mg/m^2/d BCNU: 80-90 mg/m^2/d		Myelosuppression
Creagan, 1987 (n=9)	VAL-083: 60-70 mg/m^2/d VP-16-213: 60-80 mg/m^2/d CDDP 20 mg/m^2/d	4 week cycle: VAL-083: once per day VP-16-213 x 3 days CDDP x 3 day	Myelosuppression

In the study by Espana (1978), patients with malignant glioma were given VAL-083 at a dose of 150 mg/m^2 IV at 21-day intervals in conjunction with radiation, and in Eagan 1982, patients received 70 mg/m^2 VAL-083 IV in combination with 90 mg/m^2 BCNU, with repeat cycles of treatment every 5 – 7 weeks. In both of these studies, toxicities were not a major concern. No patients were discontinued from drug due to toxicity, and there were no drug-related deaths.

[23] Eagan et al. Brief Communication: Phase I Study of a Five-Day Intermittent Schedule for 1,2:5,6-dianhydrogalactitol (NSC-132313). Journal of the National Cancer Institute. 1976:56(1)179-181

Similarly, in studies of single-agent VAL-083 in patients with cancer, a variety of dose regimens have been used.

The most common regimen was 25-30 mg/m^2/day every 5 days, with re-treatment every 2 to 5 weeks. Toxic effects were noted on white blood cell (WBC) and platelet counts.

For example, nadir of 2,100/μL (lymphopenia) and 88,000/μL (thrombocytopenia), respectively was observed with a regimen of 25 mg/m^2/day every 5 days, with re-treatment every 5 weeks.[24] A dose of 40mg/m^2/day for five days resulted in a median platelet nadir of 31,000/μL and WBC nadir of 2,300/μL.[25] In general, nadir occurred within three weeks and returned to normal within 7 days. Anemia, nausea and vomiting were usually mild to moderate. No renal, hepatic, central nervous system, cardiac, or pulmonary toxicity was identified.

A dose of 50 mg/m^2/day x 5 days every two weeks was used in a study of children with leukemia, and patients with refractory cancers were treated with a VAL-083 dosing regimen of 50 mg/m^2 twice a week for 4 weeks, then twice weekly for 2 weeks and every 6 weeks for maintenance refractory cancers (Finklestein 1985).

According to the Chinese product label, the recommended dosing regimen for the treatment of solid tumors is 40mg per day over a 5 day course, followed by 2 weeks intermission between courses.

In DelMar Pharmaceutical's current US Phase I/II clinical trial, Dose escalation is being undertaken to establish a safe, "modernized" dosing regimen for glioblastoma patients who have been pre-treated with bevacizumab. The DelMar dosing regimen uses a cycle of treatment on the first three days of every three weeks.

A summary of recent, ongoing and planned dose cohorts compared to the historical regimen used in NCI-sponsored Phase II studies is presented in the table below:

DOSING REGIMEN & STUDY	**SINGLE DOSE**	**Acute Regimen** *(single cycle)*		**Comparative Cumulative Dose** *(@ 35 days)*	**Dose Density** *(dose per week)*	**Status**
NCI GBM historical regimen *(Eagan etal)* daily x 5 q 5wks *(cycle = 35 days)*	25 mg/m^2	**x5 days =**	125 mg/m^2	125 mg/m^2	25mg/m^2/wk	Historical Studies: *Myelosuppression observed*
DelMar VAL-083 regimen daily x 3 q 3wks *(cycle = 21 days)*	30 mg/m^2	x3 days =	90 mg/m^2	180 mg/m^2	30mg/m^2/wk	No DLT
	40 mg/m^2		120 mg/m^2	240 mg/m^2	40mg/m^2/wk	No DLT
	50 mg/m^2		150 mg/m^2	300 mg/m^2	50mg/m^2/wk	ongoing
	60 mg/m^2		180 mg/m^2	360 mg/m^2	60mg/m^2/wk	planned

NCI-CTCAE Grade 1 lymphopenia (LLN to >3,000/μL) and thrombocytopenia (platelet counts LLN to >75,000/μL) at doses above 20mg/m^2/day x 3 days had been observed in GBM treated to date in the current study; however, no serious adverse events related to study drug or dose limiting toxicity (DLT) has been encountered at doses up to 40mg/m^2/day x 3 days.

