Post-market clinical trial of dianhydrogalactitol in the treatment of relapsed or refractory non-small cell lung cancer

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ABSTRACT # 998:

The median overall survival time for patients with stage IV non-small cell lung cancer (NSCLC) is 4 months, and 1- and 5-year survival is less than 16% and 2%, respectively. NSCLC is usually treated with surgery followed by radiation and treatment with platinum-based regimens or in some cases Tyrosine Kinase Inhibitors (TKIs). Unfortunately, long-term prognosis with platinum-based therapies is poor, and TKI resistance has emerged as a significant unmet medical need. Dianhydrogalactitol (VAL-083) is a structurally unique bi-functional alkylating agent mediating interstrand DNA crosslinks at N^7 of guanine. It has previously demonstrated activity against NSCLC in NCI-sponsored preclinical and clinical trials and is approved for treatment of lung cancer in China *(Approval No. Guoyao Zhunzi H45021133)*; however, it is currently not widely known or used for the treatment of NSCLC.

Recent preclinical data suggest that VAL-083 may be a therapeutic option for drug-resistant NSCLC. VAL-083 has superior activity to cisplatin in both *in vitro* and *in vivo* models of NSCLC, including TKI-resistant NSCLC. When combined with either cisplatin or oxaliplatin *in vitro*, VAL-083 demonstrates significant superadditivity ($p<0.05$) and synergism (CI < 1) for both combinations in NSCLC cell lines A549, H1975 and H460.

When tested in a standard syngeneic mouse fibrosarcoma model (RIF-1 cell-line in C3H mice), VAL-083 (10 mg/kg) was superior to cisplatin (4 mg/kg) in tumor growth delay. Mice were treated with a single IP injection of either cisplatin, VAL-083 or VAL-083 followed immediately by cisplatin. Combination treatment of with cisplatin produced a more than additive effect by delaying growth 8.65 days.

In another *in vivo* model using NSCLC cell-line A549 in Rag2mice, VAL-083 was given as part of a combination treatment with cisplatin. Tumour growth delays of 11, 18 and 25 days were observed for 2 mg/kg cisplatin in combination with 2, 2.5 or 3 mg/kg VAL-083, respectively, while no significant tumour growth delay was observed between untreated and Cisplatin (2 mg/kg). The median survival time was increased by 2 days for cisplatin alone, while the combination of VAL-083 (2 mg/kg, 2.5 mg/kg and 3 mg/kg) with cisplatin (2 mg/kg) increased survival by 17 days, 17 days, and 14 days, respectively.

The preclinical data strongly suggest VAL-083 as a potential treatment for drug-resistant NSCLC. A planned open-label phase IV (post market) clinical trial will investigate the activity of VAL-083 in relapsed or refractory NSCLC assessed by objective response rates, complete and partial response rates and stable disease. VAL-083 will be dosed in accordance with the approved label (40 mg/day) and the results will provide guidance to treating physicians under the context of VAL-083's current approval in China, as well as serve as proof of concept for expanded development in the rest of the world.

BACKGROUND

VAL-083 is a bifunctional alkylating agent causing interstrand DNA crosslinks at N7 of guanine, which is believed to be distinct from the mechanisms of other alkylating agents (e.g. cisplatin or BCNU). VAL-083 has demonstrated *in vitro* activity against a range of NSCLC cell lines, including cisplatin-resistant and tyrosine kinase inhibitor (TKI)-resistant cell lines.[1] VAL-083 furthermore demonstrated activity against TKI-resistant NSCLC *in vitro* and *in vivo*[2]. During the 1970s and 1980s, VAL-083 was investigated in a number of clinical trials in the United States and Europe 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 (for representation, 2 of these studies are shown in table 1)[3-7]. 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.

In a standard *in vivo* model, VAL-083 recently showed superior activity to cisplatin and combination treatment of VAL-083 with cisplatin produced a more than additive effect (see table 2).

VAL-083 is approved in China for the treatment of chronic myelogenous leukemia and lung cancer. VAL-083 is currently undergoing clinical studies for refractory glioblastoma multiforme in the United States and has received orphan drug designation in EU and the U.S. for the treatment of gliomas.

Table 1. Historical clinical trials showing activity of VAL-083 as single agent and as part of a cisplatin combination treatment for lung cancer.

