Title

ACTR-71. FULL ENROLLMENT RESULTS FROM THE PHASE 1/2, MULTICENTER, OPEN-LABEL STUDY OF MARIZOMIB (MRZ) ± BEVACIZUMAB (BEV) IN RECURRENT WHO GRADE IV MALIGNANT GLIOMA (GLIOBLASTOMA, RGBM)

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Clinical trials have showed that bevacizumab is beneficial for patients with recurrent glioblastoma and partially effective against newly diagnosed glioblastoma. However, glioblastoma patients with poor performance status (PS) were excluded from these clinical trials, and the efficacy of bevacizumab in such patients is unknown. Fifty-two patients with glioma were treated with bevacizumab between June 2013 and February 2016 in our institute. Of these patients, we focused on 29 patients with recurrent glioblastoma. We retrospectively analyzed the efficacy of bevacizumab in patients with recurrent glioblastoma and poor PS classified using the Karnofsky performance status ≤60 in comparison to historical controls which included patients who were not treated with bevacizumab before approval of bevacizumab in our institute. Progression-free survival was significantly longer in the bevacizumab arm than in the control arm only among patients with poor PS (poor PS: 5.3 months vs 2 months, P = 0.0362; good PS: 6.3 months vs. 3.4 months, P = 0.4163). Meanwhile, overall survival was better in the bevacizumab arm for both patients with good and poor PS, although the differences were not significant (good PS: 17.4 months vs. 10.3 months, P = 0.1009; poor PS: 7.8 months vs. 6.1 months, P = 0.4698). Serious adverse events occurred only in patients with poor PS. Bevacizumab extended PFS by 3 months in recurrent glioblastoma patients with poor PS. In consideration of the possibility of serious adverse events, however, bevacizumab use should be carefully considered in patients with poor PS.

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MRZ – an irreversible, brain-penetrant, pan-proteasome inhibitor with anti-glioma preclinical activity – was evaluated in BEV-naïve rGBM patients. **METHODS:** Phase 1 (P1) MRZ+BEV, 3 + 3 MRZ dose-escalation (N=6, 3, 3 at 0.55, 0.7, 0.8 mg/m2) followed by dose-expansion (N=24, 0.8 mg/m2). Phase 2 (P2) MRZ monotherapy (N=30, 0.8 mg/m2). Treatments (IV, 28-day (D) cycles): MRZ (10min infusion) D1, 8, 15; BEV (10 mg/kg) D1, 15. Tumor response (RANO criteria) every other cycle; MRZ and BEV PK, and proteasome inhibition in blood evaluated in P1. **RESULTS:** as of 14Apr2017: P1 mean age 55 yrs, 64% male, mean treatment duration 5.3 cycles, 1 patient active; P2 56 yrs, 57% male, 2.5 cycles, 6 patients active. One DLT (fatigue) in P1 at 0.55 mg/m2, no other DLTs. P1 treatment-related AEs (TRAEs Grade ≥3 in ≥2 patients): hypertension, headache, confusional state, fatigue, hallucination, proteinuria; three Grade 4 SAEs (appendicitis perforated, depressed level of consciousness, not-related; blindness, BEV-related), three Grade 5 SAEs (2 PD, not-related; intracranial hemorrhage, BEV-related). P2 TRAEs (Grade ≥3 in ≥2 patients): fatigue, hallucination, lethargy; one Grade 4 SAE (hallucination). P1 overall response (≥PR) 44% (16/36) including 1 CR, 15 PR; overall survival (OS) at 6/9/12 months (mos) 75/60/39%, median 9.4mos; OS 68/45/15% (median 7.2mos) in unmethylated MGMT (uMGMT, N=22), 78/78/67% (median not reached) in methylated MGMT (N=10). In P2: 1 PR, 6 SD; 4 patients (3 SD, 1 PR) ongoing at 5–10 cycles. P1 patients experiencing ≥1 CNS-related AEs (any grade: ataxia/balance disorder/dizziness/dysarthria/fall/gait disturbance/hallucination) have increased OS (83/74/45%, median 11.4mos, N=23) versus patients without these AEs (59/34/25%, median 6.3mos, N=13). **CONCLUSIONS:** MRZ monotherapy and MRZ+BEV active in rGBM overall and in uMGMT. Possible therapeutic improvement in patients experiencing CNS AEs will be explored in ongoing P2 MRZ+BEV extension allowing intra-patient MRZ dose-escalation if no CNS AE in first cycle (0.8 mg/m2).