[24]Egan etal (1979)
[25]Eagan etal (1981)

Summary of hematologic-related safety data observed to date in the DelMar clinical trial to date

Cohort	Dose & Hematologic Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	up to 10 mg/m^2						
1 - 4	*LYMPHOPENIA*	*0*	*0*	*0*	*0*	*0*	*0*
	THROMBOCYTOPENIA	*0*	*0*	*0*	*0*	*0*	*0*
	20 mg/m^2						
5	*LYMPHOPENIA*	*1*	*0*	*0*	*0*	*0*	*1*
	THROMBOCYTOPENIA	*0*	*0*	*0*	*0*	*0*	*0*
	30 mg/m^2						
6	*LYMPHOPENIA*	*0*	*0*	*0*	*0*	*0*	*0*
	THROMBOCYTOPENIA	*1*	*0*	*0*	*0*	*0*	*1*
	40 mg/m^2						
7	*LYMPHOPENIA*	*1*	*0*	*0*	*0*	*0*	*1*
	THROMBOCYTOPENIA	*0*	*0*	*0*	*0*	*0*	*0*
8	**50 mg/m^2**			***Ongoing***			

8. Clinical Pharmacokinetics and Bio-distribution of VAL-083

The current clinical formulation of VAL-083 is for intravenous use. The drug is orally bioavailable and has demonstrated clinical activity following oral administration.[26] VAL-083 readily enters the CNS and crosses the blood brain barrier.

In humans, intravenously administered doses of 50mg/m^2 given as a 1-hour infusion, produced peak plasma concentrations of 1.9 to 5.6µg/ml.[27] The elimination of VAL-083 is biphasic with an alpha half-life of 3.9 minutes and a beta half-life of 312.3 minutes. Overall, the primary route of elimination is metabolism to a series of highly polar metabolites, which are excreted in the urine.

Plasma half-life as stated in the published literature is short, about 1-2 hours. The drug appears to reach steady state rapidly in the plasma. At high doses plasma concentrations and AUC increase only slightly with dose escalation; for example, the AUC changed only from 32.7±11.2 to 39.4±9.5 when the dose was raised from 690 to 1050 mg/m^2.[28]

Human Pharmacokinetics *(*=single dose 50mg VAL-083)*

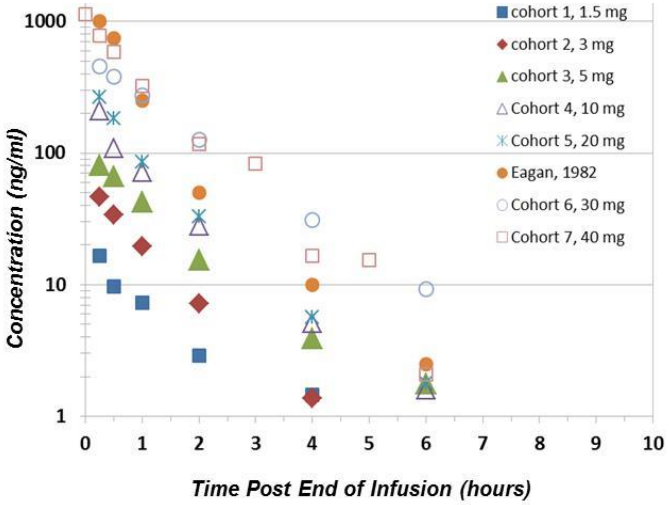
Plasma				
t½	T_{max}	C_{max}*	AUC*	Protein Binding
2.05 hr (1-4hr)	1-2hr	3.6µg/ml	22µg/h-ml	20-30%

