

initial diagnosis of recurrence, exposing an unmet need to find novel therapies to treat recurrent disease. Bromodomain and extraterminal (BET) proteins are chromatin readers that affect transcription of genes. The oral BET inhibitor (BETi) OTX-015 has shown promise in a dose-escalation, phase I study in patients with acute leukemia and other BET inhibitors are currently in phase I studies for the treatment of primary brain tumors. We have recently shown that BET inhibition increases DNA damage and mitotic catastrophe in oncogenic cells by increasing transcription-replication conflicts and downregulating expression of key DNA damage checkpoint proteins, and have also shown its efficacy in decreasing tumor burden and improving survival when combined with TMZ in intracranial mouse models of glioma. We have also demonstrated that BETi's synergize with Olaparib by downregulating expression of the BRCA-driven DNA damage repair pathway and further leverages additive effects when triply combined with other DNA damaging agents such as Lomustine to decrease tumor burden and improve survival in patient-derived mouse models of GBM and medulloblastoma. We therefore hypothesize that the synergistic and additive effects of this triple combination seen in our preclinical studies will achieve therapeutic benefits in patients with recurrent GBM.

CLRM-05. DRUG-RELEASING MICRODEVICES TO PREDICT RESPONSES TO TARGETED THERAPIES IN PATIENTS WITH GLIOMAS

SarahBlitz¹, Christine Dominas², Michael J Pannell², E Antonio Chiocca^{2,1}, Patrick Y Wen^{3,1}, Oliver Jonas^{2,1}, Pierpaolo Peruzzi^{2,1}; ¹Harvard Medical School, Boston, MA, USA. ²Brigham and Women's Hospital, Boston, MA, USA. ³Dana-Farber Cancer Institute, Boston, MA, USA

Genomic studies of tumor specimens are becoming standard of care in patients with gliomas to characterize druggable molecular features. Unfortunately, with the exception of IDH1-R132 mutation and MGMT promoter methylation, molecular markers have failed to predict clinical responses to drugs, and the impact of targeted therapies remains minimal. There is a need for a high-throughput, patient-specific, and significantly predictive method to inform a most effective personalized therapy. This pilot trial tests the safety and feasibility of drug-releasing microdevices which are temporarily implanted into the tumor during a standard craniotomy. They release microdoses of up to 20 drugs or drug combinations into surrounding tissue in a controlled spatial distribution. The devices, together with a cuff of surrounding tumor tissue, are removed at the end of surgery, and the tissue is analyzed for biological and molecular response markers allowing for in situ characterization of the drug efficacy. Four patients have been enrolled to date, out of a total planned of six. Two microdevices were implanted into each tumor (8 total devices). Average indwelling time in tumor tissue was 139 minutes. Eight devices (100%) were successfully retrieved, and all surgeries were completed without immediate (<24 hours) or delayed (<30 days) complications. Seven (87%) specimens were of adequate quality, allowing for planned histological and molecular studies. For all analyzed specimens, the intraoperative incubation time was sufficient to observe: 1) Drug concentration gradients; 2) Differential molecular signs of cell toxicity (DNA damage and Caspase 3 activation); 3) Whole genome transcriptional changes; 4) Tumor microenvironment composition; and 5) Preliminary evidence of concordance between the biological readout obtained from microdevice analysis and clinical response. Drug-releasing microdevices were well tolerated, seamlessly integrated in standard craniotomy workflow, and allowed for collection of a significant amount of data related to the differential efficacy of multiple drugs in a personalized manner.

CLRM-06. COMPARISON OF INDIVIDUALIZED ANTI-CANCER THERAPY REGIMENS RECOMMENDED BY A MULTIDISCIPLINARY MOLECULARLY-DRIVEN TUMOR BOARD IN A PEDIATRIC DIPG CLINICAL TRIAL (PNOC003) VERSUS THOSE SELECTED BY THE CNS-TAP TOOL

HollyRoberts¹, Karthik Ravi¹, Allison Schepers², Bernard Marini², Cassie Kline³, Sabine Mueller⁴, Carl Koschmann¹, Andrea Franson¹; ¹University of Michigan Medical School, Ann Arbor, MI, USA. ²University of Michigan Department of Clinical Pharmacy and Pharmacy Services, Ann Arbor, MI, USA. ³Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. ⁴University of California San Francisco School of Medicine, San Francisco, CA, USA

