Title

RTID-03. A PHASE I CLINICAL TRIAL TO EVALUATE MTD OF PERAMPANEL AND MEMANTINE IN COMBINATION WITH STANDARD CHEMORADIOTHERAPY FOR THE TREATMENT OF PATIENTS WITH NEWLY DIAGNOSED GBM –A STUDY DESIGN

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brospinal fluid regions surrounding the grey matter and in ventricles shunt electric current from anode to cathode, hindering delivery of the current required to produce 4 V/cm at the tumor/peritumor target. Thus, we consider two new delivery methods for TTFields. First, the transcranial array can be made more focal and directional, following modeling and development of electrode arrays used in spinal cord and deep brain stimulation. Our finite element modeling shows that similarly-designed TTFields electrode arrays can deliver field strength focally to a tumor target approaching 4 V/cm. Second, pre- or post-resection, TTFields can be delivered via electrode arrays surgically placed in the tumor or tumor resection cavity (intra-tumoral delivery), circumventing the resistive skull and CSF shunting effects. Such intra-tumoral arrays can deliver 4 V/cm to the tumor/peritumor region, opening up the potential to replicate clinically the 100% efficacy of TTFields *in vitro* and in animal models. Thus, new TTFields delivery may lead to unlimited survival of GMB patients via a side-effect free treatment modality.

RBIO-05. MITOTIC ENRICHMENT AS AN EFFICIENT STRATEGY TO RADIOSENSITIZE GLIOBLASTOMA

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Their location and highly aggressive nature renders glioblastoma (GBM) among the most deadly and devastating of human malignancies. Despite extensive treatment involving surgery and adjuvant chemo-radiotherapy, the prognosis is still dismal and novel treatment strategies are urgently needed. Of all existing adjuvant therapies, radiotherapy contributes the most to extending the median overall survival. Increasing the efficacy of existing radiotherapeutic regimens is therefore a logical avenue to improve the survival of GBM patients. We have developed a novel radiosensitization strategy called 'induction of mitotic enrichment'. It has long been known that the radiosensitivity of a cell depends on the phase of the cell cycle and that especially mitotic cells are especially vulnerable. Enriching the tumor for mitotic cells by arresting them during division prior to each radiotherapy fraction should therefore render the tumor population more sensitive to irradiation. Ideally, induction of mitotic enrichment should be reversible and non-cytotoxic to prevent healthy tissue toxicity and be compatible with clinically applied hyperfractionated radiotherapy regimens. We have now identified an orally available targeted tubulin polymerization inhibitor that can achieve repeated and reversible mitotic enrichment for up to 10 hours prior to radiotherapy, without causing cytotoxicity *in vitro* or healthy tissue toxicity *in vivo*. Most importantly, this tubulin inhibitor efficiently radiosensitizes a range of preclinical GBM models *in vitro* and *in vivo*, including GSC models, and significantly improves survival, but only in a mitotic enrichment setup when given 6-8 hours prior to radiotherapy to allow accumulation in mitosis. We are currently expanding our preclinical development of mitotic enrichment as a radiosensitization strategy to other mitotic targets and different intra- and extracranial cancer models representing several diseases for which radiotherapy is a mainstay treatment. In parallel, we are preparing a phase 0 trial to demonstrate induction of mitotic enrichment in human GBM.

RBIO-06. IMPLEMENTATION OF HUMAN INDUCED PLURIPOTENT STEM CELL DERIVED CEREBRAL ORGANOIDS TO MODEL NORMAL TISSUE RADIORESPONSE

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Treatment-related sequelae following cranial irradiation have life changing impacts for patients and their caregivers. Characterization of the basic response of human brain tissue to irradiation has been difficult due to a lack of preclinical models. The direct study of human brain tissue *in vitro* is becoming possible due to advances in stem cell biology, neuroscience, and tissue engineering with the development of organoids as novel model systems which enable experimentation with human tissue models. We sought to establish a cerebral organoid (CO) model to study the radioresponse of normal human brain tissue. COs were grown using human induced pluripotent stem cells and a modified Lancaster protocol. Compositional analysis during development of the COs showed expected populations of neurons and glia. We confirmed a population of microglia-like cells within the model positive for the makers Iba1 and CD68. After 2-months of maturation, COs were irradiated to 0, 10, and 20 Gy using a Shepard Mark-II Cs-137 irradiator and returned to culture. Subsets of COs were prepared for immunostaining at 30- and 70-days post-irradiation. To examine the effect of irradiation on the neural stem cell (NSC) population, sections were stained for SOX2 and Ki-67 expression denoting NSCs and proliferation respectively. Slides were imaged and scored using the CellProfiler software package. The percentage of proliferating NSCs 30-days post-irradiation was found to be significantly reduced for irradiated COs (5.7% (P=0.007) and 3.4% (P=0.001) for 10 and 20 Gy respectively) compared to control (12.7%). The reduction in the proliferating NSC population subsequently translated to a reduced population of NeuN-labeled mature neurons 70 days post-irradiation. The loss of proliferating NSCs and subsequent reduction in mature neurons demonstrates the long-term effects of radiation. Our initial results indicate COs will be a valuable model to study the effects of radiation therapy on normal and diseased human tissue.