Cerebral Spinal Fluid				
t½	T_{max}	C_{max}	AUC	Protein Binding
20 hr (3-24)	2 hr			negligible

Pharmacokinetic observations from DelMar Pharmaceuticals' current clinical study in the United States confirm literature-based plasma PK data. Data from cohorts 1-7 demonstrate dose-dependent linear systemic exposure with a short plasma 1-2 h terminal half-life; Cmax at the highest dose tested (cohort 7,

[26]DeJageer et al. Dianhydrogalactitol (NSC-132313): Phase II study in solid tumors: A Report of the E.O.R.T.C. Early Cinical Trial Cooperative Group. Eur. J Cancer 1989 Jul:15(7):971-974.
[27]Eagan et al. Phase II Studies of Dianhydrogalactitol-Based Combination Chemotherapy for Recurrent Brain Tumors. Oncology. 1982:38:4-6.
[28]Kerpe-Fronius et al. Relation between dose, plasma concentration and toxicity in a phase I trial using high dose intermittent administration of an alkylating agent, diactyldianhdrogalactitol. Cancer Chemother Pharmacol. 1986.

40 mg/m^2) ranged from 1130 to 739 ng/mL (7.7 to 5.1 µM). These data are correlated with the PK profile published in the scientific literature (Eagan et al 1982) as shown in the following figure:



Based on published literature, it has been established that VAL-083 enters the CSF rapidly, peaking at 1-2 hrs and is slowly eliminated, with a half-life of 20 hrs (vs. 1-2 hrs in plasma). Rapid entry into the CNS is characterized by a concentration in the CSF of 40-50% of plasma levels at simultaneous time points.[29] Analysis of PK exposure in the CSF will be undertaken at higher doses in the current Phase I/II study.

Published preclinical and clinical research demonstrates that VAL-083 is selective for tumor tissue, with up to 28-fold higher accumulation in CNS tumor tissue.[30]

9. Manufacturing

VAL-083, which is also known as “Weimutrin” or “Dianhydrodulcitol” in the Chinese market, is approved in China for the treatment of CML and lung cancer.

VAL-083 is supplied as pure drug product for reconstitution exclusively by Guangxi Wuzhou Pharmaceutical (Group) Co. Ltd., a wholly owned subsidiary of Zhongheng Group, a publicly listed company in China (SHG: 600252). VAL-083 is not commercially available outside of China. Guangxi Wuzhou Pharmaceuticals currently holds the only license from the SFDA for the manufacture of VAL-083 for Injection in China (Approval No. Guoyao Zhunzi H45021133) and is compliant with Ministry of Health (MoH) Decree No.79 for the manufacture of an injectable pharmaceutical.

DelMar Pharmaceuticals is collaborating with Guangxi Wuzhou Pharmaceuticals to implement FDA-acceptable cGMP practices into manufacture of the active pharmaceutical ingredient (API) and finished drug product.

[29]Horváth et al. Pharmacokinetics and metabolism of dianhydrogalactitol DAG in patients: a comparison with the human disposition of dibromodulcitol DBD. Eur J Cancer Clin Oncol. 1986 Feb;22(2):163-71.
[30]Eckhardt et al Uptake of Labeled Dianhydrogalactitol into Human Gliomas and Nervous Tissue. Cancer Treat Rep. 1977:61:841-847.

For current clinical studies in the United States, DelMar has acquired the finished drug product from the Chinese manufacturer, for release under Good Manufacturing Practice (cGMP) in the United States based on an internally developed analytical methods and expanded specifications.

10. Intellectual Property

VAL-083 has been granted orphan drug status for the treatment of gliomas in the United States and the European Union. DelMar Pharmaceuticals intends to seek data and orphan drug protections in other international jurisdictions where it is available. This strategy extends to new indications in China where new indications established under a Category 1 or Category 2 SFDA approval obtain a 5 year safety review period, exclusive of patent protections which may exist on the product.

