1 and 15 of 28-day cycles. RESULTS: Between 2015 and 2020, 10 subjects were enrolled at MBZ 50mg/kg/day (n=3), 100mg/kg/day (n=4), and 200mg/kg/day (n=3). One subject assigned to 100mg/kg/day was not evaluable. Seven subjects had a diagnosis of diffuse midline glioma, 1 subject had anaplastic astrocytoma, and 1 subject had a spinal HGG. All subjects received radiation. There were no dose limiting toxicities. The most frequent G3/G4 adverse events were neutropenia (n=3), and lymphopenia (n= 4). The overall response rate was 33% with 2 subjects achieving a partial response and 1 subject achieving a complete response sustained for 10 months. The PFS and OS from the start of study treatment were 4.7 months and 11.4 months, respectively. CONCLUSION: MBZ was safe and well tolerated when administered with BVCZ and CPT-11 at doses up to 200mg/kg/day. Further studies are needed to determine the efficacy of this treatment.

EPCT-03. WORKING TOGETHER TO ACCELERATE THE PRECLINICAL TO CLINICAL TRANSLATION OF DRUG DELIVERY SYSTEMS FOR CHILDREN'S BRAIN TUMOURS

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Children's brain tumours are the biggest cancer killer in children and young adults. Several techniques, such as intra-cerebrospinal fluid chemotherapy, ultrasound-mediated blood-brain barrier disruption, convection enhanced delivery, polymer delivery systems, electric field therapy, and intra-arterial and intra-nasal chemotherapy, have the potential to transform the treatment of brain tumours in children. However, there have been very few clinical trials to evaluate these. In 2021, the CBTDDC (Children's Brain Tumour Drug Delivery Consortium) and the ITCC (Innovative Therapies for Children with Cancer) brain tumour group established a Clinical Trials Working Group comprising international researchers and clinicians to address this issue. This partnership highlighted the main challenges in preclinical to clinical translation of paediatric CNS drug delivery as: (1) a lack of specific funding for prototype development and/or scale-up for clinical trials; (2) difficulties in navigating the regulatory landscape; (3) lack of accurate preclinical models; and (4) increased need for multi-centric working. In response to this, we ran a hybrid workshop in November 2021 on 'Clinical Trial Readiness for CNS Drug Delivery'. At this workshop, around 50 delegates (comprising clinicians, researchers, trial regulatory experts, policy makers, and representatives from funding organisations, brain tumour charities and industry) came together to discuss issues around funding, preclinical models and regulatory processes. We have established speciality-specific working groups to build on the workshop discussions, with the aim of producing recommendations around the use of preclinical models and drug delivery techniques according to brain tumour type. We have also used the workshop presentations and discussions to create a 'Roadmap' document for preclinical to clinical translation, which will be freely shared with the neuro-oncology research community. We continue to liaise with funders and regulatory bodies to address the changes that are needed in these areas. If you would like to join our network, contact: cbtddc@nottingham.ac.uk

EPCT-04. STEREOTACTIC BIOPSY SPLIT-COURSE RADIATION THERAPY FOR DIFFUSE MIDLINE GLIOMA OF THE PONS (SPORT-DMG): EARLY PHASE II ENROLLING CLINICAL TRIAL

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Diffuse midline glioma (DMG) of the pons remains the leading cause of death among pediatric patients with brain tumors, despite numerous attempts to intensify treatment. While standard treatment includes 54Gy in 30 fractions of radiation over six weeks of time, nearly all patients progress within the treatment field, and many experience symptomatic radionecrosis with steroid dependence. Symptom improvement typically begins after 20Gy to the tumor. Both hypofractionation and reirradiation after recurrence have been found to be safe for patients with DMG. Our study aims to enroll patients with newly diagnosed pontine DMG aged >1 year (no maximum age), and collect molecular information about DMG via stereotactic biopsy, followed by a short 2 week course of 25Gy in 10 fractions of radiation, with volumes guided by MRI with tractography reconstruction and FDOPA PET radiotracer uptake. Patients are followed closely and can complete the 25Gy in 10 fraction radiation course up to 3 times total for meeting radiographic and clinical progression criteria. Our primary endpoint is to estimate the time to progression from diagnosis to after receiving the second 25Gy course, and to compare this to the historical 7 month standard from diagnosis to progression after one 54Gy course. We aim to improve the time interval where patients are asymptomatic at home while minimizing time receiving daily treatments. Other endpoints will include the patient quality of life, caregiver quality of life, PFS intervals after each course, overall survival, and toxicity.

