initial diagnosis of recurrence, exposing an unmet need to find novel therapies to treat recurrent disease. Promodomain 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 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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Genetic studies of tumor specimens are becoming standard of care in patients with gliomas to characterize druguable 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 microdevces 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 microdevice analysis 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 cell death and necrosis. The devices 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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Genomic sequencing of diffuse intrinsic pontine gliomas (DIPG) has revealed genome 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 teams was assembled to develop molecular profiles and a treatment plan for 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 by targeted 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% (10/26) of the selected agents (36/95) were the same 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 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 also plasma and radiomics 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 imaging analyses was developed to triage biomarkers unlikely to succeed in identifying patient groups with clinically relevant 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 PEDIATRIC BRAIN TUMOURS
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INTRODUCTION: Brain tumors 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 intraluminal chemotherapy. Up to date, there have been very few clinical trials to evaluate these. In addition, custom-built hardware, novel surgical
procedures and the testing and licensing of implantable devices add difficulty at the regulatory level. METHODS: The authors participated in an international workshop funded by the charity Children with Cancer UK in 2016, where different experimental techniques aimed at optimising CNS drug delivery were discussed. Following this and two subsequent workshops run by the CBTDTC (Children’s Brain Tumour Drug Delivery Consortium), the CBTDTC and the ITCC (Innovative Therapies for Children with Cancer) brain tumour group launched the ‘Clinical Trials Working Group’, for Central Nervous System Drug Delivery’. This aims to accelerate clinical trials to assess the safety and effectiveness of drug delivery devices for the treatment of paediatric brain tumours. RESULTS: On 1 March, 2021, GDBeau and Mr. Reza Movassaghian (Consultant Paediatric Neurosurgeon at Great Ormond Street Hospital) hosted the first steering group meeting, comprising 38 leading brain tumour research scientists and clinicians from the UK, EU and US. CONCLUSION: The ideas generated during the March meeting are driving the agenda for a Clinical Trials Workshop that will be held at the American Society of Clinical Oncology in 2021. In particular, a ‘Roadmap’ document for pre-clinical to clinical translation needs to be created and shared with the paediatric neuro-oncology research community. We present this abstract to the CNS Clinical Trials Meeting to raise awareness of this initiative with the large number of relevant stakeholders who will be attending the event.

CLRM-09. INCORPORATING EXTERNAL CONTROL ARM IN MDNA55 RECURRENT Glioblastoma REGISTRATION TRIAL

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BACKGROUND: Drug development in recurrent glioblastoma multiforme (rGBM) is challenging. For randomized controlled trials (RCTs) similar accrual rates and limited life-prolonging treatment options may delay accrual and introduce bias through differential dropout of control patients. Comparing results of a single-arm Phase 2b trial of intratumoral delivery of MDNA55 (an interleukin-4 receptor targeted fusion protein) to an external control arm, we sought early efficacy insights and consider the FDA of incorporating an ECA in a Phase 3 registrational trial. METHODS: Using propensity score weighting, we compared rGBM patients from the Phase 2b trial (NCT02838895) (2017-2019) to patients from rGBM registries who had received standard of care therapies (2011-2019) and met eligibility requirements. Propensity scores were estimated using a logistic regression model with 11 covariates. We compared the propensity score weighted groups according to demographic and disease attributes before and after weighting and compared overall survival between the two groups. RESULTS: Using propensity score weighting, 43 (98.6%) of 44 evaluable MDNA55 patients and 40.80 weighted ECA patients (from 62 unweighted registry patients) were identified for comparison. MDNA55 and ECA patients were balanced on all baseline characteristics (i.e., standardized mean difference ≤ 0.15). Compared to ECA, MDNA55 patients had a 37% lower hazard of death (hazard ratio 0.63, 95% confidence interval: 0.39,1.02). CONCLUSION: In advance of a Phase 3 trial, comparison of Phase 2b trial results to an ECA suggests that MDNA55 may be efficacious in rGBM. In view of the known challenges associated with drug development for rGBM, these results provided a proof-of-concept for the design of a novel hybrid Phase 3 trial. This planned Phase 3 trial incorporates propensity score weighting to create a composite hybrid randomized and external control arm, an approach preferred by the FDA over full replacement of a randomized control with an external control.