Genetic sequencing of diffuse intrinsic pontine gliomas (DIPG) has revealed genomic heterogeneity, fueling an interest in individualized targeted therapies. A feasibility study, PNOC003: Molecular Profiling for Individualized Treatment Plan for DIPG (NCT02274987), was completed within the Pacific Pediatric Neuro-Oncology Consortium in which a multidisciplinary tumor board reviewed molecular and genomic profiling of each participant's tumor to make targeted therapy recommendations. Separately, our team de-

veloped the Central Nervous System Targeted Agent Prediction (CNS-TAP) tool, which combines pre-clinical, clinical, and CNS penetration data with patient-specific genomic information to derive numeric scores for anticancer agents to objectively evaluate these therapies for use in patients with CNS tumors. We hypothesized that agents highly-scored by CNS-TAP would overlap with agents recommended by the PNOC003 tumor board. For each study participant, we retrospectively utilized the genomic profiling report to identify actionable alterations and incorporated these data into CNS-TAP to find the highest-scoring agents. We compared these CNS-TAP-recommended agents with recommendations from the tumor board for each of the 28 PNOC003 participants. Overall, 93% of patients (26/28) had at least one agent recommended by both the tumor board and CNS-TAP. Additionally, 38% of all agents (36/95) chosen by the tumor board were also selected by CNS-TAP. When only molecularly targeted anticancer agents were included in a sub-analysis, 60% of agents (34/57) were recommended by both methods. At present, we are prospectively evaluating the CNS-TAP tool within PNOC008: A Pilot Trial Testing the Clinical Benefit of Using Molecular Profiling to Determine an Individualized Treatment Plan in Children and Young Adults with High-Grade Glioma (NCT03739372). The CNS-TAP tool recommendations are shared during the PNOC008 molecular tumor board meetings once a consensus treatment recommendation has been reached. Subsequent analyses will focus on any adjustments in therapy decisions within the tumor board that result from the CNS-TAP tool output.

CLRM-07. INCREASING EFFICIENCY IN EARLY PHASE MULTICENTER IMAGING BIOMARKER TRIALS: EMERGING STRATEGIES FROM THE GABLE (GLIOBLASTOMA ACCELERATED BIOMARKER LEARNING ENVIRONMENT) TRIAL

DanielBarboriak¹, Jon Steingrimsson², Constantine Gatsonis², David Schiff³, Lawrence Kleinberg⁴; ¹Duke University Medical Center, Department of Radiology, Durham, NC, USA. ²Brown University, Department of Biostatistics, Providence, RI, USA. ³University of Virginia Neuro-Oncology Center, Charlottesville, VA, USA. ⁴Johns Hopkins University and The Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA

Validated biomarkers that more accurately predict prognosis and/or measure disease burden in patients with high-grade gliomas would help triage which treatment strategies are most promising for evaluation in Phase III multicenter trials. Multicenter trials to evaluate imaging biomarkers in this group face particular challenges; these trials have historically been slow to accrue and have not recently succeeded in validating new imaging biomarkers useful in treatment development. Due to variability in image acquisition protocols, scanner hardware, image analysis, and interpretive schemes, promising results obtained in single centers are poor predictors of success in the multicenter setting. Multicenter preliminary data to support further evaluation of imaging biomarkers is rarely available. The need for more efficient trial designs that bring multicenter data earlier into the process of biomarker development has become increasingly clear. In this presentation, the planning process within ECOG-ACRIN's Brain Tumor Working Group for a platform multicenter trial called GABLE (Glioblastoma Accelerated Biomarker Learning Environment trial) designed to evaluate biomarkers for distinguishing pseudoprogression from true progression in patients with newly diagnosed GBM is described. In our planning process, it was determined that efficiencies can be gained from evaluating multiple biomarker types in parallel rather than serially; in the context of the proposed trial, not only conventional imaging biomarkers but plasma biomarkers and radiomic biomarkers can be evaluated simultaneously. Patient tolerance limits the feasibility of evaluating multiple non-standard-of-care imaging biomarkers in parallel. For this group of biomarkers, a "fast-switching" serial evaluation strategy using multiple interim analyses was developed to triage out biomarkers unlikely to succeed in identifying patient groups with clinically significant differences in median survival. For biomarker triage, an endpoint of event-free survival (events of either death or NANO progression) was proposed. Simulations were used to evaluate alpha and beta error using this evaluation strategy.

CLRM-08. TRIAL WORKING GROUPS FOR PAEDIATRIC BRAIN TUMOURS

Ruman Rahman¹, DavidWalker¹, Emma Campbell¹, Kristian Aquilina²; ¹University of Nottingham, Nottingham, UK. ²Great Ormond Street Hospital, London, UK

INTRODUCTION: Brain tumours are the biggest cancer killer in children and young adults. Several recent developments have the potential to change the outlook for these children, including intra-CSF chemotherapy, ultrasound-mediated blood-brain barrier disruption, convection enhanced delivery, polymer delivery systems, electric field therapy, and intra-arterial and intra-nasal chemotherapy. To date, there have been very few clinical trials to evaluate these. In addition, custom-built hardware, novel surgical