ACTR-46. AG120, A FIRST-IN-CLASS MUTANT IDH1 INHIBITOR IN PATIENTS WITH RECURRENT OR PROGRESSIVE IDH1 MUTANT GLIOMA: RESULTS FROM THE PHASE 1 GLIOMA EXPANSION COHORTS

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INTRODUCTION: Isocitrate dehydrogenase 1 (IDH1) mutations occur in approximately 70% of low grade gliomas and in up to 6% of glioblastomas, and lead to an altered metabolic state associated with increased production of 2-hydroxyglutarate (2-HG) which causes genetic and epigenetic dysregulation leading to oncogenesis. AG120 is a potent oral inhibitor of mutant IDH1 demonstrating suppression of 2-HG in preclinical models and reduced tumor growth in the xenograft TS603 glioma model. In the dose escalation portion of this phase 1 study, AG120 was administered daily over a 28 day cycle at doses up to 1200mg in 20 patients with IDH1 mutant glioma who had measurable disease by RANO criteria. AG120 demonstrated a favorable safety profile and preliminary clinical activity with a 31% (95% CI: 15–49) objective response rate with grade 2 or higher tumor responses in 12 of 24 patients (50%) at 6 months of follow-up. Patients were restaged per RANO criteria every 6 weeks with response assessments via RANO. RESULTS: Twenty-four patients were enrolled in seven dose-escalation cohorts (140–220 mg/m2). No DLTs were reported. Median and 6-month PFS were 5.5 mo. [95% CI: 4.1–8.2] and 40%, respectively. At time of abstract submission, median and 1-year OS were 12.9 mo. [95% CI: 10.9–17.9] and 60%, respectively, after 20.2 mo. Median follow-up. CONCLUSION: TPI 287 dose-escalation cohorts (140–220 mg/m2). No DLTs were reported and myelosuppression (n=3) was the only drug-related grade 3/4 adverse event. Ten patients achieved SD and 1 patient showed progressive disease at first scan. Among 20 patients evaluable for response, ORR was 60% (12/20), 3 complete, 9 partial. The median and 6-month PFS was 5.5 mo. [95% CI: 4.1–8.2] and 40%. At time of abstract submission, median and 1-year OS were 12.9 mo. [95% CI: 10.9–17.9] and 60%, respectively, after 20.2 mo. Median follow-up. CONCLUSION: TPI 287 dose-escalation cohorts (140–220 mg/m2). No DLTs were reported. Median and 6-month PFS were 5.5 mo. [95% CI: 4.1–8.2] and 40%, respectively. At time of abstract submission, median and 1-year OS were 12.9 mo. [95% CI: 10.9–17.9] and 60%, respectively, after 20.2 mo. Median follow-up. CONCLUSION: TPI 287 dose-escalation cohorts (140–220 mg/m2). No DLTs were reported. Median and 6-month PFS were 5.5 mo. [95% CI: 4.1–8.2] and 40%, respectively. At time of abstract submission, median and 1-year OS were 12.9 mo. [95% CI: 10.9–17.9] and 60%, respectively, after 20.2 mo. Median follow-up. CONCLUSION: TPI 287 dose-escalation cohorts (140–220 mg/m2). No DLTs were reported. Median and 6-month PFS were 5.5 mo. [95% CI: 4.1–8.2] and 40%, respectively. At time of abstract submission, median and 1-year OS were 12.9 mo. [95% CI: 10.9–17.9] and 60%, respectively, after 20.2 mo. Median follow-up. CONCLUSION: TPI 287 dose-escalation cohorts (140–220 mg/m2). No DLTs were reported. Median and 6-month PFS were 5.5 mo. [95% CI: 4.1–8.2] and 40%, respectively. At time of abstract submission, median and 1-year OS were 12.9 mo. [95% CI: 10.9–17.9] and 60%, respectively, after 20.2 mo. Median follow-up. CONCLUSION: TPI 287 dose-escalation cohorts (140–220 mg/m2). No DLTs were reported. Median and 6-month PFS were 5.5 mo. [95% CI: 4.1–8.2] and 40%, respectively. At time of abstract submission, median and 1-year OS were 12.9 mo. [95% CI: 10.9–17.9] and 60%, respectively, after 20.2 mo. Median follow-up. CONCLUSION: TPI 287 dose-escalation cohorts (140–220 mg/m2). No DLTs were reported. Median and 6-month PFS were 5.5 mo. [95% CI: 4.1–8.2] and 40%, respectively. At time of abstract submission, median and 1-year OS were 12.9 mo. [95% CI: 10.9–17.9] and 60%, respectively, after 20.2 mo. Median follow-up. CONCLUSION: TPI 287 dose-escalation cohorts (140–220 mg/m2). No DLTs were reported. Median and 6-month PFS were 5.5 mo. [95% CI: 4.1–8.2] and 40%, respectively. At time of abstract submission, median and 1-year OS were 12.9 mo. [95% CI: 10.9–17.9] and 60%, respectively, after 20.2 mo. Median follow-up.
Abstracts

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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MRZ is an irreversible, brain-penetrant, pan-proteasome inhibitor (PI) with anti-MG efficacy preclinically in vitro and in vivo. The safety, pharmacokinetics, and activity of MRZ+BEV is evaluated in BEV-naive G4 MG patients in 1st or second line (treatment of record, 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 dosed 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 ≥1.6 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.

ACTR-51. PRELIMINARY SUPPORT FOR 4-DEMETHYL-4-CHOLESTERYLOXACYRONYLPCENLOMEDINE (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 III trial [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 3-4 Gy fractionated RT on 21 days. The Phase II dose schedule was 2-tiered: 85.4 mg/m2 for subjects with liver involvement and 98.7 mg/m2 for subjects with normal livers. In vitro, human NSCLC adenocarcinoma cells (H-2866) growing in culture (106 cells/mL) were pretreated with DM-CHOC-PEN at concentrations from 0.1 to 2.0 µg/mL for 24 hrs, drug washed, re-fed fresh medium and then 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 metastases. DM-CHOC-PEN 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 ≥1.6 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.

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 we compared AN patients with good and poor hearing after surgery (Koos III and IV) 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 30.9 months (range 3–263). 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 III, 162 as grade II, 45 and as grade 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 III vs IV and radiological tumor control. Median PTA of Koos III tumors increased from 37.2 dB before to 49.5 dB after resection (in situ) and of excised tissue (ex vivo) using a NIR camera. At last follow-up after SRS 94% of the patients showed radiological 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 METASTASIZED PRIMARY MALIGNANT BRAIN TUMORS

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BACKGROUND: Indoleamine 2, 3-dioxygenase (IDO) is a key immune-modulatory 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 30 to 90% of glioblastoma (GBM). IDO has no exclusive restrictions and is reported in glial, stromal, and immune cells. 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