Reference	Enrollment/ Evaluation	Design	Drug dose and regimen	Diagnosis Inclusion	Results
Haas *et al*., 1976[5]	37/37	Phase I, dose-escalation VAL-083 single agent	VAL-083 IV 30 mg/m^2/day x 5 days or 21mg/m^2/day x 10 days	Phase I	Squamous cell carcinoma ORR 50% (6/12) Adenocarcinoma ORR 25% (4/16)
Eagan *et al*., 1981[7]	40/37	Open-label, single-arm VAL-083 as part of cisplatin/doxorubicin combination	Three-drug regimen: VAL-083: 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 54% (20/37) Median survival 229 days

Table 2. When tested side-by-side in a standard syngeneic mouse fibrosarcoma model (RIF-1 cell-line in C3H mice), VAL-083 was superior to cisplatin in tumor growth delay *in vivo*. Mice were treated with a single IP injection of either cisplatin, VAL-083 or VAL-083 followed immediately by cisplatin. Combination treatment of with cisplatin produced a more than additive effect by delaying growth 8.65 days.

Treatment	Dose (mg/kg)	Days to 4 x Median tumor size	Tumor growth 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

References:

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Open label post-market (Phase IV) clinical study of dianhydrogalactitol (VAL-083) in relapsed or refractory Non-Small Cell Lung Cancer

This is a phase 4 study of VAL-083 in treatment of NSCLC patients who have failed standard platinum doublet therapy. Up to 20 patients will be enrolled into the study. Study patients will receive VAL-083 intravenous (IV) dose of 40 mg/day for five consecutive days, with 1-2 weeks rest, for two courses, followed by maintenance therapy 40 mg/day IV for five consecutive days every 28 days. Patients will continue to receive treatment until withdrawal criteria are met or the patient receives up to 12 cycles of therapy, whichever comes first. Patients will be monitored for objective responses, progression-free survival, survival, and quality-of-life (using a quality-of-life instrument for patients with lung cancer). Following tumor assessments at screening, evaluation of tumor response conforming to RECIST v1.1 will be documented prior to every other new 28-day maintenance treatment cycle, commencing with maintenance Cycle #2.

Primary goals

To determine activity of VAL-083 in NSCLC patients who have failed standard platinum doublet therapy, as assessed by disease control rate, defined as objective response rate, complete (CR) and partial (PR) response rates, and stable disease (SD) in order to provide guidance to treating physicians under the context of VAL-083's current approval in China.

Secondary goals

To determine the progression-free survival rate of NSCLC patients who have failed standard platinum doublet therapy when treated with VAL-083.

To determine the overall survival of NSCLC patients who have failed standard platinum doublet therapy when treated with VAL-083.

To evaluate the quality of life and impact on disease symptoms following treatment with VAL-083.

Study duration

The study will be considered complete when the last patient either experiences disease progression or an intolerable toxicity, or withdraws from the study. The study will take approximately 1-2 years to enroll.

Inclusion/exclusion criteria for clinical study of dianhydrogalactitol in relapsed or refractory NSCLC

Summary of key inclusion Criteria:

- Patients must be greater than or equal to 18 years
- Histologically or cytologically confirmed diagnosis of non-small cell lung cancer
- Must have failed prior platinum-containing doublet chemotherapy, but no more than two additional lines of chemotherapy treatment
- Must have recovered from all treatment-related toxicities to Grade 1 or less, and must have recovered from all recent surgery
- Must have a life expectancy of greater than or equal to 12 weeks

Summary of key exclusion Criteria:

- History of other malignancy which could affect compliance with the protocol or interpretation of results
- Patients with leptomeningeal involvement
- Prior anti-cancer therapy (e.g., biologic or other targeted therapy, or chemotherapy) within 4 weeks prior to treatment initiation
- Patients who have received an investigational agent within the past 30 days prior to treatment initiation
- Palliative radiotherapy within 2 weeks prior to treatment initiation
- Patients who have not recovered from adverse events of previous therapies
- Known active uncontrolled systemic infection or other concurrent illness, or history of HIV seropositive status

VAL-083 is active in cisplatin-resistant and TKI-resistant NSCLC cell lines

VAL-083 has a distinct mechanism of action from other alkylating agents (e.g. cisplatin) and has shown activity against cisplatin-resistant and TKI-resistant NSCLC cell lines *in vitro*[1].

