Title

ACTR-45. A PHASE 1, MULTICENTER, OPEN-LABEL STUDY OF MARIZOMIB (MRZ) WITH TEMOZOLOMIDE (TMZ) AND RADIOTHERAPY (RT) IN NEWLY DIAGNOSED WHO GRADE IV MALIGNANT GLIOMA (GLIOBLASTOMA, ndGBM)

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ALS: In 2015, we adopted a current practice protocol of treating all primary GBM patients with TTFs during the adjuvant TMZ component of their therapy. We used support groups and consistent messaging across specialties to encourage all patients to initiate TTFs. Thirty-four patients underwent maximal surgical debulking, completed radiotherapy with concurrent TMZ, and initiated adjuvant TMZ. We performed this univariate and multivariate analysis of patient, tumor, and treatment related factors to assess their association with overall survival. **RESULTS:** Of the 34 patients, 20 were male and the median age was 62 years (range, 26 to 79). ECOG performance status was 0 in 20 patients, 1 in 10, 2 in 3, and 4 in 1. Seventeen patients underwent GTR, while 11 had STR and six had biopsy only. We divided TTF compliance into 3 subgroups: 9 patients that refused to start TTFs, 15 patients with monthly compliance of 1 to 75%, and 10 patients with compliance greater than 75%. With a median follow up of 9.7 months, the median overall survival for all patients was 19 months and the 1-year survival was 59%. Univariate analysis of factors associated with 1-year survival revealed TTF compliance (refused, 0% vs. compliance 1–75%, 65% vs. compliance >75%, 83%, p=0.04), ECOG performance status (ECOG 2–4, 0% vs. ECOG 0/1, 63%, p<0.001), extent of resection (biopsy only, 0% vs. STR, 67% vs. GTR 79%, p<0.001) and age (>65, 36% vs. ≤65, 65%, p=0.06) as significant. On multivariate analysis TTF compliance (p=0.001), ECOG performance status (p=0.02), and extent of surgical resection (p=0.01) remained significant. **CONCLUSIONS:** TTF compliance is associated with improved OS and is independent of performance and resection status. The neuro-oncology community should focus on barriers to TTF use.

ACTR-44. AUTOPSY STUDY ON THE EFFECTS OF TUMOR TREATMENT FIELDS IN RECURRENT GLIOBLASTOMA: PRELIMINARY RESULTS AND TRIAL DESIGN

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BACKGROUND: Optune therapy with tumor treatment fields (TTFields) is approved for the treatment of recurrent glioblastoma due to a recent clinical trial that showed better quality of life and comparable overall survival to conventional therapy. In the newly diagnosed setting, the addition of TTFields to standard therapy consisting of surgery, radiation and temozolomide has also been shown to prolong tumor progression and improve overall survival. TTFields are low-intensity, alternating frequency electric fields that have been shown to disrupt cell division and subsequently tumor growth. Apoptosis and cell cycle arrest have been seen in vitro, and shown in mice and rabbit tumor models. Though preclinical studies are ongoing, glioblastoma patients who have undergone TTFields therapy have not yet been assessed at autopsy to determine both the pathological signature of TTFields therapy, and the pattern of failure. **METHODS:** Whole brain samples were acquired and analyzed pathologically from two recurrent GBM patients at autopsy. One patient served as a control and one considered a test patient who had undergone TTFields therapy. Tissue samples were acquired from regions suspicious of tumor and treatment effects. Samples were paraffin embedded and hematoxylin and eosin (H&E) stained, and pathologically reviewed by a board certified pathologist. Samples were then compared. **RESULTS:** The patient who underwent TTFields therapy showed regions of necrosis and increased cellular debris compared to the control patient who had pseudo-palisading and radiation necrosis. **CONCLUSION:** These findings suggest there is increased apoptosis in patients treated with TTFields compared to those on chemoradiation alone. Recruitment is ongoing for expansion of this study to include 10 patients treated with TTFields at recurrence and 10 at treated at initial diagnosis. Patients will be recruited from brain donation. Pathology will be compared to control patients naïve of TTFields therapy.

