and a phase 2/ 3 clinical study tested Toca511 in combination with TocaFC in patients undergoing planned resection for recurrent glioblastoma (rGBM) or anaplastic astrocytoma (rAA). The last trial was completed in 2019, and although the Phase 2/3 study did not meet the primary objective, patients who appeared to benefit from the treatment elected to continue TocaFC through an expanded access or compassionate use pathway. Seven patients continued on treatment: 3 men and 4 women; 5 with rGBM, 2 with rAA. Duration of treatment with TocaFC ranges from 29 months to 7 years and 5 months (average 49.2 months). Six patients who are still on active treatment with TocaFC have either stable disease or complete response. TocaFC is well tolerated in these patients, typical side effects include diarrhea. Some patients with rGBM or rAA appear to benefit from extended TocaFC treatment after Toca511. Individual cases will be discussed.

CTNI-04. RECURRENT GLIOBLASTOMA LONG-TERM SURVIVORS TREATED WITH CUSP9V3

Marc-Eric Halatsch[1], Richard Kast[2], Georg Karpel-Massler[3], Benjamin Mayer[4], Oliver Zolk[5], Bernd Schmitz[6], Angelika Scheuerle[7], Ludwig Maier[8], Lars Bullinger[9], Regine Mayer-Steinacker[9], Carl Schmidt[10], Katharina Zeiler[9], Ziad Elshaer[10], Patricia Panther[10], Birgit Schmelzle[11], Anke Hallmen[9], Annika Dwucet[10], Markus D. Siegelin[12], Mike-Andrew Westhoff[13], Kristine Beckers[14], Gauthier Bouche[14], and Tim Heiland[10]; [1]Department of Neurosurgery, Cantonal Hospital of Winterthur, Winterthur, Switzerland, [2]IIAIGC Study Center, Burlington, VT, USA, [3]Ulm University, Ulm, USA, [4]Institute for Epidemiology and Medical Biometry, Ulm University, Ulm, Germany, [5]Department of Clinical Pharmacology, Ulm University Hospital, Ulm, Germany, [6]Division of Neuroradiology, Department of Diagnostic and Interventional Radiology, Ulm University Hospital, Ulm, Germany, [7]Division of Neuropathology, Department of Pathology, Ulm University Hospital, Ulm, Germany, [8]Central Pharmacy, Ulm University Hospital, Ulm, Germany, [9]Division of Hematology and Oncology, Department of Internal Medicine, Ulm University Hospital, Ulm, Germany, [10]Department of Neurosurgery, Ulm University Hospital, Ulm, Germany, [11]Institute of Experimental Cancer Research, Ulm University Hospital, Ulm, Germany, [12]Columbia University, New York, NY, USA, [13]Ulm University Medical Center, Ulm, Germany, [14]Anticancer Fund, Bruxelles, Belgium

CUSP9v3 is a new treatment regimen for glioblastoma. It consists of continuous daily use of 9 drugs repurposed from general medicine. Their primary non-oncology uses are given in parentheses: aprepitant (nausea), auranofin (rheumatoid arthritis), celecoxib (pain), captopril (hypertension), disulfiram (alcohol abuse), itraconazole (fungal infection), minocycline (bacterial infection), ritonavir (viral infection) and sertraline (depression). All drugs have preclinical or clinical data indicating that they can retard glioblastoma growth, as reviewed in the published background papers. In CUSP9v3 all 9 medicines are given daily with added metronomic, low-dose (20 mg/m^2 BSA twice daily) temozolomide. After 3 years of daily, uninterrupted use of CUSP9v3, of an initial cohort of 10 recurrent glioblastoma patients, as of May 2021, 3 are alive, functioning well, progression-free at 44, 44, and 57 months after recurrence and CUSP9v3 started. We report now that there were no unexpected toxicities from this combination of 10 daily drugs, although all patients required dose reduction of one or more of the drugs. CUSP9v3 was reasonably well-tolerated. Ritonavir, temozolomide, captopril and itraconazole were the drugs most frequently requiring dose reduction or pausing. The most common adverse events were nausea, headache, fatigue, diarrhea and ataxia. There were no treatment-related deaths. In the 3 long-term survivors, the median neutrophil-to-lymphocyte ratio decreased from 2.5 to 1.5 during CUSP9v3 treatment. In the group of the 3 shortest-term survivors that ratio increased from 4.7 to 14.3. CUSP9v3 follows the injunction of Palmer et al. that cancer therapy can be constructed using drug combinations that are independently effective, with non-overlapping mechanisms of action, and non-overlapping resistance pathways. We interpret the data accrued over the last few decades on the ever-shifting spatial and temporal growth drives active at any given moment in glioblastoma as requiring a complex pharmacological approach like CUSP9v3.

CTNI-05. PRELIMINARY RESULTS OF THE NERATINIB ARM IN THE INDIVIDUALIZED SCREENING TRIAL OF INNOVATIVE GLIOBLASTOMA THERAPY (INSIGHT): A PHASE II PLATFORM TRIAL USING BAYESIAN ADAPTIVE RANDOMIZATION