CLRM-10. THE INTER-RELATIONSHIP BETWEEN MULTIMODAL LONGITUDINAL BIOMARKERS OF NEURAL DAMAGE, INFLAMMATION, AND COGNITION AFTER CAR T CELLULAR THERAPY: A SINGLE-CENTER PROSPECTIVE OBSERVATIONAL TRIAL (NCT04614987)

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BACKGROUND: Immune effector cell associated neurotoxicity syndrome (ICANS) remains a devastating, frequent complication of chimeric antigen receptor (CAR) T cell therapy for advanced-stage hematologic malignancies. Symptoms range from encephalopathy and headaches to aphasia, strokes, and diffuse cerebral edema. Persistent mild cognitive symptoms have also been reported. Unfortunately, the underlying, pathophysiologic mechanisms driving ICANS is poorly understood. Current proposed models center on systemic inflammatory changes leading to endothelial dysfunction, blood-brain barrier (BBB) breakdown, and systemic cytokine and/or monococyte infiltration into the central nervous system (CNS). However, these models do not integrate predisposing risk factors for the development of ICANS. We previously demonstrated that pre-infusion plasma neurofilament light chain (NFL), a marker of neurodegeneration, may predict development of ICANS. Early elevations in NFL suggest development of ICANS is also related to pre-existing neuroaxonal injury. The longitudinal relationship between latent neuroaxonal injury, blood brain barrier (BBB) integrity, neuroinflammation, and cognition remains unknown. METHODS: This prospective, observational trial examined the relationship between multi-modal (blood, cerebrospinal fluid (CSF), neuroimaging) biomarkers and cognition in a cohort of twenty patients undergoing standard-care CAR T cell therapy. Biomarkers for neural injury most include blood and CSF NFL and volumetric measures derived from structural magnetic resonance imaging (MRI). Biomarkers for neuroinflammation include blood and CSF glial fibrillary acidic protein (GFAP) and quantification of white matter hyper-intensity burden on MRI. BBR integrity will be quantified using the serum/CSF albumin ratio. Finally, neuropsychological performance testing will assess cognitive performance across multiple cortical domains including attention, memory, and executive function. Participants will undergo a baseline (pre-infusion) examination, follow-up evaluation (eight in total, voluntary lumbar puncture (LP), MRI scan, and cognitive testing) on post-infusion day 3 (D3), D30, D90, and D180. The primary outcome is percent change in a given biomarker level. RESULTS/CONCLUSIONS: This ongoing trial has 2 of 20 planned participants enrolled.

CLRM-11. BENCH TO BEDSIDE NEURO-ONCOLOGY: ADVOCATING FOR A CLINICALLY RELEVANT STRATEGY AS UNDERSCORED BY THE PANDEMIC

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INTRODUCTION: The basic science research endeavor has been abundantly and astonishingly successful in the last three decades in elucidating the mechanisms of neuro-oncology disease and in suggesting therapeutic strategies. Clinical successes have lagged behind, and translation of promising laboratory findings into clinical practice is rare. We hypothesize that one important reason for this discordance is the use of different paradigms for designing laboratory and clinical trials, and that utilizing clinically relevant paradigms could improve clinical trial study impact. METHODS: We identified all preclinical-neuro-oncology therapeutic trials published in four high-impact journals between 11/2018 and 4/2019 and assigned a level of evidence (LOE) to each study using the American Academy of Neurology LOE preclinical studies. Eight evaluable phase three studies of COVID vaccines were identified and all preclinical studies preceding the trials. RESULTS: Of the 26 neuro-oncology articles identified, 85% had a LOE of IV and 15% were class III. An analysis of successful human trials showed significantly more high quality laboratory studies supporting “successful” compared to “unsuccessful” trials (p=0.048). This same pattern was identified in phase III trials of COVID. Twenty antiviral trials failed to meet the primary endpoint; all were preceded by class III or IV LOE preclinical studies. Eight of the three studies of COVID vaccines were identified, all of which met their primary endpoints. These were supported with a mix of Class II (n=4) and III/IV (n=4) preclinical studies. Higher LOE by AAN criteria is associated with successful COVID therapeutic trials (p=0.0034). CONCLUSIONS: Despite rigorous, elegant, and enlightening laboratory experiments, successful translation to human therapeutics remains rare. Envisioning basic science research through the lens of clinical therapeutics represents a challenging but surmountable paradigm shift that may reverse this pattern and create a more successful research enterprise in neuro-oncology and beyond.

CLRM-12. HYBRID DESIGNS FOR USING EXTERNAL CONTROLS IN PHASE 3 Glioblastoma TRIALS

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While recent Phase 3 glioblastoma (GBM) trials have failed to establish novel therapies, they potentially provide a high-quality source of external control patients treated with temozolomide. We consider hybrid two-stage adaptive designs that leverage these external controls to safely accelerate Phase 3 GBM trials. The basic strategy is that first patients are randomized 1:1 between the control and experimental arms, then an interim check measures similarity between the trial’s control patients and potential external controls, and finally if this interim similarity is high the randomization ratio is changed accordingly and the external controls are used in the final analysis. An extensive simulation study is conducted to assess operating characteristics and we discuss when these hybrid designs can accelerate GBM therapy development while maintaining strict error control.