Title

ACTR-66. A PHASE 1, OPEN-LABEL, PERIOPERATIVE STUDY OF IVOSIDENIB (AG-120) AND VORASIDENIB (AG-881) IN RECURRENT IDH1 MUTANT, LOW-GRADE GLIOMA: UPDATED RESULTS

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BACKGROUND: Therapies targeting multiple survival pathways are desirable for high-grade gliomas. TG02 (Zotiraciclib), a CDK9 inhibitor, regulates transcription and metabolism of tumor cells and synergizes with temozolomide. A phase I/II trial was launched to test the TG02/temozolomide combined treatment in recurrent high-grade astrocytomas. Phase I results are reported here. METHODS: Adults with recurrent high-grade astrocytoma, KPS≥60, adequate organ function, < 2 prior relapses were enrolled. Primary endpoint was dose limiting toxicity (DLT) in cycle1 in each arm. Bayesian optimal interval design was employed to determine the maximum tolerated dose (MTD) with the target DLT rate of 35% and the toxicity profile of the combination of TG02 (starting dose 200mg orally on days1,12,15, and 26) and temozolomide, either as a dose-dense (DD; 125mg/m2/d, 7on/7off, Arm1) or metronomic (MN; 50mg/m2/d, Arm2) dosing schedule on a 28-day cycle. RESULTS: Thirty-eight patients were evaluable; median age 50.7, KPS 90. Of 18 evaluable patients in Arm1, at TG02 dose-level 200mg, 1/6 had a DLT: Gr3 diarrhea; at dose-level 250mg, 3/12 had DLTs: Gr4 neutropenia for over 5 days, Gr3 elevated ALT, and Gr3 fatigue. Of 20 evaluable patients in Arm2, at TG02 dose-level 200mg, 1/6 had a DLT: recurrent Gr3 neutropenia; at dose-level 250mg, 5/12 had a DLT: Gr3 elevated ALT, Gr3 fatigue, and Gr4 neutropenia; at dose-level 300mg,1 of 2 had a DLT: Gr4 febrile neutropenia, Gr4 elevated ALT, Gr4 elevated AST. TG02 dose-level of 250mg was declared as the MTD in both Arms. Using the MDASI-BT, patients with high symptom burden had increased symptoms during cycle1 but became stable as they continued treatment. CONCLUSION: The combination of TG02 at the MTD of 250mg with DD or MN temozolomide was tolerated. Cohort expansion continues at the MTD in both arms. Objective responses have been observed, suggesting activity of this regimen and supporting continued investigation.

ACTR-63. PHASE I DOSE ESCALATION STUDY OF PROCASPASE ACTIVATING COMPOUND-1 (PAC-1) IN COMBINATION WITH TEMOZOLOMIDE IN PATIENTS WITH RECURRENT ANAPLASTIC ASTROCYTOMA OR GLIOBLASTOMA

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BACKGROUND: Procaspase activating compound -1 (PAC-1) is a small molecule that catalyzes conversion of procaspase-3 to caspase-3 which induces apoptosis in cancer cells. Glioblastoma (GBM) is among the tumors with high concentrations of procaspase-3 and low levels of caspase-3. PAC-1 crosses the blood brain barrier and has been shown to synergize with temozolomide (TMZ) in canine malignant glioma and meningioma that arise spontaneously. METHODS: This is a multicenter phase 1 dose-escalation study to assess the maximum tolerated dose (MTD) of PAC-1 administered days 1–21 in combination with TMZ days 8–12 at a dose of 150 mg/m2 of each 28 day cycle in subjects with recurrent anaplastic astrocytoma (AA) or GBM. A modified Fibonacci 3 + 3 design is used with up to 4 dose levels of PAC-1 (375, 500, 625 and 750 mg/day). Neurologic toxicity, including cognitive function, is closely monitored throughout the trial. INTERIM DATA: A total of 14 subjects have been enrolled to-date. Of these, 7 at dose level 1, PAC-1 375 mg/day (6 GBM, 1 AA; median age 58y, range 25–75) and 7 at dose level 2, PAC-1 500 mg/day (5 GBM, 2 AA; median age 51y, range 35–60). Best responses to-date were 2 subjects with a partial response and 2 with stable disease. Grade 3 (hepatotoxicity) and 4 (cerebral edema) was reported as possibly related to PAC-1 in 1 patient at dose level 1. The median number of cycles received was 4 (range, 1–12+) at dose level 1 and 2 (range, 1–3) at dose level 2. Enrollment to dose level 2 has been completed and data analysis is ongoing. Updated response and toxicity as well as pharmacokinetic data will be presented.