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Proteasome inhibition sensitizes glioma cells to TMZ and RT, providing a novel therapeutic strategy for ndGBM. MRZ -- an irreversible, brain-penetrant, pan-proteasome inhibitor with anti-glioma preclinical activity -- is being evaluated in ndGBM patients (NCT02903069). The phase 1 study (MRZ at 0.55, 0.7, 0.8, 1.0, and 1.2 mg/m^2) is accruing in separate concomitant (MRZ+TMZ+RT) and adjuvant (MRZ+RT) treatment cohorts (3 + 3 design), followed by dose-expansion at the recommended phase 2 dose in concomitant followed by adjuvant treatment cohorts. Concomitant treatment (42 days (D)): MRZ (10 min IV infusion) D1, 8, 15, 29, 36; RT total dose 60 Gy; TMZ (75 mg/m^2, PO QD). Adjuvant treatment (28D-cycle): MRZ D1, 8, 15; TMZ (150–200 mg/m^2, PO QDX5). Tumor response (RANO criteria) measured at beginning and end of concomitant treatment, and every other cycle during adjuvant treatment; MRZ and TMZ PK in concomitant treatment D1-2, 8–9. Mean age 55 yrs (60% male) for 20 patients in 14Apr2017 interim analysis (cohorts 1–3 have completed accrual in concomitant treatment, cohorts 1 and 2 have completed accrual and 2 patients are enrolled in adjuvant cohort 3); one DLT (fatigue) in the 0.7 mg/m^2 adjuvant cohort. Most common treatment-related AEs (≥4 pts): fatigue, nausea, vomiting, decreased appetite, dizziness, hallucination; three Grade 3 SAEs (fatigue, hallucination, vomiting; all MRZ-related); two Grade 2 SAEs (nausea, confusional state, MRZ-related). Seventeen of the 20 patients included in this interim analysis remain on study: 7 of 9 concomitant patients are continuing in adjuvant treatment (longest beginning adjuvant cycle 7); of 11 adjuvant pts, two beginning cycle 9. The study is ongoing at 1.0 mg/m^2 for both concomitant and adjuvant dose-escalation cohorts. Together the data demonstrate that the combination of MRZ with standard of care in ndGBM is well tolerated and may provide novel therapeutic benefit in this unmet need.

ACTR-46. AG-120, A FIRST-IN-CLASS MUTANT IDH1 INHIBITOR IN PATIENTS WITH RECURRENT OR PROGRESSIVE IDH1 MUTANT GLIOMA: UPDATED RESULTS FROM THE PHASE 1 NON-ENHANCING GLIOMA POPULATION

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INTRODUCTION: Isocitrate dehydrogenase 1/2 (IDH1/2) mutations occur in >70% of low-grade gliomas (LGG) and lead to an altered metabolic state associated with production of D-2-hydroxyglutarate (2-HG), resulting in genetic/epigenetic dysregulation and oncogenesis. AG-120 is a potent oral inhibitor of mutant IDH1 (mIDH1) under clinical evaluation in an ongoing phase 1 study that treated 66 pretreated (median 2 prior systemic therapies) glioma patients in dose escalation and expansion cohorts. Safety and preliminary results were presented previously (SNO2016). We present updated results from the non-enhancing glioma patient population. **METHODS:** Key eligibility: mIDH1 recurrent or progressive disease, ECOG 0–1, no surgery/radiation within 6 months. MRI response was assessed every 8 weeks using RANO and LGG-RANO criteria by local and independent central review. Exploratory analyses: change in tumor growth rate (FLAIR tumor volume, non-enhancing glioma expansion cohort) and pharmacodynamic evaluations of tissue and serum. **RESULTS:** As of 10March2017, 35 patients with non-enhancing glioma were enrolled in dose escalation (n=11) and expansion (n=24), and 51% (n=18) remain on AG-120. M/F 23/12, median age 38 years, 1p19q intact in 54% (n=19) of patients, 74% reported anticonvulsant use. Frequent (≥5 patients) adverse events (AEs) grade 1–2: diarrhea (26%), headache (26%), nausea (20%), anemia (17%), neutrophil decrease (17%), and vomiting (17%). 7 (20%) patients experienced a grade 3–4 AE (hypophosphatemia most frequent, n=2, unrelated), with no dose reduction due to AEs. 73% and 88% of patients achieved stable disease as best response in the dose escalation (RANO) and expansion (LGG-RANO) cohorts, respectively. Median duration on AG-120 was 14.7 months (range 1.4–25.0); 63% remained on AG-120 for ≥1 year. Updated safety, response, and exploratory imaging analyses will be presented. **CONCLUSIONS:** AG-120 monotherapy is associated with