RANDOMIZED TRIALS IN DEVELOPMENT

RTID-01. RADIOSURGERY FOLLOWED BY TUMOR TREATING FIELDS FOR BRAIN METASTASES (1-10) FROM NSCLC IN THE PHASE 3 METIS TRIAL

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BACKGROUND: Tumor Treating Fields (TTFields) are non-invasive, loco-regional, anti-mitotic treatment modality comprising alternating electric fields. TTFields have demonstrated efficacy in preclinical non-small cell lung cancer (NSCLC) models. TTFields treatment to the brain was safe and extended overall survival in newly-diagnosed glioblastoma. The objective of the METIS study [NCT02831959] is evaluation of the efficacy and safety of TTFields in NSCLC patients with brain metastases. METHODS: NSCLC patients (N=270) with 1-10 brain metastases were randomized 1:1 to stereotactic radio surgery (SRS) followed by continuous TTFields ((150 kHz, > 18 hours/day) within 7 days of SRS or supportive care. The portable device delivered TTFields to the brain using 4 transducer arrays, while patients received the best standard-of-care for systemic disease. Patients were followed every two months until second intracranial progression. Key inclusion criteria: KPS ≥70, new diagnosis of 1 inoperable or 2–10 supra- and/or infratentorial brain metastases from NSCLC amenable to SRS; and optimal therapy for extracranial disease. Prior WBRT, surgical resection of metastases, or recurrent brain metastases were exclusionary. Primary endpoint was time to 1st intracranial progression. Secondary endpoints included time to neurocognitive failure (HVLT, COWAT and TMT), overall survival, radiological response rate (RANO-BM and RECIST V1.1); quality-of-life; adverse events; time to first/second intracranial progression for patients with 1–4 and 5–10 brain metastases; bi-monthly intracranial progression rate from 2–12 months; and time to second intracranial and distant progression. The sample size (N=270) was calculated using a log-rank test (Lakatos 1988 and 2002) with 80% power at two sided alpha of 0.05 to detect a hazard ratio of 0.57. On September, 2019, an independent Data Monitoring Committee (DMC) reviewed METIS trial data collected to that point. The DMC concluded that no unexpected safety issues had emerged and recommended continuation of the METIS study as planned.

RTID-03. A PHASE I CLINICAL TRIAL TO EVALUATE MTD OF PERAMPANEL AND MEMANTINE IN COMBINATION WITH STANDARD CHEMORADIOTHERAPY FOR THE TREATMENT OF PATIENTS WITH NEWLY DIAGNOSED GBM –A STUDY DESIGN

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BACKGROUND: Glioblastoma (GBM) is the most aggressive malignant brain tumor in adults with poor prognosis. Effective treatment is urgently needed. Recent studies demonstrated cross-talk between neuron and glioma through neuro-transmitter glutamate receptors (AMPA and NMDA receptors) promotes glioma invasion and progression in vitro and in vivo. Therefore, dual blocking AMPA and NMDA receptor therapy is a potential strategy to prevent and treat GBM progression, particularly given the fact that the two blockers act through different anti-glioma mechanism. OBJECTIVE/HYPOTHESIS: We hypothesize that adding Perampanel (an AMPA receptor blocker) and Memantine (a NMDA receptor antagonist) to standard temozolomide plus radiation therapy for the treatment of newly diagnosed GBM patients may be well tolerated and have a safe profile to prevent tumor progression, seizure recurrence or cognition impairment from radiation. STUDY DESIGN: 3 + 3 DESIGN: Maximum Tolerated Dose (MTD) is dose level at which 0/3 or 1/6 patients experience DLT with the next higher dose having at least 2/3 or 2/6 patients encountering DLT. MTD will not be more than FDA approved maximized doses for Perampanel (12 mg daily) and Memantine (20 mg bid) for the treatment of neurological diseases. Once the MTD is found, the patient will continue at MTD for the completion of concurrent chemoradiation therapy plus completion of 6 cycles of adjuvant temozolomide therapy. SUMMARY: A Phase I trial to study the safety and toxicity of combined Perampanel and Memantine with

