Title

ACTR-31. PHASE 1 STUDY OF AG-881, AN INHIBITOR OF MUTANT IDH1 AND IDH2: RESULTS FROM THE RECURRENT/PROGRESSIVE GLIOMA POPULATION

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DNA damage caused by TMZ or RT sensitizes tumors to PARP inhibitors, especially in highly replicating tumors (eg, GBM). Pamiparib is a selective PARP1/2 inhibitor with potent PARP trapping that can cross the blood-brain barrier and has shown synergistic cytotoxicity with TMZ in non-clinical experiments. At 60mg BID, the human-equivalent dose-to-trough brain concentrations above the nonclinical efficacy threshold, pamiparib was generally well tolerated and showed antitumor activity in early clinical studies (NCT02361723; NCT03333915). This ongoing dose-escalation/expansion study (NCT03150862) will determine the safety/tolerability and antitumor effects of pamiparib (60mg BID)+RT and/or TMZ. The dose-escalation component consists of three arms. Arm A will establish tolerable duration of pamiparib (2, 4, 6 weeks)+RT in newly diagnosed GBM patients with unmethylated MGMT promoter (unmethyl-GBM). In Arm B, newly diagnosed patients with unmethyl-GBM will receive pamiparib+RT with increasing TMZ doses. Enrollment in Arm B will commence once RP2D for pamiparib+RT is established. In Arm C, patients with recurrent/refractory methylated- or unmethyl-GBM receive pamiparib with increasing TMZ doses. As of 28 March 2018, 15 patients were enrolled (A: 2-wk, n=3; 4-wk, n=6; C: TMZ [40mg], n=6). One DLT (grade 3 nausea) was reported in Arm C. Across arms, pamiparib-related AEs occurring in >3 patients were nausea (n=6) and fatigue (n=5). Two patients experienced three pamiparib-related AEs grade 3 (diarrhea [A: 4-wk, n=1]; fatigue and nausea [C: n=1]). All three resolved with concomitant medication and treatment interruption (A) or discontinuation (C). Of the seven patients with 1 tumor assessment, one (A: 4-wk) achieved an unconfirmed PR; four (A: 2-wk, n=2; 4-wk, n=2) had SD, and two (A: 2-wk, n=1; C: n=1) had PD. Preliminary data suggests pamiparib at 60mg BID is generally well tolerated by patients when administered 4 weeks concurrently with RT for newly diagnosed unmethyl-GBM and when combined with 40 mg TMZ for recurrent/refractory GBM.

ACTR-31. PHASE 1 STUDY OF AG-881, AN INHIBITOR OF MUTANT IDH1 AND IDH2: RESULTS FROM THE RECURRENT/PROGRESSIVE GLIOMA POPULATION

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INTRODUCTION: Isocitrate dehydrogenase 1 and 2 mutations (mIDH1/2) occur in >70% of low-grade gliomas and secondary glioblastomas, and lead to genetic and epigenetic dysregulation, promoting tumorigenesis. AG-881 is an oral, potent, brain-penetrant inhibitor of mIDH1/2 under phase 1 clinical evaluation in gliomas and other solid tumors. Here we present clinical data from the glioma population. METHODS: Patients with recurrent/progressive mIDH1/2 glioma received AG-881 daily in continuous 28-day cycles. A Bayesian model was used for dose escalation. Dose-limiting toxicity (DLT) definition: Grade 3 AG-881-related adverse event (AE) in Cycle 1 or by sponsor designation. Blood samples were collected for pharmacokinetic (PK)/pharmacodynamic (PD) evaluations. MRI response every 8 weeks by RANO and RANO-LGG criteria. RESULTS: As of 28Mar2018, 52 patients with glioma had received AG-881 and 17 (32.7%) remained on treatment. Grade 2/3 = 90.4%; median age = 42.5 years; IDH1/2: 48/3; median no. prior therapies = 2 (range 1–6). Five initial dose levels tested: 25mg (n=6), 50mg (n=5), 100mg (n=10), 200mg (n=14), and 300mg (n=5). To confirm safety and PK, a 10mg dose level was tested (n=6) and 6 additional patients enrolled in the 50mg cohort. Common (>20%) AEs across glioma patients regardless of attribution: ALT increased (44.2%), AST increased (38.5%), headache (34.6%), fatigue (30.8%), nausea (26.9%), seizure (21.2%). Five patients experienced DLTs at 100mg: Grade 2 ALT/AST that resolved to Grade 1 with dose modification (n=4) or discontinuation (n=1). Among the evaluable glioma population: 2% minor response, 75% stable disease, 21% progressive disease, and 2% missing as best overall response. CONCLUSION: Maximum tolerated dose/recommended phase 2 dose was not reached by Bayesian model; clinical team recommendation was to proceed with doses <100mg in patients with glioma. The 10mg and 50mg doses are being explored in an ongoing perioperative glioma study. Updated safety, PK, and imaging response analyses will be presented.

