Abstract # CTNI-26

Phase 2 study of dianhydrogalactitol (VAL-083) in patients with *MGMT*-unmethylated, bevacizumab-naïve glioblastoma in the adjuvant or recurrent setting

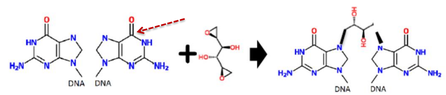
Barbara O'Brien[1], Marta Penas-Prado[4], Carlos Kamiya-Matsuoka[1], Shiao-Pei Weathers[1], Alfred Yung[1], Monica Loghin[1], Rebecca Harrison[4], Nazanin Majd[1], Stephanie Knight[1], Jeffrey Bacha[3], Dennis Brown[2], Gregory Johnson[2], John Langlands[2], Richard Schwartz[2], Sarath Kanekal[2], Anne Steino[2], Lorena Lopez[2], John de Groot[4]

[1]Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Kintara Therapeutics, Inc., San Diego and Menlo Park, California, USA; [3]Formerly affiliated with DelMar Pharmaceuticals, Inc; [4]Formerly affiliated with The University of Texas MD Anderson Cancer Center, Houston, TX, USA

BACKGROUND

VAL-083 is a novel bi-functional DNA targeting agent that rapidly induces interstrand cross-links at N^7-guanine, leading to DNA double-strand breaks (DSBs) and ultimately cell death.[1] VAL-083's unique cytotoxic mechanism circumvents MGMT-mediated chemoresistance and maintains cytotoxic activity in cancer cells deficient in DNA mismatch repair (MMR).[2,3] The N^7-targeting mechanism differs from temozolomide (TMZ) and nitrosoureas, enabling VAL-083 to overcome MGMT-mediated chemoresistance.

FIGURE 1. *The N^7-targeting mechanism of action of VAL-083*



2 guanine bases on DNA *VAL-083* *VAL-083 – interstrand crosslink (ICL)*

This distinct mechanism of action of VAL-083 suggests that VAL-083 may offer a treatment alternative against tumors with MMR-, or MGMT-mediated resistance to chemotherapeutic agents, including temozolomide and nitrosoureas.[1,2,3]

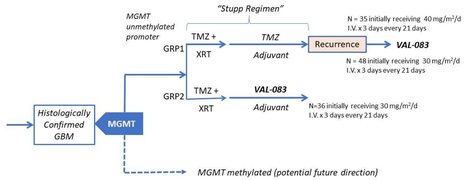
Study Design: An open label, single-arm, biomarker-driven, Phase 2 study of VAL-083 treatment for MGMT unmethylated bevacizumab-naïve glioblastoma in the recurrent or adjuvant setting

Group 1:

- To determine if treatment with VAL-083 improves overall survival (OS) in patients with *MGMT*-unmethylated recurrent GBM.
- Comparison of survival will be made to historical control for lomustine of median OS = 7.2 months (EORTC 26101, for patients with recurrent *MGMT*-unmethylated GBM treated with lomustine alone)[5].
- Up to 83 evaluable patients with recurrent/progressive GBM will be enrolled. This will include 35 patients initially treated at 40 mg/m^2/d and up to 48 patients initially treated at 30 mg/m^2/d.

Group 2:

- To determine if treatment with VAL-083 in *MGMT*-unmethylated GBM improves progression-free survival (PFS) in newly diagnosed patients when given as adjuvant therapy post chemoradiation with TMZ.
- Median PFS will be compared to historical control, temozolomide (6.9 months) (Tanguturi, et al. 2017)[6].
- Up to 36 newly diagnosed GBM patients who have completed chemoradiation treatment with TMZ and received no subsequent adjuvant TMZ will be enrolled.



(Clinicaltrials.gov Identifier: NCT02717962).

REFERENCES

1: Zhai B, et al. Cell Death and Disease. (2018)9:1016; 2: Zhai B, et al. Cancer Res. July 2017: 77(13), abstract #248; 3: Fouse S, et al. Neuro Oncol. (2014). v16(Supll 5), ET-18; 4: Stupp et al. N Engl J Med 2005; 352(10):997-1003; 5: Wick, W et al (2017) N.Eng.J.Med. 377:1954-1963, 6: Tanguturi SK, et al. NeuroOncol;19(7):908-917 (2017); 7: NCCN guidelines (CNS cancers, 2017).

GROUP 1 (RECURRENT GBM)

Status as of 25 October 2021

- 35 subjects (35 efficacy evaluable) enrolled with starting dose of 40 mg/m^2/day x 3 days every 21 days – enrollment completed.
- 54 subjects (48 efficacy evaluable of 48 planned), enrolled with starting dose of 30 mg/m^2/day x 3 days every 21 days – enrollment completed.
- All subjects have completed treatment.

Safety

- The main treatment related adverse events (Grade 3 and higher) have been decreased platelet counts, lymphocyte count, neutrophil count and headache.
- Fewer subjects experienced a Dose Limiting Toxicity (DLT) at cycle 1 at 30 mg/m^2/d than at 40 mg/m^2/d (Table 1).
- SAEs possibly related to VAL-083 starting dose were as follows:
  - 5/35 (14.3%) subjects experienced an SAE possibly related to VAL-083 at a starting dose of 40 mg/m^2/day;
  - 5/54 (9.3%) subjects experienced an SAE possibly related to VAL-083 at a starting dose of 30 mg/m^2/day.
- The average number of cycles completed by patients at a starting dose of 40 mg/m^2 was 2.8 (10 subjects with ≥3 cycles), and at a starting dose of 30 mg/m^2 was 3.5 (22 subjects with ≥ 3 cycles).

