Title

ACTR-50. MARIZOMIB (MRZ) WITH BEVACIZUMAB (BEV) IN WHO GRADE IV MALIGNANT GLIOMA (G4 MG): FULL ENROLLMENT RESULTS FROM THE PHASE 1, MULTICENTER, OPEN-LABEL STUDY

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(NIR) imaging agent composed of the tumor-targeting peptide, chlorotoxin and the NIR fluorescent dye, indocyanine green. It has the potential to selectively label brain and other tumors. This Phase 1 dose escalation study characterized the safety and fluorescence imaging of BLZ-100 in adults with newly diagnosed or recurrent glioma. An IV injection was given before surgery (range 3 -29 hours). Dose escalation utilized a "3+3" design with 5 pre-specified dose levels. Dose limiting toxicity (DLT) was defined as any ≥ Grade 3 BLZ-100 related adverse event (AE) within 7 days of dosing. Safety measures included AEs, laboratory measures, vital signs, and electrocardiograms. Fluorescent images were taken before and after resection (in situ) and of excised tissue (ex vivo) using a NIR camera system suitable for surgery. A total of 17 subjects were enrolled and received doses from 3 to 30 mg. No DLT was observed and none of the treatment-emergent AEs were associated with BLZ-100 dosing. There were 9 cases with WHO Grade III and IV disease and 8 with WHO grade I and II. Fluorescent signal in excised tumor samples increased with increasing dose, with robust fluorescence noted consistently at doses ≥18 mg. Fluorescence was noted in both early (day of) and late (next day) interval (time between imaging and excision) cases, however, the earlier time interval appeared better. Cases with high grade disease had more subjects positive (7/9) and more intense signal compared to those with low grade disease (3/8) based on both in situ and ex vivo imaging. The location of fluorescent signal in excised specimen was concordant with pathology confirmed tumor. These data support the potential use of BLZ-100 for FGS of gliomas.

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MRZ is an irreversible, brain-penetrant, pan-proteasome inhibitor (PI) with anti-MG efficacy preclinically in vitro and in vivo. The safety, pharmocokinetics, and activity of MRZ+BEV is evaluated in BEV-naïve G4 MG patients (pts) in first or second relapse (no prior anti-angiogenic or PI therapy), in a 3+3 dose-escalation (MRZ 0.55 (6 pts), 0.7 (3 pts), and 0.8 mg/m2 (3 pts)) followed by dose-expansion (0.8 mg/m2, 24 pts). Treatments administered IV, 28-day cycles: MRZ (10 min) days 1, 8, & 15; BEV (10 mg/kg) days 1 & 15. Tumor response assessed every other cycle by RANO criteria; MRZ and BEV pharmacokinetics, and proteasome inhibition in circulating blood cells also evaluated. Data reported as of 17 May 2016; median age 55 yrs (range 27–76 yrs), 64% male, Karnofsky score ≥70. Duration of dosing 0.5–11.6 months to date; treatment ongoing in 16 pts. Study treatment-related Grade ≥3 AEs: fatigue, headache, hypertension, hallucination, confusional state, ataxia; one Grade 4 SAE (appendicitis perforated, not related to study treatment), one Grade 5 SAE (intracranial hemorrhage, BEV-related). One pt (cohort 1) had DLT (fatigue); no other DLTs occurred. N=36 for the intent-to-treat population; 30 pts efficacy evaluable by RANO criteria. Overall response (≥ partial response, PR) 39% (14/36, including 5 with complete target lesion response and 2 unconfirmed PRs); 11 stable disease, 5 progressive disease. PFS 6-months is 39%; median OS not yet reached. MGMT status known for 15 of 36 pts; 14 unmethylated (uMGMT), 1 methylated. Seven of 14 uMGMT pts achieved ≥PR; 49% PFS 6-months in uMGMT subgroup. Preliminary activity in uMGMT subgroup suggests therapeutic advantage provided by brain-penetrant PI in comparison with BEV single agent (Taal et al., 2014). MRZ+BEV combination is well tolerated with promising early signs of efficacy in recurrent G4 MG pts.

ACTR-51. PRELIMINARY SUPPORT FOR 4-DEMETHYL-4-CHOLESTERYLOXYCARBONYLPENCLOMEDINE (DM-CHOC-PEN) AS A CHEMOSENSITIZER IN CANCERS INVOLVING THE CNS

