with isocitrate dehydrogenase (IDH) wildtype World Health Organization (WHO) grade III / IV glioma at first relapse. Twenty patients were enrolled from 2019-2020 and treated with intravenous infusions of L19TNF. In the phase I part of the study, 6 patients were assigned to two different dose levels of L19TNF and a dose of 13 µg/kg was established as the recommended dose. In the phase II part 14 patients were treated at the recommended dose. No dose-limiting toxicities were observed and survival follow-up is ongoing. In almost all patients, we observed treatment-associated emerging tumor necrosis. For patients that had re-surgery at progression on or after treatment with L19TNF, we demonstrated increased numbers of tumor-infiltrating lymphocytes compared to the tumor tissue obtained at primary diagnosis. Translational studies to better understand the effects of L19TNF on a molecular and immunophenotypic level are ongoing. ClinicalTrials.gov Identifier: NCT 03779230

SYST-04. TRAM-01: A PHASE 2 STUDY OF TRAMETINIB FOR PATIENTS WITH PEDIATRIC GLIOMA WITH ACTIVATION OF THE MAPK/ERK PATHWAY.

SébastienPerreault[1], Valérie Larouche[2], Uri Tabori[3], Cynthia Hawkins[3], Sarah Lippé[1], Benjamin Ellezam[1], Jean-Claude Decarie[1], Luis H. Ospina[1], Yves Theoret[1], Leandra Desjardins[1], Marie-Élaine Metras[1], Serge Sultan[1], Edith Cantin[2], Marie-Eve Routhier[2], Maxime Caru[4], Stephanie Vairy[5], Genevieve Legault[6], Eric Bouffet[3], Lucie Lafay-Cousin[7], Juliette Hukin[8], Craig Erker[9], Nada Jabado[6]; [1]CHU Sainte-Justine, Montreal, Canada. [2]CHUL, Quebec, Canada. [3]The Hospital for Sick Children, Toronto, Canada. [4]CHOP, Philadelphia, USA. [5]CHUS, Sherbrooke, Canada. [6]CUSM, Montreal, Canada. [7]Alberta Children's Hospital, Calgary, Canada. [8]Children's BC Hospital, Vancouver, Canada. [9]IWK, Halifax, Canada

BACKGROUND: Pediatric low-grade gliomas (PLGG) are the most frequent brain tumors in children. It is known that the majority of PLGG have activation of the MAPK/ERK pathway. METHODS: This ongoing multicenter phase II trial includes three progressing/refractory PLGG groups: NF1 patients, KIAA1549-BRAF fusion patients and patients with other activation of the MAPK/ERK pathway (excluding V600E). The primary objective was to evaluate the overall response rate based on RANO criteria after daily oral trametinib administration for 18 cycles, lasting 28 days each. Secondary objectives include the assessment of progression-free survival, tolerability of trametinib, serum levels of trametinib and quality of life evaluation during treatment. RESULTS: As of February 12 2021, 50 patients have been enrolled (NF1: n=10; KIAA1549-BRAF fusion: n=31; other: n=9 including 5 patients with FGFR1 alterations). Median age is 8.8 years (range 2.4-25.5). Median follow-up is 17.5 months (range 4.7-28.5). Forty-three patients are evaluable. The overall response includes: 4 partial response (PR) (9%), 18 minor response (MR) (42%), 17 stable disease (40%), 4 progressive disease (9%). Median time to response is 5.5 months (range 2.4-13.8). Median duration of response is 6.1 months (range 0.6-26.5). Progression free survival at 12 months is 79.9% (95% CI 68.5-93.6%) and median progression free survival has not yet been reached. Treatment was discontinued for 30 patients: 16 after completing 18 cycles as planned, 5 for progressive disease, 5 for adverse events, 4 for other reasons. A total of 8 patients progressed after discontinuation of treatment including 6 patients (37.5%) that completed 18 cycles. Five of these patients had achieved minor response prior to discontinuation. CONCLUSION: Trametinib is a potentially effective targeted therapy for patients with recurrent/refractory PLGG. Treatment was overall well tolerated. This ongoing trial will continue to gather data on response rate, duration of response and safety of trametinib for PLGG.

SYST-05. PHASE 2 STUDY OF VAL-083 AND RADIOTHERAPY IN NEWLY DIAGNOSED MGMT-UNMETHYLATED GBM

Zhong-ping Chen[1], Cheng-cheng Guo[1], Qun-ying Yang[1], Jia-wei Li[1], Shao-xiong Wu[1], Jeffrey Bacha[2], Greg Johnson[3], JohnLanglands[3], Claire Kwan[3], Sarath Kanekal[3], Richard Schwartz[3], Dennis Brown[3]; [1]Sun Yat-Sen University Cancer Centre, Guangzhou, China. [2]Delmar Pharmaceuticals Inc., Menlo Park, CA, USA. [3]Kintara Therapeutics Inc., Menlo Park, CA, USA