In addition to Orphan Drug protection, DelMar employs a strategy for obtaining new patent claims to protect the intellectual property associated with the development of 'old' drugs for modern indications has been validated by companies such as Celegene, Cephalon, Chemgenex and Salmedix. In general, this strategy includes new patent filings claiming:

- The use of the drug in new patient populations, such as those failing modern biologic therapies which had not yet been invented at the time of the drug's original study;
- Novel label claims, such as modernized dosing administration to improve efficacy and reduce toxicity;
- Improvements to the manufacturing process;
- New analytical methods required for product approval under "Current Good Manufacturing Practice" (cGMP) guidelines;
- Identification and control of the chemical composition of the active pharmaceutical ingredient and the final drug product; and
- Composition of matter claims for new chemical entities in the "surrounding" or related chemical space.

Two new United States patents and one international patent have been issued for VAL-083 have issued to DelMar Pharmaceuticals and provide patent protection at least through 2030.

11. Proposed Repositioning Strategy for NSCLC in China

NSCLC is an unmet medical need in China, and globally, for those patients who are either refractory to or develop resistance to standard-of-care, including TKIs.

VAL-083 is approved for the treatment of lung cancer in China; however, the direct translation of the label: *"VAL-083 can rapidly shrink the size of lung tumors"*, requires further exploration to unlock potential value in the modern treatment paradigm. A strategy of developing specific data to be supported by appropriate market education and product promotion needs to be undertaken.

The historical literature clearly indicates VAL-083 has activity against NSCLC both as a single agent and in combination chemotherapy, and therefore may prove to be valuable in refractory disease, or in a front-line setting as an alternative chemotherapy in doublet with carboplatin or cisplatin.

Both VAL-083 and the platinum-based chemotherapies exhibit their primary cytotoxic activity through N7 cross-links. The mechanisms of cross-linkage are different being intra-strand and inter-strand for platinum agents and VAL-083, respectively. DelMar is undertaking research to further explore the mechanistic differences between VAL-083 and platinum-based chemotherapies.

In a recent study conducted by DelMar Pharmaceuticals, VAL-083 proved superior to cisplatin and the combination of VAL-083 with cisplatin was more than additive. These data suggest the potential for VAL-083 to become part of standard platinum doublet therapy in the treatment of solid tumors.

VAL-083 has been demonstrated to be active in TKI resistant tumors *in vitro* therefore may offer a potential immediate solution for patients in China suffering from TKI-resistant NSCLC.

VAL-083 readily crosses the blood brain barrier and could potentially be used to treat patients experiencing lung-cancer metastasis to the CNS.

The prior approval of VAL-083 in China provides an opportunity to explore activity in NSCLC populations that could potentially benefit from VAL-083 therapy in a post-market "Phase IV-like" setting. A roadmap for product repositioning based on unmet needs in NSCLC, existing knowledge about the mechanism of VAL-083 and the drug's activity against lung cancer combined with new pre-clinical and clinical data would enable realization of this opportunity.

DelMar Pharmaceuticals has developed a detailed non-clinical research plan to investigate VAL-083 in NSCLC. Specific research to assess the activity of VAL-083 in scenarios representing an unmet medical need in NSCLC is being undertaken. Research will include, evaluation of relative cytotoxicity of VAL-083 in NSCLC cell lines including assessment of activity against platinum-resistant phenotypes and TKI-resistant phenotypes. Similar research will be carried out *in vivo*. The goal of this research is to develop specific data to support VAL-083 product re-positioning in lung cancer, particularly NSCLC. These data are anticipated to be presented or published in peer reviewed settings.

In addition to non-clinical research, post-market clinical studies can be undertaken to support VAL-083 product repositioning in NSCLC. Study design will be undertaken with leading key opinion leaders in China and North America.

A clinical study protocol has developed to explore VAL-083 in NSCLC patients who are resistant or refractory to platinum doublet therapy. Additionally, the potential to treat NSCLC patients whose cancer has spread to the brain can easily be explored.

