In vivo efficacy of VAL-083 in the treatment of non-small cell lung cancer

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Abstract: # 824

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 treatment with either Tyrosine Kinase Inhibitors (TKIs) (e.g. erlotinib, gefitinib) or platinum-based regimens (e.g. cisplatin). TKIs have resulted in improved outcomes for patients with EGFR mutations; however, TKI resistance has emerged as a significant unmet medical need, and long-term prognosis with platinum-based therapies is poor. Additionally, the incidence of brain metastases in patients with NSCLC with a poor prognosis, VAL-083 is a structurally unique bi-functional alkylating agent mediating interstrand DNA crosslinks at the N7 position of guanine, thus differing in mechanism of action from TKIs and cisplatin. VAL-083 exerts the blood-brain barrier and accumulates in tumor tissue. VAL-083 has demonstrated activity against NSCLC in preclinical and clinical trials, both as a single agent and in combination with other treatments. Suggesting VAL-083 may be a therapeutic option for drug-resistant NSCLC and NSCLC patients with brain metastases. Despite this, VAL-083’s current label and support expanded global development. - insensitive) and H1975 (TKI-resistant (H1975)) tumors have to our knowledge not been addressed before.

The purpose of this study is to evaluate the activity of VAL-083 in in vivo models of drug-resistant NSCLC in comparison to other drugs, including cisplatin. RAG2 mice bearing subcutaneous human adenocarcinoma xenograft tumors of either TKI-resistant (H1975)- and -sensitive (A549)- derived xenografts and H1975-resistant (H1975)-resistant, were used for xenograft tumor models in female RAG2 mice. VAL-083 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. Disease progression is evaluated by tumor volume, clinical observations and body weight measurements. Blood samples are analyzed for CBC/differential analyses to assess myelosuppression or other changes in blood chemistry. These results suggest that VAL-083 may be a viable treatment option for NSCLC patients failing TKI-therapy, especially where platinum-based therapy has already failed or is predicted to give sub-optimal results. These data have important immediate implications in the treatment of NSCLC in China, where VAL-083 is approved for as a chemotherapy for the treatment of lung cancer, and for future clinical development in the rest of the world.

Background

VAL-083 is a bifunctional alkylating agent causing methylation of N7 guanine and interstrand crosslinks, which is believed to be distinct from the mechanisms of other alkylating agents (e.g. cisplatin or BLM). VAL-083 has demonstrated activity against a range of NSCLC cell lines in vitro (see table 3)

Conclusions

In an established model of non-small cell lung cancer, VAL-083 provided superior efficacy (Tumor Growth Delay) and safety (Body Weight loss) in the treatment of TKI-resistant (A549) tumors in comparison to standard cisplatin therapy. Preliminary results suggest further that VAL-083 is superior to cisplatin treatment in TKI-resistant (H1975) tumors.

Methods

- Cell number for inoculation was

- Tumor Growth Inhibition

- Treatment initiated at average tumor volume 100-150

- Table 2. Treatment protocol for testing the efficacy of VAL-083 in comparison to cisplatin in the treatment of female RAG2 mice bearing subcutaneous A549 human lung adenocarcinoma xenograft tumors.

- Figure 3. Tumor volume (Means ± S.D.) for all mice until day 70 (last day for untreated control group). Arrow indicates first treatment dose on day 37.

- Figure 4. Tumor volume (Means ± S.D.) for the complete duration of the study.

- Table 3. Analysis parameters for the 5 groups in A549 model

- Table 4. Analysis parameters for the 5 groups in H1975 model

- Control

- Table 5. Analysis parameters for the 5 groups in H1975 model

- Control

- Figure 6. Tumor volume (Means ± S.D.) for all mice until day 70 (last day for untreated control group). Arrow indicates first treatment dose on day 17.

- Table 6. Analysis parameters for the 5 groups in A549 model

- Control

- Figure 7. Tumor volume (Means ± S.D.) for the complete duration of the study.