ACTR-32. 5-ALA FLUORESCENCE IS A POWERFUL MARKER FOR DETECTION OF UNEXPECTED GLIOBLASTOMA TISSUE DURING SURGERY OF RADIOLOGICALLY SUSPECTED LOW-GRADE GLIOMAS

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BACKGROUND: Precise tissue sampling during resection of suspected low-grade gliomas (LGG) is the basis for an accurate histopathological diagnosis to enable adequate patient management. In the course of malignant transformation of initial LGG, small intratumoral areas of glioblastoma tissue can potentially arise that might be unrecognized during surgery and thus result in treatment failure. Recently, 5-aminolevulinic acid (5-ALA) induced fluorescence was identified as intraoperative marker for visualization of focal intratumoral WHO grade III areas. The aim of this study is thus to clarify if 5-ALA is also capable to identify areas of unexpected glioblastoma tissue during surgery of radiologically suspected LGG. METHODS: Our database at the Medical University of Vienna and University of California, San Francisco was screened for adult patients with 5-ALA fluorescence-guided resection of a suspected glioma with non-significant MRI contrast-enhancement (CE; no, patchy/faint or focal CE). In this study, only patients with newly diagnosed lesions were included. In contrast, recurrent gliomas and biopsy only cases were excluded. In all patients, histopathological diagnosis was established according to the WHO classification. RESULTS: Altogether, 7 patients (median age: 53 years, range: 30–66 years) with histological diagnosis of a glioblastoma were identified despite initial radiological suspicion of LGG. Of these, no CE was found on preoperative MRI in two cases (29%), patchy/faint CE in two cases (29%) and focal CE in three cases (42%). During surgery, intratumoral areas with focal 5-ALA induced fluorescence were observed in all 7 patients. In contrast, no visible fluorescence was found in the remaining intratumoral regions. CONCLUSIONS: Our study indicates that 5-ALA induced fluorescence is able to identify intratumoral areas containing even focal glioblastoma tissue in radiologically suspected LGG. Thus, the 5-ALA technique will in future markedly improve tissue sampling during resection of suspected LGG to allow a precise histopathological diagnosis and optimized postoperative patient management.

ACTR-33. TUMOR TISSUE PENETRATION AND PHARMACODYNAMICS OF ONC201 IN ADULT RECURRENT GLIOBLASTOMA PATIENTS

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BACKGROUND: ONC201 selectively antagonizes DRD2, crosses the blood-brain barrier and induces apoptosis in high grade gliomas and other advanced cancers. ONC201 efficacy is pronounced in glioma cells that harbor low DRD5 expression and is associated with induction of the ATF4/CHOP/DR5-mediated integrated stress response pathway. DRD2 antagonism also induces activation of NK and other immune cells. We previously reported the single agent activity of ONC201 in 17 adult patients with recurrent glioblastoma that demonstrated the safety, systemic pharmacodynamics, and a durable objective response when administered orally once every 3 weeks. Here, we evaluated the intratumoral drug concentrations and pharmacodynamic activity of ONC201 in adult recurrent glioblastoma patients that were treated on a weekly schedule. METHODS: Six patients >18 years old with first recurrence of glioblastoma who were eligible for salvage surgical resection were enrolled. ONC201 was administered orally as 625 mg once a week. Salvage surgery was performed approximately 24 hours after the second dose of ONC201 and patients continued on ONC201 until radiographic and/or clinical progression. Tumor tissue was flash-frozen and formalin-fixed for assessment of intratumoral drug concentrations by