It is anticipated that NSCLC clinical studies in China will be conducted based on physician sponsored protocols submitted to local ethical committees. Small sample sizes with objective response rates as endpoints with dosing regimens within the context of the currently approved label will be considered.

These studies will serve as the basis for publications and physician education efforts to promote the repositioning of VAL-083 for the treatment of NSCLC under the currently approved label in China, which could provide near-immediate patient benefit. Separately, these data can form the basis for expansion of clinical research with VAL-083 against NSCLC on a global basis.

12. Market Opportunity

Given the prevalence of NSCLC in China and the challenges associated with treatment, DelMar believes that VAL-083 has a significant market opportunity under its currently approved label in China.

Historically, the approval of VAL-083 was on a provincial basis and was limited to Guangxi province and the primary promotion of VAL-083 was for CML. The "nationalization" of the approval in 2006 roughly coincides with the launch of Gleevec™ in China. Because of the strong interest from physicians and distributors in modern high-margin targeted therapies, VAL-083 was never appropriately launched in the wider Chinese marketplace once its approval was expanded to include all of China.

DelMar Pharmaceuticals believes that the development of specific data to support product repositioning combined with appropriate promotions lead by respected key opinion leaders could result in significant product growth in China. Because the drug was never launched in major cities such as Shanghai, Beijing, or Guangzhou DelMar believes that developing appropriate new data would result immediate and significant opportunity for marketing an incumbent drug as a new product in major urban Chinese markets.

Revenue Opportunity in Major Urban Centers of Beijing, Shanghai and Guangzhou

		Current Incidence (based on WHO statsistics)		
Population of 3 major urban centers (PEK, SHG, GHZ)	Incidence per 100,000 (Lung)	All	TKI Resistant	BIM Deletion
55,000,000	35	19,250	9,625	4,043

		Current revenue opportunity (millions)		
Annual evenue per patient based on current pricing and dosing structure		All	TKI Resistant	BIM Deletion
¥57,600.00	RMB	1,108.8	554.4	232.848
$9,290	USD	178.8	89.4	37.6

		2025 Estimate		
CAGR = 9.2%		All	TKI Resistant	BIM Deletion
	RMB	2,436.9	1,218.5	511.8
	USD	393.1	196.5	82.5

DelMar believes that there may be opportunities to seek premium pricing for refractory cancers; however, the margins and revenue potential based on the current pricing structure are significant.

Data developed through post-market clinical repositioning studies can be used as the basis to support regulatory filings for expanded global development of VAL-083 in the treatment of NSCLC.

13. References

(alphabetical list)

13.1. Charpidou et al. EGFR mutations in non-small cell lung cancer--clinical implications. In Vivo. 2008 Jul-Aug;22(4):529-36.

13.2. Chinese Product Label for VAL-083

13.3. Chiuten et al. Clinical Trials with the Hexitol derivatives in the U.S. Cancer. 1981:47:442-451.

13.4. Costa et al. BIM Mediates EGFR Tyrosine Kinase Inhibitor Induced Apoptosis in Lung Cancers with Oncogenic EGFR Mutations PLOS MedV4:10(2007):1669-80

13.5. DeJageer et al. Dianhydrogalactitol (NSC-132313): Phase II study in solid tumors: A Report of the E.O.R.T.C. Early Cinical Trial Cooperative Group. Eur. J Cancer 1989 Jul:15(7):971-974.

13.6. Dunn et al. VAL083, a novel N7 alkylating agent, surpasses temozolomide activity and inhibits cancer stem cells providing a new potential treatment option for glioblastoma multiforme. American Association of Cancer Research 2012 Annual Meeting. Permanent Abstract No. 811

13.7. Eagan et al. Brief Communication: Phase I Study of a Five-Day Intermittent Schedule for 1,2:5,6-dianhydrogalactitol (NSC-132313). Journal of the National Cancer Institute. 1976:56(1)179-181

13.8. Eagan et al. Dianhydrogalactitol and Radiation Therapy in the Treatment of Supratentorial Glioma. JAMA 1979:241(19):2046-50.

