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AZD1775 is an oral small molecular inhibitor of the G2/M checkpoint regulator Wee1. The Adult Brain Tumor Consortium 1202 trial (NCT01849146) is a phase I, open label, multicenter dose-finding study of AZD1775 in combination with standard RT and TMZ followed by an IDD study for patients undergoing surgery for recurrent GBM. Dose of AZD1775 was increased in a 3 + 3 design M-F during concurrent RT/TMZ and x 5d/28d cycle with adjuvant TMZ in separate cohorts. A combination cohort with both concurrent and adjuvant AZD1775 at MTD and analysis of PK/PD and IDD at MTD in patients undergoing surgery for recurrent GBM followed. MTD was 200 mg for concurrent with 2/6 patients experiencing DLTs (grade 4 neutropenia, grade 3 ALT elevation). MTD for the adjuvant cohort was 425 mg with 1/6 patients experiencing DLT (grade 4 decrease in ANC). 6/12 patients experienced DLTs when cohorts were combined, however, five during the concurrent phase. Three patients had grade ≥3 ALT/AST elevation, one had grade 3 afib, and one had grade 4 neutropenia/thrombocytopenia, grade 3 dehydration/fatigue/muscle weakness. A sixth patient had grade 4 neutropenia in the first adjuvant cycle. Following amendment, an additional 6 patients were enrolled with 150 mg (concurrent) and 425 mg (adjuvant) combination and are in the observation period with one DLT currently. Drug concentration in contrast enhancing and non-enhancing brain tumor was 4–8 x and 0.5–2.6 x greater than plasma, respectively for patients on IDD portion. CONCLUSIONS: AZD1775 in combination with RT/TMZ at 200 mg qd M-F with concurrent RT/TMZ and 425 mg qd x 5d/28d cycle in combination with adjuvant TMZ had unacceptable DLT rate in the concurrent phase. A cohort with 150 mg concurrent/425 mg adjuvant has competed accrual with acceptable rates of toxicity currently in observation. AZD1775 has good penetration to non-enhancing and enhancing tumor areas.

ACTR-15. SAFETY AND PRELIMINARY ACTIVITY OF PT2385, A FIRST-IN-CLASS HIF2-ALPHA INHIBITOR, PLANNED INTERIM ANALYSIS OF AN OPEN LABEL, SINGLE-ARM PHASE II STUDY IN PATIENTS WITH RECURRENT GLIOBLASTOMA

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BACKGROUND: Hypoxia inducible factor 2-alpha (HIF2a) is a stress response transcription factor that mediates the cellular response to hypoxia. HIF2a is an underexplored target in glioma. PT2385 is a first-in-class oral HIF2a inhibitor with favorable blood-brain barrier penetrating properties and *in vivo* single-agent activity against glioblastoma (GBM). METHODS: A single-arm open-label phase II study of adults with bevacizumab-naïve first recurrence of GBM following chemoradiation with measurable disease was conducted within the Adult Brain Tumor Consortium. PT2385 was administered at the recommended phase II dose (800 mg b.i.d.). The primary study outcome is objective radiographic response (CR+PR). Secondary objectives are safety, overall survival, and progression-free survival. Patients at selected study sites underwent pH-weighted amine-CEST MRI imaging to quantify tumor acidity at baseline and explore associations with drug response. Results of planned interim analysis are presented. RESULTS: 24 patients were enrolled; mean age 61 ± 11 years, 63% male, 92% white, median KPS 80. MGMT promoter was methylated in 46%, unmethylated in 50%, and indeterminate in 1 patient. Prior surgery included biopsy (8%), subtotal (38%) and gross total resection (54%). To date, 21 patients have progressed at a median of 7.7 weeks (95%CI 4.66–12.3 weeks). No objective radiographic responses have been observed. Three patients continue on treatment at a median of 19 weeks (95%CI 12–19.1). The drug was well tolerated with expected side effect profile. Common Grade 1–2 drug-related adverse events were anemia, dyspnea, and thrombocytopenia. Grade 3–4 drug-related adverse events included hypoxia (n=2, 8%), anemia (n=1, 4%), and hypophosphatemia (n=1, 4%). At baseline, pH-weighted MRI showed high levels of acidity and intratumoral heterogeneity. PK and PD data are forthcoming. CONCLUSIONS: Results of this planned interim analysis suggest that single-agent PT2385 has acceptable safety but minimal activity in glioblastoma patients after first recurrence. Ongoing analysis will explore patterns of progression and correlate these with tumor acidity measurements.