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BACKGROUND: DM-CHOC-PEN is a poly-chlorinated pyridine cholesteryl carbonate that has completed a Phase I/II study [AACR #1185, 2013; #CT129, 2016] in subjects with primary brain cancers and metastatic cancers involving the CNS. We review clinical and in vitro data that support radiosensitizing properties of DM-CHOC-PEN. PATIENTS AND METHODS: DM-CHOC-PEN was administered as a 3-hr IV infusion once every 21 days. The Phase II dose schedule was 2-tiered: 85.8 mg/m2 for subjects with liver involvement and 98.7 mg/m2 for subjects with normal livers. In vitro, human NSCLC adenocarcinoma cells (H-2086) growing in culture (106 cells/mL) were pre-treated with DM-CHOC-PEN (0.1 -1.0 μg/mL) for 24 hrs, drug washed, re-fed fresh medium and then 48 h later irradiated (RT @ 6, 9, 12 Gy). RESULTS: Fifty three (53) subjects have been treated to date. Five (5) subjects (3-NSCLC & 2-sarcomas) required surgery for persistent CNS lesions. DM-CHOC-PEN was identified in all samples. Two of those 5-subjects (1-sarcoma/1-NSCLC) plus 4 - additional subjects with persistent NSCLC lesions involving the CNS were treated then received SRS or WBRT. All had excellent results (OS 8+ - 26+ mos). Support from in vitro studies was: for DM-CHOC-PEN (0.1 -1.0 μg/mL) – cell kill was 50 & 100% @ 0.4 & 1.0 μg/mL, resp.; for RT (6, 9 &12 Gy) – cell kill was 20 & 65% @ 6 & 12 Gy, resp. [100% kill was not observed @ this dose range]; for DM-CHOC-PEN (0.25 μg/mL) + RT (6–12 Gy) – Cell kill was 80 & 100% @ 6 & 12 Gy, resp. Thus, in combination – less drug (0.25 μg/mL) and RT of 12 Gy – produced a 100% cell kill. CONCLUSION: DM-CHOC-PEN may act as cytotoxic drug for cancer in the CNS that is also a radiosensitizer.

ACTR-52. CLINICAL AND RADIOLOGICAL LONG TERM OUTCOME OF ACOUSTIC NEUROMAS (KOOS GRADE I – IV) AFTER STEREOTACTIC RADIOSURGERY

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INTRODUCTION: In the management of acoustic neuroma (AN) stereotactic radiosurgery (SRS) has evolved as widely accepted treatment option for small-sized tumors (Koos I and II). For larger AN (Koos III and IV) microsurgery is treatment of choice. However, for patients not suitable for microsurgery SRS might be an alternative that balances tumor control, hearing preservation. METHODS: In this single center retrospective analysis (1991 - 2015) we included all patients with previously untreated AN who underwent single session LINAC or Cyberknife® based SRS. Patient data were analyzed and correlated (Pearson`s coefficient) with the different Koos grades in terms of tumor control, preservation of hearing, course of median pure tone averages (PTA) and adverse events rated by Common Terminology Criteria for Adverse Events (CTCAE; v4.03). RESULTS: 301 patients (f:m=151:150, median age 59 years ±13.6, range 17–84) were identified with a mean follow-up of 50.9 months (range 3–265). Mean tumor volume was 1.85 ml ±2.4 (range 0.1–23.7). With regard to the Koos classification 52 patients were considered as grade I, 162 as grade II, 42 and 45 as grade III and IV, respectively. At last follow-up after SRS 94% of the patients showed radiological tumor control. There was no significant correlation ($p < 0.113$) between Koos grades I/II vs III/IV and radiological tumor control. Median PTA of Koos I/II tumors increased from 37,2 dB prior to SRS up to 55,6 dB at last follow-up and in case of Koos III/IV tumors from 46,2 dB up to 68,2 dB. The rate of transient facial nerve dysfunction and transient trigeminal nerve impairment each with CTCAE grade 1/2 occurred with a higher rate in Koos III/IV tumors. CONCLUSION: SRS for AN shows reliable long term tumor control and a high rate of hearing preservation and without considerable permanent side effects. Therefore, SRS can be proposed as safe and effective treatment option for AN, even with higher Koos grades.

ACTR-53. INTERIM ANALYSIS OF PHASE 1B/2 COMBINATION STUDY OF THE IDO PATHWAY INHIBITOR INDOXIMOD WITH TEMOZOLOMIDE FOR ADULT PATIENTS WITH TEMOZOLOMIDE-REFRACTORY PRIMARY MALIGNANT BRAIN TUMORS

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BACKGROUND: Indoleamine 2, 3-dioxygenase (IDO) is a key immunemodulatory enzyme within the IDO Pathway that inhibits CD8+ T cells and enhances the suppressor activity of Tregs. IDO is expressed in a large proportion of solid tumors including 50 to 90% of glioblastoma (GBM). IDO high expression is correlated with poor prognosis in GBM. IDO pathway inhibitors such as indoximod can improve anti-tumor T cell response slowing the tumor growth in vivo. We have demonstrated a synergistic effect of indoximod when combined with temozolomide (TMZ) and radiation in a syngeneic orthotopic brain tumor model. The purpose of this phase 1b/2 study is to determine the safety and preliminary efficacy of indoximod in