standard chemo-radiation therapy to treat patients with newly diagnosed glioblastoma (GBM). To find Maximum Tolerated Dose (MTD) Levels of Perampanel and Memantine at concurrent chemoradiation therapy phase and adjuvant chemotherapy phase to prepare for future phase II or III trial.

RTID-04. A RANDOMIZED PHASE II TRIAL TO COMPARE THE EFFICACY OF STANDARD VERSUS COMBINATION THERAPY (PERAMPANEL, MEMANTINE PLUS STANDARD) IN THE TREATMENT OF PATIENTS WITH NEWLY DIAGNOSED GBM-A STUDY DESIGN

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BACKGROUND: Glioblastoma (GBM) is the most aggressive malignant brain tumor in adults with poor prognosis. Effective treatment is urgently needed. Recent studies demonstrated neurogliomal synaptic communication through AMPA and NMDA receptors promotes glioma invasion and progression in vitro and in vivo. Therefore, dual blocking AMPA and NMDA receptor therapy is a potential enhancing strategy to prevent and to treat GBM progression given the two blockers act through different anti-glioma mechanisms. OBJECTIVE/HYPOTHESIS: We hypothesize that adding AMPA blocker Perampanel (An anti-seizure medication) and NMDA blocker Memantine (An anti-dementia medication) to standard temozolomide plus radiation therapy (Stupp's regimen) for the treatment of newly diagnosed GBM may prevent tumor progression. It may also reduce the frequency of onset/recurrence of seizure episodes and possibly improve radiation related cognition impairment. STUDY DESIGN: This is a randomized, active controlled, open label, two arm phase II study of efficacy of treatment of GBM with combination therapy (dual AMPA and NMDA receptor blockers plus standard therapy) versus standard therapy. In the combination therapy arm, patients take Perampanel 2 mg daily and Memantine 5 mg bid, starting from -14 days to +14 days from initiation of concurrent chemo-radiation therapy. Titrating up at a 2 mg increment for Perampanel and 5 mg bid increment for Memantine until reaching MTD. If the patient has AE >= grade 2, then reduce doses at a decrement of 2 mg for Perampanel and decrement of 5 mg bid for Memantine. In the standard therapy arm, the patients are treated with Stupp's regimen. PRIMARY AND SECONDARY ENDPOINTS: PFS, 12, 24 month survival rates and response duration. Safety will be assessed by CTCAE V5. We will use Kaplan-Meier estimates for survival data and a stratified log-rank test for the randomization strata.

RTID-05. INDIGO: A GLOBAL, RANDOMIZED, DOUBLE-BLIND, PHASE 3 STUDY OF VORASIDENIB (AG-881) VS PLACEBO IN PATIENTS WITH RESIDUAL/RECURRENT GRADE II GLIOMA WITH AN ISOCITRATE DEHYDROGENASE 1/2 (IDH1/2) MUTATION

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BACKGROUND: Low-grade gliomas (LGGs; WHO grade II) are incurable and ultimately progress to high-grade gliomas. The current treatment options are surgery followed by observation ("watch and wait") for patients with lower risk for disease progression or postoperative chemoradiotherapy (high-risk population). There are no approved targeted therapies. *IDH1* and *IDH2* mutations (m*IDH1/2*) occur in approximately 80% and 4% of LGGs, respectively, and promote tumorigenesis via neomorphic production of D-2-hydroxyglutarate. Vorasidenib, an oral, potent, reversible, brain-penetrant pan-inhibitor of mIDH1/2, was evaluated in 76 patients with glioma in two phase 1 studies (dose escalation and perioperative) and was associated with a favorable safety profile at daily doses below 100 mg. Preliminary clinical activity was observed in non-enhancing glioma patients in both studies, with an objective response rate (ORR) of 18.2% and median progression-free survival of 31.4 months in the dose escalation study. METHODS: Approximately 366 patients will be randomized 1:1 to vorasidenib (50 mg QD) or matched placebo and stratified by 1p19q status (intact vs co-deleted). Key eligibility criteria: age ≥ 12 years; grade II oligodendroglioma or astrocytoma (per WHO 2016 criteria) not in need of immediate treatment and without high-risk features; centrally confirmed m*IDH1/2* status; ≥ 1 surgery for glioma with most recent ≥ 1 year but ≤ 5 years before randomization, and no other anticancer therapy; Karnofsky performance status ≥ 80%; and centrally confirmed measurable, non-enhancing disease evaluable by magnetic resonance imaging. Crossover from placebo to the vorasidenib arm is permitted upon centrally confirmed radiographic progression per RANO-LGG criteria. Primary endpoint: progression-free survival assessed by independent review. Secondary endpoints: safety and tolerability, tumor growth rate assessed by volume, ORR, overall survival, and quality of life. Clinical data will be reviewed regularly by an independent data monitoring committee. The study is currently enrolling patients in the US, with additional countries planned (NCT04164901).