Isabel Arrillaga-Romany[1], Lorenzo Trippa[2], Geffrey Fell[2], Eudocia Quant Lee[2], Rifaquat Rahman[3], Mehdi Touat[2], Christine McCluskey[2], Jennifer Bruno[2], Sarah Gaffey[4], Jan Drappatz[5], Andrew Lassman[6], Evanthia Galanis[7], Manmeet Ahluwalia[8], Howard Colman[9], L. Burt Nabors[10], Jaroslaw Hepel[11], Heinrich Elinzano[11], Thomas Kaley[12], Ingo K. Mellinghoff[13], David Schiff[14], Ugonma Chukwueke[2], Rameen Beroukhim[2], Lakshmi Nayak[2], J. Ricardo McFaline-Figueroa[2], Tracy Batchelor[15], Christine Lu-Emerson[16], Wenya Linda Bi[4], Omar Arnaout[4], Pierpaolo Peruzzi[17], Daphne Haas-Kogan[4], Shyam Tanguturi[4], Daniel Cagney[4], Ayal Aizer[4], Mary Welch[18], Lisa Doherty[2], Maria Lavallee[2], Brittany Fisher-Longden[2], Shanna Dowling[2], Jack Geduldig[19], Fiona Watkinson[2], Sandro Santagata[21], David Meredith[2], E. Antonio Chiocca[22], David Reardon[2], Keith Ligon[3], Brian Alexander[4], and Patrick Wen[23]; [1]Massachusetts General Hospital, Boston, MA, USA, [2]Dana-Farber Cancer Institute, Boston, USA, [3]Dana-Farber/Brigham and Women's Cancer Center, Boston, MA, USA, [4]Foundation Medicine, Boston, USA, [5]University of Pittsburgh School of Medicine, Pittsburgh, PA, USA, [6]Columbia University Irving Medical Center, New York Presbyterian Hospital, New York, NY, USA, [7]Mayo Clinic, Rochester, MN, USA, [8]Miami Cancer Institute, Miami, FL, USA, [9]University of Utah - Huntsman Cancer Institute, Salt Lake City, UT, USA, [10]University of Alabama at Birmingham, Birmingham, AL, USA, [11]Lifespan / Rhode Island Hospital, Providence, RI, USA, [12]Memorial Sloan Kettering Cancer Center, New York, NY, USA, [13]Memorial Sloan Kettering, New York, NY, USA, [14]UVA Health, Charlottesville, VA, USA, [15]Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA, [16]MaineHealth, Scarborough, USA, [17]The Harvey Cushing Neuro-Oncology Laboratories, Boston, MA, USA, [18]Columbia / New York Presbyterian, New York, NY, USA, [21]Brigham and Women's Hospital, Boston, MA, USA, [22]Harvey Cushing Neuro-oncology Laboratories, Department of Neurosurgery, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA, [23]Center For Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

BACKGROUND: EGFR is amplified in over 50% of glioblastoma and 20-30% have EGFRvIII mutations. Neratinib is a potent inhibitor of EGFR/HER2 approved for metastatic HER2+ breast cancer. To efficiently evaluate the potential impact of neratinib on overall survival (OS) in newly-diagnosed glioblastoma and to simultaneously develop information regarding potential genomic biomarker associations, neratinib was included as an arm on the Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT) trial. INSIGhT is a phase II platform trial using response adaptive randomization and deep genomic profiling to more efficiently test experimental agents in MGMT unmethylated glioblastoma and accelerate identification of novel therapies for phase III testing. Initial randomization was equal between neratinib, control, and two other experimental arms but subsequent randomization was adapted based on efficacy as determined by progression-free survival (PFS). We report preliminary results for the neratinib arm. METHODS: Patients with newly diagnosed MGMT-unmethylated glioblastoma were randomized to receive either radiotherapy with concomitant and adjuvant temozolomide or standard radiochemotherapy followed by adjuvant neratinib (240 mg daily). Treatment continued until progression or development of unacceptable toxicities. The primary endpoint was OS. Association between neratinib efficacy and EGFR amplification was also investigated. RESULTS: There were 144 patients (70 control; 74 neratinib). Neratinib was reasonably well-tolerated with no new toxicity signals identified. PFS was compared (HR 0.84; p=0.38, logrank test – not significant) between the neratinib (median 6.05 months) and control (median 5.82 months) arms. For patients EGFR pathway activation the PFS HR was 0.53 (p-value=0.03 – significant, median PFS: neratinib, 6.21 months, control, 5.26 months). However, there was no significant improvement in OS in EGFR amplified/mutated patients (HR 1.05; p-value 0.87) between neratinib (median 14.2) compared to the control arm (median 14.6). CONCLUSION: Neratinib prolonged PFS in the EGFR positive subpopulation but there was no overall PFS benefit, or any OS improvement.

CTNI-06. TRAM-01: A PHASE 2 STUDY OF TRAMETINIB FOR PATIENTS WITH PEDIATRIC GLIOMA WITH ACTIVATION OF THE MAPK/ERK PATHWAY

Sébastien Perreault[1], Valérie Larouche[2], uri tabori[3], Cynthia Hawkins[4], sarah Lippe[5], Benjamin Ellezam[5], Jean-Claude decarie[5], Luis H Ospina[5], yves theoret[5], Leandra Desjardins[5], Marie-Elaine Metras[2], serge Sultan[5], Edith Cantin[2], Marie-Eve Routhier[2], Maxime Caru[5], Stephanie Vairy[6], Geneviève Legault[7], Eric Bouffet[8], Lucie Lafay-Cousin[9], Juliette Hukin[10], Craig Erker[11], and Nada Jabado[12]; [1]Department of Neurosciences, CHU Sainte Justine, Montreal, Canada, [2]CHU de Québec, Quebec, QC, Canada, [3]SickKids, Toronto, ON, USA, [4]The Hospital for Sick Children, Toronto, Ontario, ON, Canada, [5]CHU Sainte-Justine, Montreal, Quebec, QC, Canada, [6]CHU de Sherbrooke, Sherbrooke, QC, Canada, [7]McGill, Montreal, QC, Canada, [8]The Hospital for Sick Children, Toronto, ON, Canada, [9]Alberta Children's Hospital, Calgary, AB, Canada, [10]BC Children's Hospital, Vancouver, BC, USA, [11]IWK Health Center, Halifax, NS, Canada, [12]Department of Human Genetics, McGill University, Montreal, QC, 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