EPCT-05. PHASE IB STUDY OF UNESBULIN (PTC596) IN CHILDREN WITH NEWLY DIAGNOSED DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) AND HIGH-GRADE GLIOMA (HGG): A REPORT FROM THE COLLABORATIVE NETWORK FOR NEURO-ONCOLOGY CLINICAL TRIALS (CONNECT)

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BACKGROUND: The B-cell-specific Moloney murine leukemia virus integration site-1 (BMI-1) protein, implicated in self-renewal and DNA-damage signaling, is highly expressed in DIPG and HGG. Preclinically, BMI-1 modulation by unesbulin (PTC596 [which mediates hyperphosphorylation and subsequent degradation of BMI-1]) leads to DIPG/HGG cell proliferation blockade, mitotic abnormalities, and tumor cell sensitization to radiation-induced DNA damage. METHODS: This phase Ib study sought to determine the maximally tolerated dose/ recommended phase 2 dose (RP2D) of unesbulin administered concurrently with radiotherapy and adjuvantly in children with newly diagnosed DIPG or HGG. Patients were enrolled according to a Rolling-6 design and received oral unesbulin twice weekly during radiotherapy and as maintenance therapy. RESULTS: Twenty-seven patients enrolled (median age: 8.5 years [range: 2-18]), including 18 patients with DIPG and nine patients with HGG. Unesbulin was administered in capsule formulation in the first nine patients, then tablet formulation for subsequent patients. Within the capsule formulation group, three dose-limiting toxicities (DLTs) were observed in two patients on dose level 2 (grade 4 neutropenia). Within the tablet formulation group, four DLTs were experienced by three patients on dose level 2 (grade 3 ALT elevation, grade 3 dehydration/vomiting, grade 3 decreased ejection fraction, grade 4 neutropenia). Dose level 1 was declared the RP2D, and six additional patients enrolled in the expansion cohort at this dose without DLTs. Most common drug-related grade 3/4 toxicities were neutropenia (48%), leucopenia (35%), and elevated ALT (26%). Similar pharmacokinetic profiles were observed for capsule and tablet formulations, consistent with adult data. Survival outcomes and genomics results will be shared at time of presentation. CONCLUSIONS: The RP2D of unesbulin in children newly diagnosed with DIPG or HGG is 200mg/m2 twice weekly, concurrent with and following radiotherapy. The recently opened surgical cohort will assess intratumoral pharmacokinetics and inhibition of tumor BMI-1 signaling, with results forthcoming.

EPCT-06. PHASE I STUDY OF RIBOCICLIB AND EVEROLIMUS POST-RADIOTHERAPY IN CHILDREN WITH NEWLY DIAGNOSED DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) AND HIGH-GRADE GLIOMA (HGG): UPDATED REPORT FROM THE COLLABORATIVE NETWORK FOR NEURO-ONCOLOGY CLINICAL TRIALS (CONNECT)