RTID-06. ENHANCING TUMOR TREATING FIELDS THERAPY FOR RECURRENT GLIOBLASTOMA WITH TARGETED AND INDIVIDUALIZED SKULL REMODELING SURGERY. A MULTI-CENTER RANDOMIZED PHASE 2 TRIAL

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BACKGROUND: We present an upcoming(Sep. 2020) randomized, comparative, multi-center, investigator-initiated, interventional, phase 2 trial testing the efficacy of a novel therapeutic concept for recurrent glioblastoma(GBM). The intervention combines personalized targeted skull remodeling surgery(SR-surgery) with Tumor Treating Fields(TTFields) and best practice medical oncological therapy. SR-surgery involves strategically placed burr holes to strengthen the electric field in the tumor region. Preclinical studies indicate that SR-surgery provides a marked and focal enhancement(~100%) of TTFields. We recently concluded a phase 1 safety/feasibility study indicating promising clinical efficacy and no clinically significant toxicity related to the intervention. This subsequent randomized, comparative phase 2 trial aims to validate superior efficacy of the treatment. METHOD: We will utilize a comparative, 1:1 randomized, minimax two-stage phase 2 design with an expected sample size of 70 patients, interim futility analysis at 1-yr follow-up of the first 52 patients and a maximum sample size of 84 patients. Patients will receive either 1)TTFields and best practice medical oncological treatment(control arm) or 2) SR-surgery plus TTFields and best practice medical oncological treatment (interventional arm). Major eligibility criteria include age ≥ 18 years, supratentorial GBM, Karnofsky performance score(KPS) ≥ 70, focal tumor, and lack of uncontrollable epilepsy or significant co-morbidity. The study is designed to detect a 20% increase in the overall survival rate 12 months(OS12) assuming OS12=40% in the control group and OS12= 60% in the intervention group. Secondary endpoints include hazard ratio of overall survival and progression-free survival, objective response rate, QoL, KPS, steroid dose, and toxicity. Patients will be followed for the whole trial period(36 months). The average expected follow-up is 18 months and includes regular assessment of toxicity, response and QoL. Endpoint data will be collected at the end of the trial, occurrence of suspected unexpected serious adverse reactions(SUSARs) or unacceptable serious adverse events(SAEs), withdrawal of consent, or loss-to-follow-up.

RTID-07. HUMAN PLACENTAL HEMATOPOIETIC STEM CELL DERIVED NATURAL KILLER CELLS (CYNK-001) FOR TREATMENT OF RECURRENT GLIOBLASTOMA

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Glioblastoma (GBM) is the most aggressive primary brain tumor with dismal prognosis. Recent advances of immunotherapy in cancer have sparked interest in the use of cell therapy for treatment of GBM. Active transfer of Natural Killer (NK) cells is of particular interest in GBM because NK cells are capable of exerting anti-tumor cytotoxicity without the need for antigen presentation and sensitization, processes that are impaired in GBM. CYNK-001 is an allogeneic, off-the-shelf product enriched for CD56+/CD3- NK cells expanded from placental CD34+ cells manufactured by Celularity. Here, we demonstrate in vitro cytotoxicity of CYNK-001 against several GBM lines and its in vivo anti-tumor activity in a U87MG orthotopic mouse model via intracranial administration resulting in 94.5% maximum reduction in tumor volume. We have developed a phase I window-of-opportunity trial of CYNK-001 in recurrent GBM via intravenous (IV) and intratumoral (IT) routes. In the IV cohort, subjects receive cyclophosphamide for