When VAL-083, cisplatin and oxaliplatin were tested in a panel of 9 human NSCLC cell lines, VAL-083 was active against all tested NSCLC cell lines irrespective of p53 status, including TKI-resistant cell lines H1975, H460, and H1299. [8] Furthermore VAL-083 activity is less dependent of p53 status than cisplatin and oxaliplatin (Figure 1). These results suggest VAL-083 activity in TKI-resistant NSCLC and a distinct mechanism of action from cisplatin and oxaliplatin. Furthermore, in an *in vivo* model of TKI-resistant NSCLC using A549 cells, VAL-083 showed superior activity to cisplatin in inhibting tumor growth and VAL-083 produced a significant survival benefit ($p = 0.0446$) compared to untreated control (Figure 2).

Taken together, these results suggest VAL-083 as a potential therapeutic option for refractory drug-resistant NSCLC.

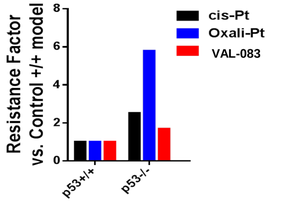

Figure 1. resistance factors for cisplatin, oxaliplatin and VAL-083 in molecularly engineered isogenic models of HCT-116 with (p53+/+) or without (p53-/-) p53.

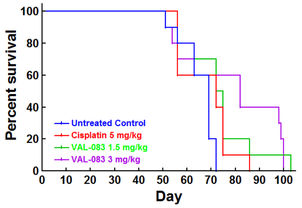

Figure 2. Kaplan-Meier survival plot of VAL-083 (1.5 or 3 mg/kg) or cisplatin (5 mg/kg) in female Rag2 mice with subcutaneous NSCLC of A549 origin.

Combination of VAL-083 with cisplatin or oxaliplatin in *in vitro* models of H460, A549 and H1975 NSCLC

The combination of VAL-083 with either cisplatin or oxaliplatin in the human NSCLC models demonstrated significant superadditivity ($p\leq0.05$) and/or synergism (CI<1) for both combinations. Significantly, this cytotoxic effect of VAL-083 in combination with either platinum drug was observed in both TKI-resistant (H1975 and H460) and TKI-sensitive (A549) NSCLC cells. These results suggest non-overlapping mechanism of action between the platinum drugs and VAL-083, and support the potential for synergistic benefit for a combination of VAL-083 and platinum-based therapies in the treatment of lung cancer. Recent *in vivo* results with A549 cells in Rag2 mice support these findings.

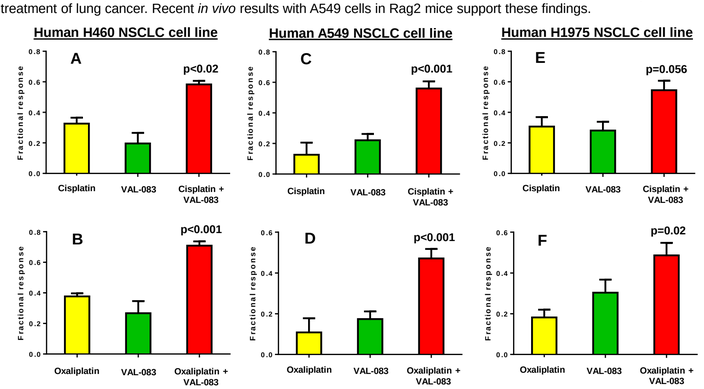

Figure 3. The cytotoxic effect of VAL-083 in combination with cisplatin (**A,C,E**) or oxaliplatin (**B,D,F**) on H460 cells (**A,B**), A549 cells (**C,D**) or H1975 cells (**E,F**) *in vitro*. Data, where applicable, are shown as Mean +/- SE, N=4-7.

CONCLUSIONS

- **New preclinical data supports potential of VAL-083 as a valuable therapeutic option in the modern treatment of lung cancer, particularly in patients who have failed or are unlikely to respond to current standard of care.**
- **The planned clinical trial will provide guidance to treating physicians under the context of VAL-083's current approval in China and establish proof of concept to support global clinical development of VAL-083 in NSCLC.**
- **The combination of VAL-083 with platinum-based chemotherapy warrants further study as a potential treatment for newly diagnosed NSCLC.**