Title

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

Journal

Neuro-oncology, 22(Suppl 2)

ISSN

1522-8517

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Publication Date

2020-11-01

Peer reviewed

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.

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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