ACTR-64. PHASE 2 STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS AND CLINICAL ACTIVITY OF PI3K/mTOR INHIBITOR GDC-0084 IN GBM PATIENTS WITH UNMETHYLATED O_6-METHYLGUANINE-METHYLTRANSFERASE (MGMT) PROMOTER STATUS

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BACKGROUND: GDC-0084 is a potent, oral, selective small molecule inhibitor of class I phosphoinositide 3-kinase and mammalian target of rapamycin (PI3K/mTOR). GDC-0084 crosses the blood-brain barrier and achieves a brain / plasma ratio of approximately 1.0. GDC-0084 was given as once daily dosing in a phase 1 study (Wen *et al*, J Clin Oncol 34, 2016(15) suppl.2012) in 47 patients with recurrent high-grade gliomas. The adverse events were generally consistent with the established PI3K/mTOR inhibitor class-effects. The MTD identified was 45mg once daily. METHODS: The current study is conducted in the newly diagnosed GBM patient with unmethylated MGMT promotor status upon completion of standard adjuvant XRT/TMZ. It has a 2-part design: an open-label, dose-escalation phase to assess the safety, tolerability, MTD (Part 1, followed by an expansion cohort (Part 2) commencing once MTD is established. Dose-escalation started at 60mg, and progressed in 15mg increments, per standard 3 + 3 rules. Part 2 recruits 20 patients, who are randomized to take GDC-0084 at the identified MTD, in fed and fasted states. RESULTS: Part 1 of the study is complete. There were no DLTs among 3 pts treated at the 60mg. Among 6 pts treated at 75mg, DLTs were identified as hyperglycaemia (symptomatic) and oral mucositis. Adverse effects seen were generally modest, manageable and consistent with the PI3K-class. PK parameters are in line with phase 1 data. Part 2 recruitment is ongoing. CONCLUSION: GDC-0084 displays a safety profile consistent with previous data in recurrent high-grade glioma but appears better tolerated in the newly diagnosed GBM setting. An MTD of 60mg is identified.

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BACKGROUND: Ivosidenib (AG-120, IVO) is a first-in-class oral inhibitor of mutant isocitrate dehydrogenase 1 (mIDH1), and vorasidenib (AG-881, VOR) is an oral, potent, brain-penetrant inhibitor of mIDH1/2. Both have been evaluated in glioma patients in ongoing phase 1 studies. In orthotopic glioma models, IVO and VOR reduced 2-hydroxyglutarate (2-HG) levels by 85% and 98%, respectively, despite different brain-to-plasma ratios (< 0.04 vs 1.33). METHODS: Patients with recurrent, nonenhancing, WHO-2016 grade 2/3, mIDH1-R132H oligodendroglioma or astrocytoma undergoing craniotomy were randomized 2:2:1 to IVO 500mg QD, VOR 50mg QD, or no treatment (cohort 1), or 1:1 to IVO 250mg BID or VOR 10mg QD (cohort 2), for 4 weeks preoperatively. Postoperatively, patients continued receiving IVO or VOR (control patients were randomized 1:1 to IVO or VOR). Tumors were assessed for mIDH1 status, cellularity, and 2-HG and drug concentrations. Treated subjects were compared with controls and mIDH1/wild-type banked reference samples. Primary endpoint: tumor 2-HG concentration following IVO or VOR. RESULTS: As of March 1, 2019, 27 patients (18 men; 25/2 grade 2/3) were randomized preoperatively in cohort 1 (IVO 10, VOR 12, untreated 5): 27 received drug (IVO 13, VOR 14); 1 discontinued VOR postoperatively due to disease progression. Of 26 tumors analyzed, 22 were evaluable. Mean brain-to-plasma ratios: 0.13 IVO, 1.59 VOR. Relative to untreated samples, IVO and VOR reduced tumor 2-HG by 92.0% (95% CI 73.2, 97.4) and 92.5% (95% CI 78.1, 97.7), respectively. Common (≥ 4 patients) TEAEs (all cohort 1 patients, all grades): diarrhea (37.0%), constipation, hypocalcemia, and nausea (each 18.5%), anemia, hyperglycemia, pruritus, headache, and fatigue (each 14.8%). Cohort 2 has completed accrual, with analyses ongoing. CONCLUSIONS: In cohort 1 of this phase 1 perioperative study, IVO and VOR demonstrated brain penetrance and lowered 2-HG compared with controls. Updated data from both cohorts will be presented.