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BACKGROUND: Dual inhibition of CDK4/6 and mTOR in DIPG and pediatric HGG has strong biologic rationale, given prevalent genetic alterations resulting in upregulated cell cycle and PI3K/mTOR pathways in these diseases, as well as non-overlapping agent toxicities. This study sought to evaluate safety/tolerability and determine the recommended phase 2 dose (RP2D) of ribociclib and everolimus among children with newly diagnosed DIPG and HGG post-radiotherapy. METHODS: Patients were enrolled according to a Rolling-6 design and received oral ribociclib and everolimus once daily for 21 and 28 days, respectively, starting 2-4 weeks post-completion of radiotherapy. All HGG and biopsied DIPG patients were screened for RB protein presence by immunohistochemistry. Pharmacokinetics and survival data were analyzed. RESULTS: Nineteen patients enrolled (median age: 8 years [range: 2-18]). Three patients enrolled at each of dose levels 1 and 2 without dose-limiting toxicities (DLTs). Thirteen patients enrolled at dose level 3, with one patient experiencing a DLT (grade 3 infection). One patient came off therapy prior to cycle 9 due to cardiac toxicity. The most common grade 3/4 toxicities were neutropenia (33%), leucopenia (17%), and lymphopenia (11%). Steady-state everolimus exposures in combination were 1.9±0.9-fold higher than single-agent administration. Median overall survival (OS) for 15 patients with DIPG was 13.9 months, with 12-, 24-, and 36-month OS of 53.3%, 38.9%, and 38.9%. Median event-free survival for four patients with HGG was 10.5 months. Among patients with tumor molecular profiling, two longer survivors (OS: 20, >37 months) had evidence of cell cycle upregulation with CDKN2A/B deletion and CDK4 overexpression identified. CONCLUSIONS: The combination of ribociclib and everolimus was well-tolerated post-radiotherapy in children with newly diagnosed DIPG and HGG, with a RP2D of ribociclib 170 mg/m2 days 1-21 and everolimus 1.5 mg/m2 days 1-28. Results will inform a molecularly-guided phase II study currently underway to evaluate efficacy.

EPCT-07. UPDATED REPORT ON THE PILOT STUDY OF USING MRI-GUIDED LASER HEAT ABLATION TO INDUCE DISRUPTION OF THE PERITUMORAL BLOOD BRAIN BARRIER TO ENHANCE DELIVER AND EFFICACY OF TREATMENT OF PEDIATRIC BRAIN TUMORS

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BACKGROUND: MRI-guided laser interstitial thermal therapy (LITT) is a minimally invasive, cytoreductive surgery useful for managing unresectable brain tumors. LITT disrupts the blood brain barrier (BBB) and facilitates chemotherapy delivery. We report the toxicity and outcome for pediatric brain tumors treated on a pilot trial of LITT and chemotherapy. The primary objectives were to quantify peritumoral BBB disruption following LITT and evaluate toxicity and efficacy. METHODS: The trial had two arms, A: patients with newly diagnosed gliomas underwent LITT followed by standard of care management, and B: patients with relapsed malignant brain tumors received 6 weeks of weekly doxorubicin post-LITT followed by maintenance etoposide. RESULTS: Between 2015 – 2018, six patients were enrolled: five on arm A (four with low-grade gliomas, one with high-grade glioma), one on Arm B with progressive anaplastic astrocytoma. All patients tolerated the procedure well; four experienced a transient hemiparesis post-LITT. The Arm B patient progressed and died of disease 2 months and 22 months post-LITT, respectively. The HGG patient received standard therapy and remains without disease progression 44 months post-LITT. One patient with LGG required additional treatment for disease progression 14 months post-LITT. Two patients with LGGs did not require additional therapy, now 51 and 41 months post-LITT. One patient was alive 24 weeks post-LITT and subsequently lost to follow-up. Peritumoral BBB disruption was analyzed in two ways: serum abundance of brain-derived proteins and MRI Dynamic contrast enhancement (DCE). Neuron-specific enolase were measurable in the serum of all patients, using ELISA up to 84 days post-LITT. DCE 2 weeks post-LITT demonstrated increased enhancement and FLAIR signal, consistent with BBB disruption and vasogenic edema. This effect was evident up to 4 months post-procedure. **CONCLUSION:** LITT is safe in children with brain tumors and can be combined with chemotherapy. DCE and serum brain-derived proteins can measure BBB disruption.

