NEURO-ONCOLOGY ADVANCES

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FIRST ANNUAL CONFERENCE ON CNS CLINICAL TRIALS, CO-SPONSORED BY SNO AND ASCO

Submission Categories and Abbreviations:
CLRM – Clinical Research Methods
IMMU – Immunotherapy
NEIM – Neuroimaging
SCSS – Supportive Care and Survivorship
SYST – Systemic Therapeutics

FINAL CATEGORY: CLINICAL RESEARCH METHODS

CLRM-01. MACHINE LEARNING TO UNCOVER SIGNATURES OF VULNERABILITY IN GLIOBLASTOMA UMBRELLA SIGNATURE TRIAL (GUST)

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Glioblastoma is characterized by intra- and inter-tumoral heterogeneity. A glioblastoma umbrella signature trial (GUST) posits multiple investigational treatment arms based on corresponding biomarker signatures. A contingency of an efficient umbrella trial is a suite of orthogonal signatures to classify patients into the likely-most-beneficial arm. Assigning optimal thresholds of vulnerability signatures to classify patients as "most-likely responders" for each specific treatment arm is a crucial task. We utilized semi-supervised machine learning, Entropy-Regularized Logistic Regression, to predict vulnerability classification. By applying semi-supervised algorithms to the TCGA GBM cohort, we were able to transform the samples with the highest certainty of predicted response into a self-labeled dataset and thus augment the training data. In this case, we developed a predictive model with a larger sample size and potential better performance. Our GUST design currently includes four treatment arms for GBM patients: Arsenic Trioxide, Methoxyamine, Selinexor and Pevonedistat. Each treatment arm manifests its own signature developed by the customized machine learning pipelines based on selected gene mutation status and whole transcriptome data. In order to increase the robustness and scalability, we also developed a multi-class/label classification ensemble model that's capable of predicting a probability of "fitness" of each novel therapeutic agent for each patient. Such a multi-class model would also enable us to rank each arm and provide sequential treatment planning. By expansion to four independent treatment arms within a single umbrella trial, a "mock" stratification of TCGA GBM patients labeled 56% of all cases into at least one "high likelihood of response" arm. Predicted vulnerability using genomic data from preclinical PDX models correctly placed 4 out of 6 models into the "responder" group. Our utilization of multiple vulnerability signatures in a GUST trial demonstrates how a precision medicine model can support an efficient clinical trial for heterogeneous diseases such as GBM.

CLRM-02. TRIAL IN PROGRESS: A PROSPECTIVE, MULTICENTER PHASE 2B STUDY TO ESTABLISH IMAGE INTERPRETATION CRITERIA FOR ^{18}F-FLUCICLOVINE PET IN DETECTING RECURRENT BRAIN METASTASES AFTER RADIATION THERAPY (PURSUE)

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BACKGROUND: Brain metastases represent the most common intracranial tumor in adults, occurring in 10-40% of cancer patients. Most patients undergo multimodal treatment approaches and post-treatment follow-up with conventional MRI (CE-T1-weighted and FLAIR/T2-weighted) of the brain is performed to monitor for disease recurrence. However, owing to the similar appearance of treatment-related changes like radiation necrosis with that of true recurrence, conventional MRI alone suffers from low specificity. Given the high mortality of patients with brain metastases and the considerable treatment-associated morbidity, a need remains for an imaging modality that accurately differentiates recurrence from treatment-related changes. Accurate imaging is key to preventing unnecessary surgery or changes in effective therapy in patients mistaken for disease progression as well as prevent continuation of ineffective therapy if radiation necrosis is incorrectly diagnosed. To this end, ^{18}F-fluciclovine is a synthetic amino acid-based PET imaging agent that has potential to evaluate primary and metastatic brain cancers owing to its low normal background uptake in the brain and increased uptake in brain tumors. METHODS: NCT04410367 is a prospective, open-label, single-arm, single-dose (185 MBq ± 20%) study with a primary objective to establish visual image interpretation criteria for ^{18}F-fluciclovine PET studies of recurrent brain metastases. Forty subjects with solid tumor brain metastases who have undergone radiation therapy will be enrolled across ~8 US sites if they have a reference lesion considered equivocal on MRI for recurrent disease and are planned for craniotomy. Subjects will undergo ^{18}F-fluciclovine PET <42 days after the MRI and 1–21 days before planned craniotomy. Outcome measures comprise the diagnostic performance of ^{18}F-fluciclovine PET at different thresholds of ^{18}F-fluciclovine uptake compared with histopathology, subject- and lesion-level diagnostic performance based on established image interpretation criteria, and safety evaluations. Enrolment began in August 2020 and the trial is open at the time of submission.

CLRM-03. BGB-290 AND TEMOZOLOMIDE IN TREATING ISOCITRATE DEHYDROGENASE (IDH)1/2-MUTANT GRADE I-IV GLIOMAS – A NOVEL MODEL OF AYA TRIAL DEVELOPMENT AND DEPLOYMENT

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DESCRIPTION: The lack of enrollment of AYA patients on clinical trials is well documented and multivariant. Here we present the basic science, examination of its relevance to the AYA population specifically, and the parallel deployment of two international clinical trials via a pediatric neuro-oncology and adult brain tumor consortium. DISCUSSION: In February of 2017, the laboratory of Ranjit Bindra, MD, PhD, published a manuscript describing the finding that tumors with IDH1/2 mutations induce a BRCAness state leading to PARP inhibitor (PARPi) sensitivity and synergistic interactions with temozolomide chemotherapy [2]. Despite IDH1/2 mutations being rare in the pediatric high-grade glioma population, three independent groups confirmed that the incidence is significantly increased to ~30% in the adolescent and young adult (AYA) population. Upon discovery of a high blood-brain-barrier penetrant, high potency PARPi by BeiGene Pharmaceuticals, an international trial was launched through the Pacific Pediatric Neuro-Oncology Consortium (PNOC) [3] to test this drug in an AYA specific trial recruiting patients ages 13 to 25, with a concurrent trial being run for patients older than 25 years of age through the Adult Brain Tumor Consortium (ABTC) [4].

While most trials that enroll AYA patients are forced to assess them as a unique cohort in post-analysis, if at all, the PNOC trial mentioned above was designed from the ground up with the AYA population in mind. It has allowed us to base initial dosing, recruitment strategies, psychosocial assessments, and outcomes, specifically on the AYA population. Ultimately, we expect their distinctive biology to yield unique results when compared to the ABTC trial.

We propose that this is a model that could potentially be replicated in other disease processes and early phase drugs with the buy-in of the pharmaceutical industry and early phase consortiums.

CLRM-04. PHASE I/II SAFETY AND EFFICACY STUDY OF BET BROMODOMAIN INHIBITOR OTX-015 WITH OLAPARIB AND LOMUSTINE IN PATIENTS WITH RECURRENT GLIOBLASTOMA

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Standard of care for patients with glioblastoma (GBM) includes resection with concurrent temozolomide (TMZ) and radiotherapy, with inevitable disease recurrence. Upon recurrence, tumors are often resistant to first-line therapies and/or have infiltrated eloquent or deep brain regions, precluding repeat resection. There is currently no standard of care for recurrent GBM and patients succumb to their disease burden within 12- 15 months of their

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

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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

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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 developed 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

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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

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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