VAL-083 is a novel bi-functional DNA targeting agent that induces interstrand DNA cross-links at N^7-guanine, leading to DNA double-strand breaks and cell death. In vitro and in vivo studies have demonstrated VAL-083 circumvents MGMT-mediated chemo-resistance and differentiates it from other therapies used in the treatment of GBM, including temozolomide (TMZ). VAL-083 also acts as a radiosensitizer against GBM cancer stem cells in vitro. A Phase 2 study was conducted to evaluate the safety and tolerability of VAL-083 when administered concurrently with radiation therapy (RT) in newly diagnosed MGMT unmethylated GBM. Stage 1 was a dose-escalation phase to confirm the dose of VAL-083 in this setting. Patients received VAL-083 at 20, 30, or 40 mg/m^2/day x 3 days every 21 days in combination with standard radiation treatment (RT) (2 Gy/day, 5 days/week for 6 weeks). Stage 2 was an expansion phase to enroll up to 20 additional patients at the 30 mg/m^2/day of VAL-083 with RT. A total of 29 patients were enrolled in the study and completed treatment, with 25 patients receiving 30 mg/m^2/day VAL-083. The median number of cycles completed by all patients was 9 (range 2-13). Consistent with our prior experience, myelosuppression was the most common adverse event. Pharmacokinetics (Cmax and AUC) of VAL-083 were broadly linear with respect to dose, and drug half-life was 0.8 hrs. In a sub-group of patients, levels of VAL-083 in CSF were found to be at least as high as those in plasma. The median progression free survival (PFS) for all patients enrolled was 9.3 (95%CI: 6.4-12.0) months. Eighteen (18/29; 62.1%) patients have died, and median overall survival for all patients enrolled was 19.6 (95%CI: 14.0-22.4) months. These results support the potential benefit of VAL-083 as a treatment alternative against GBM tumors with MGMT-mediated resistance to TMZ. Clinicaltrials.gov: NCT03050736.

SYST-06. PHASE II TRIAL OF PAXALISIB (GDC-0084) IN COMBINATION WITH TRASTUZUMAB FOR PATIENTS WITH HER2-POSITIVE BREAST CANCER BRAIN METASTASES (BCBM)

Jose PabloLeone[1], Nabihah Tayob[1], Alyssa Pereslete[1], Jennifer Ligibel[1], Heather Parsons[1], Wenya Bi[2], Jean Zhao[1], Eric Winer[1], Nancy Lin[1]; [1]Dana-Farber Cancer Institute, Boston, MA, USA. [2]Brigham and Women's Hospital, Boston, MA, USA

BACKGROUND: The PI3K/Akt/mTOR is an important pathway in BCBM. Mutations in PIK3CA or PTEN loss are associated with trastuzumab resistance. Inhibition of PI3K and mTOR led to durable responses in 3 of 5 patient-derived xenografts (PDX) models of BCBM. Paxalisib is a potent, brain-penetrant inhibitor of class I PI3K and mTOR. METHODS: This is a single-center, phase II study to evaluate the efficacy of the combination of paxalisib with trastuzumab for the treatment of central nervous system (CNS) metastases in patients with HER2-positive breast cancer. Patients will receive paxalisib (45 mg daily) and trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks). Two cohorts will be enrolled: Cohort A: a single-arm, two-stage, phase II cohort; and Cohort B: a pre-surgical window cohort. Inclusion criteria include unequivocal evidence of new and/or progressive HER2-positive CNS metastases, at least one measurable (≥10 mm) CNS metastasis (Cohort A), clinical indication for CNS metastasis resection (Cohort B). Primary endpoint for Cohort A is objective response rate (ORR) in the CNS per Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria. For Cohort B, the primary endpoint is the correlation between p4EBP1 levels in the resected CNS tumor tissue from patients and intracranial response to paxalisib/trastuzumab in the PDX model generated from the same patient. Secondary endpoints include overall survival, safety and patient-reported outcomes. Mandatory blood and cerebrospinal fluid with optional tumor biopsy will be collected at baseline, on-treatment and at progression. In Cohort A, we will enroll 37 patients in a Simon two-stage design. If ≥4 responses are seen, the regimen will be considered successful. This design has 90% power with alpha <10%. Cohort B will enroll 10 patients. The trial opened in February, 2019 and 8 patients have been enrolled. NCT03765983.

SYST-07. PILOT STUDY UTILIZING THE HDAC INHIBITOR BELINOSTAT WITH CHEMORADIATION FOR NEWLY-DIAGNOSED GLIOBLASTOMA

Hui-KuoShu[1], Karen Xu[1], Karthik Ramesh[1], Vicki Huang[1], Saumya Gurbani[1], Eduard Schreibmann[1], Brent Weinberg[1], Soma Sengupta[2], Alfredo Voloschin[1], Matthias Holdhoff[3], Peter Barker[3], Lawrence Kleinberg[3], Jeffrey Olson[1], Hyunsuk Shim[1]; [1]Emory University, Atlanta, GA, USA. [2]University of Cincinnati, Cincinnati, OH, USA. [3]Johns Hopkins University, Baltimore, MD, USA

PURPOSE: Glioblastomas (GBMs) are highly aggressive brain tumors with poor prognosis. Belinostat is a histone deacetylase inhibitor with blood–brain barrier permeability, anti-GBM activity, and potential to enhance chemoradiation. This clinical trial sought to determine a tolerable dose of concurrent belinostat and assess the clinical efficacy of combining this drug with standard-of-care therapy. METHODS: 13 patients each were enrolled in control and belinostat cohorts. The belinostat cohort was given a belinostat regimen (500-750mg/m^2 1x/day x 5 days) every 3 weeks (weeks 0, 3, and 6 of RT). All patients received standard temozolomide and radiation therapy (RT). Patient outcomes included progression-free survival, overall survival (OS), and analysis of recurrence pattern of the recurrent gross tumor volume (rGTV). RESULTS: Belinostat at 750 mg/m^2 produce dose-limiting toxicities (DLTs) in 2 of 3 patients while belinostat at 500 mg/m^2 did not result in DLTs. Median OS was 18.5 months for the belinostat cohort and 15.8 months for the control cohort (p=0.53). The rGTVs in the control