EPCT-08. DISEASE-SPECIFIC WORKING GROUPS WITHIN THE PACIFIC PEDIATRIC NEURO-ONCOLOGY CONSORTIUM (PNOC) AND CHILDREN'S BRAIN TUMOR NETWORK (CBTN) FACILITATE MULTI-DISCIPLINARY COLLABORATION AND TRANSLATION OF INNOVATIVE STRATEGIES IN PEDIATRIC NEURO-ONCOLOGY

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BACKGROUND: In Summer 2019, PNOC leadership developed working groups to align basic scientists, clinical researchers, and foundations for rapid translation of novel therapies for children and young adults with central nervous system tumors. Soon after, PNOC partnered with the Children's Brain Tumor Network (CBTN) to grow collaborations and augment preclinical resources. Since their inception, working groups have advanced translation of new therapies and biomarkers, developed pipelines for preclinical and clinical research, and expanded global collaborations. DESIGN: Each working group is led by 2 to 3 experts in a disease, such as medulloblastoma, diffuse midline glioma, or craniopharyngioma, or subject matter, like imaging, nursing, or diversity, equity, and inclusion. A project manager coordinates regular multidisciplinary meetings to share new findings from research laboratories, provide updates on clinical trial development (with real-time feedback and incorporation of trial endpoints and biomarkers), and invite speakers to share advancements in the disease or subject of interest. RESULTS: Eleven working groups have been created with over 200 members across the United States, Europe, Australia. More than 20 foundations, led predominantly by families, provide support and insight to guide working group efforts. Working groups have developed 4 clinical trials (n=2, diffuse midline glioma; n=1, craniopharyngioma; n=1, medulloblastoma) and completed 3 international surveys, investigating experiences of patients/families affected by craniopharyngioma, evaluating diversity and inclusion throughout the consortia, and assessing nursing and advanced practice provider needs. Additional accomplishments include a registry for atypical teratoid rhabdoid tumors, a population dataset evaluating diversity in clinical research participation across consortia, incorporation of nursing members for review and refinement of clinical trial protocols, and updated imaging case report forms for application across clinical trials. CONCLUSION: Multidisciplinary working groups within international consortia facilitate efficient translation of multi-pronged strategies to improve the care of children and young adults with central nervous system tumors.

EPCT-09. ROVER: A PHASE 1/2 STUDY OF AVAPRITINIB IN PEDIATRIC PATIENTS WITH SOLID TUMORS DEPENDENT ON KIT OR PDGFRA SIGNALING

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Prognosis for pediatric patients with advanced relapsed/refractory (R/R) solid (including central nervous system [CNS]) tumors is poor. *KIT* alterations are common in germ cell tumors and high-grade glioma (HGG); platelet-derived growth factor receptor alpha (*PDGFRA*) alterations are common in sarcoma and HGG. *H3K27M*-mutant gliomas are dependent on PDGFRA signaling. No KIT/PDGFRA targeted therapies are currently approved for pediatric patients with R/R solid or CNS tumors, or *H3K27M*-mutant gliomas. Selective KIT and PDGFRA inhibitor avapritinib demonstrated potent activity against KIT activation-loop (exon 17), juxtamembrane (exon 11), and extracellular-domain (exon 9) mutants (IC_{50}<2 nM), and PDGFRA activation-loop (D842V) mutants (IC_{50}=0.24 nM); cellular IC_{50} of PDGFRA wild-type was 95 nM. CNS penetration in preclinical models (steady-state brain-to-plasma ratios ranging from 0.74–1.00) has demonstrated potential for CNS antitumor activity. Avapritinib is approved in the USA to treat adults with unresectable/metastatic gastrointestinal stromal tumors (GIST) harboring *PDGFRA* exon 18 mutations (including D842V), and adults with advanced systemic mastocytosis. In the EU, avapritinib is approved for adults with unresectable/metastatic GIST harboring a *PDGFRA* D842V mutation. Objectives of ROVER 2-part phase 1/2, multicenter, open-label study (NCT04773782) are avapritinib safety, preliminary efficacy, and pharmacokinetics in pediatric patients aged 2 to <18 years with solid R/R tumors dependent on KIT or PDGFRA signaling, including *H3K27M*-mutant gliomas, and no alternative treatment options. Part 1 will enroll ≥12 patients; primary endpoint is confirmed age and body surface area physiologically based pharmacokinetic modeling predicted dose to provide equivalent exposure to the 300 mg adult avapritinib dose. Part 2 will enroll ≥25 patients at the recommended avapritinib dose from Part 1; the primary endpoint is objective response rate. Avapritinib once-daily will be administered in continuous 28-day cycles. Enrollment in this study is planned at 26 sites in 10 countries, including centers in North America, Europe, and Asia/Pacific.