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 CBTDDC (Children's Brain Tumour Drug Delivery Consortium), the CBTDDC 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, CBTDDC and Mr Kristian Aquilina (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 in the autumn of 2021. In particular, there was agreed consensus that 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) short survival horizons 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 consideration by 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 (NCT02858895) (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: Through propensity score weighting, 43 (98%, 43/44) 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 patients, 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 MULTI-MODAL 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 pathophysiology 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 monocytes 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 examines the relationship between multi-modal (blood, cerebrospinal fluid (CSF), neuroimaging) biomarkers and cognition in a cohort of twenty patients undergoing standard-of-care CAR T cellular therapy. Biomarkers for neural injury 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 qualification of white matter hyper-intensity burden on MRI. BBB integrity will be quantified using the serum/CSF albumin ratio. Finally, neuropsychological performance testing will assay cognitive performance across multiple cortical domains including attention, memory, and executive function. Participants will undergo a baseline (pre-infusion) examination, followed by evaluation (blood draw, voluntary lumbar puncture, 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-oncologic 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 procedures could improve laboratory study impact. METHODS: We identified all pre-clinical 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 evidence classification system. We then identified all phase III trials of therapeutics for COVID and performed the same analysis on 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 studies failed to meet the primary endpoint; all were preceded by class III or IV LOE preclinical studies. Eight evaluable phase three studies of COVID vaccines were identified, all of which met their primary endpoints. These were supported with a mix of Class I/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.