ACTR-16. PERIPHERAL BLOOD CD4+ MONONUCLEAR CELL FRACTIONS ARE ASSOCIATED WITH OVERALL SURVIVAL AT FIRST RECURRENCE OF IDH-WILDTYPE GLIOBLASTOMA AFTER STANDARD CHEMORADIOTHERAPY: SECONDARY ANALYSES OF THE PHASE II DIRECTOR TRIAL

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The alkylating agent temozolomide prolongs survival of glioblastoma patients through induction of futile DNA mismatch repair in cancer cells. Whether systemic temozolomide effects on the immune system affect outcome has not been studied in detail. To address this question, we analyzed peripheral blood mononuclear cells (PBMC) of N=52 clinically well-annotated patients with recurrent, isocitrate dehydrogenase (IDH)-wildtype glioblastoma and of N=21 healthy donors by 11-color flow cytometry. Patients were treated within the randomized phase II trial DIRECTOR, which explored the efficacy of two dose-intensified temozolomide regimens at first recurrence of glioblastoma after standard chemoradiotherapy with first-line temozolomide. There were no efficacy differences between both dose-intensified temozolomide schedules in this trial. Unsupervised clustering of flow cytometry annotations identified two patient clusters, which differed in CD4+ T-cell fractions, but not with respect to CD8+ T-cells, CD4+;CD25+;FoxP3+ regulatory T-cells, B-cells or monocytes. All control samples clustered with the $CD4_{high}$ cluster. Patients in both clusters did not differ by age, gender, O6-methylguanine-DNA-methyl-transferase (*MGMT*) gene promoter methylation, tumor volume, Karnofsky performance score (KPS), number of first-line temozolomide cycles or steroid use. Progression-free survival was similar ($CD4_{high}$ *vs* $CD4_{low}$2.1 *vs* 2.4 months, p=0.19), whereas overall survival was longer in the $CD4_{high}$ cluster of patients (12.7 *vs*8.7 months, p= 0.004). In a multivariate Cox model of overall survival that controlled for established prognostic factors, we found associations with overall survival for KPS (p=0.019), high CD4+ fractions (p=0.052) with relevant interactions with cluster assignment (p=0.058), residual tumor at study entry (p=0.068) and *MGMT* promoter methylation (p=0.072), but not age (p=0.96) or steroid use at study entry (p=0.32). There were no interactions of cluster assignment or CD4+ fractions with steroid use in this model. We conclude that temozolomide-associated CD4+ T-cell depletion may have unfavorable effects on the survival of glioblastoma patients, a finding that warrants further exploration.

ACTR-17. EVOPHOSPHAMIDE (TH-302) FOR RECURRENT GBM FOLLOWING BEVACIZUMAB FAILURE, FINAL RESULTS OF A MULTICENTER PHASE II STUDY

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INTRODUCTION: Evophosphamide is a hypoxia-activated prodrug that, when activated in hypoxic conditions, (<0.5% O2), releases the bis-alkylating agent bromo-isophosphoramide mustard (Br-IPM). Our prior phase 1 study in recurrent GBM (rGBM) with dose expansion showed preliminary activity with a 24% objective response rate and a 26% PFS rate at 4 months. METHODS: A multicenter, single-arm, two-stage prospective study, non-blinded with combination therapy with bevacizumab at 10 mg/kg intravenously (IV) every 2 weeks and TH-302 at 670 mg/m2 IV every 2 weeks, in 6 week cycles, until disease progression. The primary endpoint was progression free survival at 4 months (PFS4). Patients underwent baseline assessment for hypoxic burden by 18F-misonidazole PET, dynamic susceptibility contrast (DSC) perfusion imaging, and serum sampling for biomarker analysis. RESULTS: 36 patients received study drug. Treatment was well tolerated, with adverse events as expected and the most common toxicity rash along the perineum. The PFS4 rate was 25% which met the primary endpoint and compares favorably with historical controls (10%). Biomarker analysis revealed progression to be correlated with Tmax on DSC perfusion

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