Table 1. Dose-Limiting Toxicities (DLT) during Cycle 1 in Group 1 (Recurrent). All subjects completed at least 1 cycle.

Number and Percent of Subjects with DLT, as defined below	40 mg/m^2/d (n=35)	30 mg/m^2/d (n=54)	All (n=89)
Number of subjects with DLT*	8 (22.9%)	3 (5.5%)	11 (12.4%)
DLT due to Hematological toxicity	8 (22.9%)	2 (3.7%)	10 (11.2%)
DLT due to Non-hematological Grade 3/4 toxicity	1 (2.8%)	1 (1.9%)	2 (2.3%)
Dose reduction (Cycle 2)	9 (25.7%)[#]	5 (9.3%)[##]	14 (15.7%)

*Subjects may have experienced more than one DLT (listed above); Dose Limiting Toxicity (DLT) due to hematological toxicity included Gr 3 platelet count with hemorrhage, Gr 4 platelet count; Gr 3 ANC with fever, Gr 3 platelet count for >5 days; Treatment delay >3 weeks due to decreased platelet or absolute neutrophil count. [#] Dose reduction from 40 to 30 mg/m^2/day I.V. x 3 days every 21 days; [##] Dose reduction from 30 to 20 mg/m^2/day I.V. x 3 days every 21 days.

Overall Survival (OS)

Table 2. Median Overall Survival (mOS) in Group 1 (Recurrent) censored at last known no disease progression or last known alive. Kaplan-Meier Analysis (MedCalc.v. 20.014)

	Reference Data[5]	Starting Dose of VAL-083		
		Overall (N=83)	30 mg/m^2/d (N=48)	40 mg/m^2/d (N=35)
Number of deaths (%)		72 (86.8%)	40 (83.3%)	32 (91.4%)
Median OS (months) (95%CI)	7.2 (4.8 - 8.6)	7.6 (6.1 - 9.2)	8.0 (6.6 - 10.3)	6.5 (4.4 - 9.0)

GROUP 2 (ADJUVANT SETTING)

Status as of 25 October 2021

- 39 subjects (36 efficacy evaluable of 36 planned), enrolled with starting dose of 30 mg/m^2/day x 3 days every 21 days – enrollment completed.
- All subjects have completed treatment.

Safety

- Three (3/36; 8.3%) subject experienced a Dose Limiting Toxicity (DLT) during cycle 1.
- Six (6/36; 16.6%) subjects had a dose reduction from 30 to 20 mg/m^2/day at the start of cycle 2.
- One (1/36; 2.8%) subject experienced SAE possibly related to VAL-083.
- The average number of treatment cycles received by patients was 6.7 (range 1-13); n=36 evaluable subjects.

Progression Free Survival (PFS) and Overall Survival (OS)

- Thirty-four (34/36; 94.4%) of the evaluable subjects had exhibited disease progression. No subjects are on treatment.
- Median PFS from diagnosis censored at last date no disease progression – 9.5 months (95%CI: 8.2-10.8) (Kaplan-Meier, MedCalc. v.20.014).
- As off the cut-off, twenty-one (21/36; 58.3%) evaluable subjects enrolled in the study had died.
- Median OS from diagnosis censored at date alive - 16.5 months (95%CI: 13.6-19.3) (Kaplan-Meier, MedCalc. v.20.014).

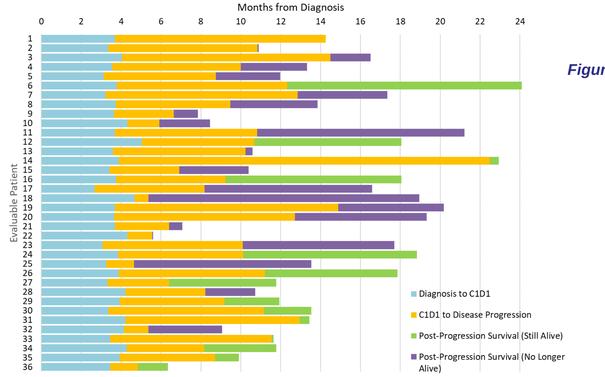


Figure 2. *Snapshot status of evaluable subjects (Group 2 Adjuvant Setting) (data cut-off 25 October, 2021).*

CONCLUSION AND FUTURE DIRECTIONS

- Consistent with prior studies, myelosuppression is the most common adverse event with VAL-083 in patients with GBM in both the recurrent and adjuvant settings.
- VAL-083 at the 30 mg/m^2/day offers a potentially less toxic treatment than 40 mg/m^2/d, and potentially greater benefit in patients with recurrent disease compared to historical control[5].
- To date, VAL-083 is well-tolerated as an alternative adjuvant treatment in unmethylated GBM to TMZ (which is of limited value in this setting[7]) and may provide an opportunity for early intervention and potential benefit for these patients compared to historical control[6].
- VAL-083 is being evaluated further in GCAR's Glioblastoma Adaptive Global Innovative Learning Environment (GBM AGILE) Study. This trial is an adaptive clinical trial platform in GBM: Newly diagnosed patients post-chemoradiation (radiation + TMZ); and patients with recurrent GBM. Patients with both methylated- and unmethylated–MGMT promoter will be enrolled.