ACTR-72. A PROSPECTIVE PHASE II RANDOMIZED TRIAL TO COMPARE INTENSITY MODULATED PROTON RADIOTHERAPY (IMPT) VS. INTENSITY MODULATED RADIOTHERAPY (IMRT) FOR NEWLY DIAGNOSED GLIOBLASTOMA (GBM)

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PURPOSE: To determine if IMPT compared to IMRT delayed time to cognitive failure in patients with newly diagnosed GBM. **METHODS:** Eligible patients were randomized to IMPT vs. IMRT. Randomization was stratified for RPA class (III-IV vs. V), Mini Mental Status Examination score (21–26 vs. 27–30) and age (< 65 vs. 65 or older). The primary endpoint was time to cognitive failure on any of the 6 cognitive outcomes (HVLT-R, TMT, COWA) with failure defined as a decline that met or exceeded the reliable change index (RCI). **RESULTS:** A total of 90 patients were enrolled (45 per arm) and 75 were evaluable with median follow-up of 14.5 (0.1, 32.1) months; median of 7.0 (0.1, 25.4) months for IMPT (n=32) vs. 25.6 (1.5, 32.1) months for IMRT (n=43). There were no differences in sociodemographic characteristics or baseline cognitive function between arms. Time to cognitive failure was shorter in the IMPT arm vs. the IMRT arm ($p<0.05$) and cumulative incidence of cognitive deterioration at 4 months was 0.593 (0.378, 0.755) IMPT vs. 0.372 (0.224, 0.52) IMRT. The number of grade 2 or higher toxicities were greater in patients who received IMRT (n=21) vs. IMPT (n=9). **CONCLUSIONS:** Preliminary results of this study suggest IMPT is not associated with a delay in time to cognitive failure but did reduce toxicity. Additional evaluation of the impact of tumor location and volume, radiation dosimetry, and tumor molecular subtypes on cognition is ongoing. Larger randomized trials are needed to determine the impact of IMPT vs. IMRT on GBM tumor control and survival.

ACTR-73. A PHASE II STUDY OF TUMOR TREATING FIELDS IN COMBINATION WITH BEVACIZUMAB AND TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED, UNRESECTABLE GLIOBLASTOMA

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BACKGROUND: Patients with newly diagnosed, unresectable glioblastoma multiforme (GBM) will usually receive concurrent temozolomide (TMZ) and radiation therapy. Some patients will also receive bevacizumab (BEV) if clinically indicated. Tumor treating fields (TTFields) have also been shown to be safe and effective for treatment of GBM. The concurrent use of TTFields in newly diagnosed, unresectable GBM patients, with the combination of TMZ and BEV may provide clinical benefit. **OBJECTIVE:** The primary objective of this phase II study is to assess the efficacy of the administration of TMZ and BEV with concurrent use of TTFields by evaluating the percentage of newly diagnosed unresectable GBM patients who are alive at 12 months. **TRIAL DESIGN:** This is an open label, single-arm, phase II protocol. Patients ≥22 years of age with histologically confirmed GBM, planned 6 weeks of concurrent chemo-radiotherapy (45-70Gy) post-biopsy concomitant with TMZ, a KPS score ≥70 and a life expectancy of >3 months are eligible to participate. All patients will complete best standard of care radiation, TMZ and BEV (6 weeks). Within two weeks of completion of this initial treatment period, study patients will be treated continuously with TTFields (Optune™). The patients will also continue with maintenance TMZ/BEV. Patients will be followed for evaluation of progression-free-survival, overall survival, quality of life (QoL), safety and exploratory objectives. This study will be carried out in two stages. The first stage will enroll a cohort of 22 patients. Enrollment and interim analysis of the first cohort of patients will be completed within 15 months. The second stage will enroll a cohort of 24 patients and will be completed within 15 months of stage 2 commencements. The duration of the study is expected to be no longer than 30 months (NCT02343549).

ACTR-74. A PHASE IB/II, OPEN-LABEL, MULTICENTER STUDY OF CAPMATINIB (INC280) ALONE AND IN COMBINATION WITH BUPARLISIB (BKM120) IN ADULT PATIENTS WITH RECURRENT GLIOBLASTOMA

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