13.9. Eagan et al. Phase II Studies of Dianhydrogalactitol-Based Combination Chemotherapy for Recurrent Brain Tumors. Oncology. 1982:38:4-6.

13.10. Eagan et al. Phase II study of the combination of dianhydrogalactitol, doxorubicin, and cisplatin (DAP) in patients with advanced squamous cell lung cancer. Cancer Treat Rep. 1981 May-Jun;65(5-6):517-9

13.11. Eagan et al. Platinum-Based Polychemotherapy Versus Dianhydrogalactitol in Advanced Non-Small Cell Lung Cancer. Cancer Treatment Reports Vol. 61, No. 7, October 1977.

13.12. Eagan et al. A role of cis-dichlorodiammineplatinum(II) in squamous cell lung cancer. Cancer Treat Rep. 1980 Jan;64(1):87-91

13.13. Eckhardt et al. Uptake of Labeled Dianhydrogalactitol into Human Gliomas and Nervous Tissue. Cancer Treat Rep. 1977:61:841-847.

13.14. Filosto, et al. Cigarette Smoke Induces Aberrant EGF Receptor Activation That Mediates Lung Cancer Development and Resistance to Tyrosine Kinase Inhibitors. Molecular Cancer Therapeutics. Advanced On-line publication. February 2012

13.15. Haas et al. Phase II evaluation of dianhydrogalactitol in lung cancer: a Southwest Oncology Group Study. Cancer Treat Rep. 1981 Jan-Feb;65(1-2):115-7

13.16. Horváth et al. Pharmacokinetics and metabolism of dianhydrogalactitol DAG in patients: a comparison with the human disposition of dibromodulcitol DBD. Eur J Cancer Clin Oncol. 1986 Feb;22(2):163-71.

13.17. Hubner et al. Multisite Phosphorylation Regulates Bim Stability and Apoptotic Activity. Molecular Cell 30(2008), 415–425

13.18. Institoris et al. *In vivo* study on alkylation site in dna by the bifunctional dianhydrogalactitol, Chem.-BioL Interactions, 35 (1981) 207--216

13.19. Johnson et al. End Points and United States Food and Drug Administration Approval of Oncology Drugs. Journal of clinical Oncology. 2003:21(7):1404-1411

13.20. Kerpe-Fronius et al. Relation between dose, plasma concentration and toxicity in a phase I trial using high dose intermittent administration of an alkylating agent, diactyldianhdrogalactitol. Cancer Chemother Pharmacol. 1986.

13.21. King et al. A common *BIM* deletion polymorphism mediates intrinsic resistance and inferior responses to tyrosine kinase inhibitors in cancer. Nature Medicine Advanced Online Publication. 18Mar/2012

13.22. Kuroda et al. (2006) Bim and Bad mediate imatinib-induced killing of Bcr/Ablþ leukemic cells, and resistance due to their loss is overcome by a BH3 mimetic. Proc Natl Acad Sci U S A 103: 14907–14912

13.23. Nemeth et al Pharmacologic and antitumor effects of 1,2:5,6-dianhydrogalactitol (NSC-132313). Cancer Chemother Rep. 1972:56:593-602.

13.24. O'Connor et al. Bim: a novel member of the Bcl-2 family that promotes apoptosis. The EMBO Journal Vol.17 No.2 pp.384–395, 1998

13.25. Vogel et al. Phase I trial of DAG administered IV in a weekly schedule. Cancer Treat Rep. 1976 Jul; 60(7):895-901. PMID: 795538

13.26. Zhonghua Yi etal. Efficacy analysis of third-generation plus platinum doublets in the first-line chemotherapy of advanced non-small cell lung cancer. Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 2012 Jun 12;92(22):1527-31 (article in Chinese)