BACKGROUND: Glioblastoma (GBM) is the most common CNS tumor. Patients with recurrent GBM have few treatment options and dismal prognosis. High expression of O6-methylguanine-DNA烷基转移酶(MGMT) is correlated with resistance to both frontline systems therapy with temozolomide (TMZ) and poor patient outcomes. DelMar Pharmaceuticals’ VAL-083 is a bi-functional alkylating agent that readily crosses the blood-brain barrier and has demonstrated activity independent of MGMT in multiple GBM cell lines and cancer stem cells in vitro. VAL-083 showed promise against CNS tumors in NCI-sponsored clinical trials. The goal of this clinical trial is to determine the approximate MTD in Phase II trials for VAL-083 as a new treatment for recurrent GBM.

METHOD: Study Population: Patients must have received GBM following surgery, radiation, TMZ and beavizumab. Phase I: Open-label, single-arm dose-escalation study (3+3 design). Patients received VAL-083 IV on days 1, 2, 3 of a 21-day cycle, until MTD was reached. Phase II: 14 additional patients enrolled at MTD to further assess safety and outcomes.

RESULTS: Phase I: 34 patients were enrolled in escalating dose cohorts (1.5–50 mg/m²) and 40 mg/m² confirmed as the MTD. Metyxusporation was the only drug-related serious adverse event (SAE). Most events were reported at dose levels ≥40 mg/m². Dose limiting toxicity (DLT) occurred around day 3 and resolved within 5 days. A dose-related and clinically meaningful survival improvement was observed. Pharmacokinetics show dose-dependent linear systemic exposure with 1-2h-1pH terminal half-life, average Cmax: 78 ± 46 ng/mL at 40 mg/m². Phase II: 48 GBM patients have been enrolled and treatment is ongoing. To date, no dose-limiting toxicities or dose reductions in the Phase II cohort have been observed. Conclusions: VAL-083 is 40 mg/m² exhibits a favorable safety profile and a dose-related trend clinically meaningful survival improvement in recurrent GBM patients was observed in Phase I. We expect to present median overall survival in the Phase II expansion cohort and proposed Phase II study design. ClinicalTrials.gov Identifier: NCT01478178.

CONCLUSIONS: The VAL-083 Survival Study is investigating the potential clinical benefit of VAL-083 in patients with recurrent GBM. VAL-083 is a bi-functional alkylating agent that readily crosses the blood-brain barrier and has demonstrated activity independent of MGMT in multiple GBM cell lines and cancer stem cells in vitro. VAL-083 showed promise against CNS tumors in NCI-sponsored clinical trials. The goal of this clinical trial is to determine the approximate MTD in Phase II trials for VAL-083 as a new treatment for recurrent GBM.

ABSTRACT

Phase II Study of Dihydroxyalactin in Patients with Recurrent Glioblastoma

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Summary Results: Phase III in Recurrent Glioblastoma Multiforme: clinicaltrial.gov identifier: NCT01478178

Safety and Pharmacokinetics

Patients received intravenous VAL-083 administered at the low dose every three weeks for the first three doses, at doses ranging from 0.1 to 100 mg/m². With one exception, no serious adverse events (SAEs) related to study drug were encountered among GBM patients. VAL-083 doses up to 40 mg/m²/day were related to SAEs as observed at VAL-083 doses of 46-60 mg/m²/day. One patient previously treated with CONA required dose de-escalation to a 4-4-4 mg/m²/day dose. At the 10 mg/m² dose level, VAL-083 was found to be well tolerated and was continued in a subsequent phase 2 dose escalation trial where patients received a dose of 10 mg/m² administered on the first three days of every three-week cycle.

Pharmacokinetic (PK) analyses show dose-dependent linear systemic exposure with 1-2 hour terminal half-life, average Cmax: 78 ± 46 ng/mL at 40 mg/m². Dose-related and clinically meaningful survival improvement was observed.

Thrombocytopenia and hypertension were the most common adverse events. Preliminary analysis of all patients receiving an observed therapy dose of VAL-083 (20 mg/m²) suggests that the VAL-083 study may offer improved survival for GBM patients following beavizumab failure in comparison to results from published studies.

Future Visits: A New Paradigm for GBM

REFERENCES


