were administered 10mg/kg of an IV formulation of 5-ALA (SONALA-001). Patients were assigned to one of three ascending acoustic energy levels of MRgFUS (200J/400J/800J, measured at transducer surface), followed by a four-day interval prior to planned tumor resection. In each patient, 50% of the enhancing and nonenhancing tumor volume was targeted with MRgFUS with the untreated tumor serving as an internal control. The Optimal Biological Dose (OBD) associated with 5-ALA SDT is the energy level associated with greatest tumor cell death. RESULTS: 8 patients were accrued across all energy levels, and none demonstrated drug- or device-related adverse events. Compared to internal control tissue, the apoptosis biomarker, cleaved caspase-3, was elevated in all patients, but most prominently at the 200J energy level. The oxidative stress biomarkers 4-hydroxynonenal, glutathione, cysteine, and thiol were elevated in treated vs. control tissues at all energy levels. The mean Cmax for 5-ALA and PpIX in plasma were 305 µM and 65 nM, respectively. No off-target histological or radiographic alterations were detected in any patient. CONCLUSIONS: This first-in-human Phase 0/1 study of a new therapeutic modality for rGBM patients demonstrates that 5-ALA SDT is safe at 200 to 800J and likely induces targeted cell death in rGBM patients via oxidative stress. At 10mg/kg of 5-ALA, the OBD is at or lower than 200J.

CTNI-14. A PHASE 0 'TRIGGER' TRIAL OF NIRAPARIB IN NEWLY-DIAGNOSED GLIOBLASTOMA PATIENTS

Nader Sanai[1], Tigran Margaryan[1], Jennifer Molloy[1], William Knight[1], Jocelyn Harmon[1], Amy Hong[1], John Wanebo[2], William Kennedy[3], Michael Garcia[2], Igor Barani[1], Wonsuk Yoo[1], An-Chi Tien[1], Artak Tovmasyan[1], and Shwetal Mehta[1]; [1]Ivy Brain Tumor Center, Phoenix, USA, [2]Barrow Neurological Institute, Phoenix, USA, [3]Barrow Neurological Institute, Phoenix, AZ, USA

BACKGROUND: Poly (ADP-ribose) polymerase (PARP) mediates DNA damage response; niraparib is an investigational PARP1/2-selective inhibitor. This Phase 0 study evaluates newly-diagnosed glioblastoma (GBM) tumor pharmacokinetics (PK) and pharmacodynamics (PD), graduating patients to a therapeutic regimen of niraparib plus fractionated radiotherapy when high unbound drug concentrations are present in gadolinium-nonenhancing tumor. METHODS: Presumed newly-diagnosed GBM patients received 4 days of niraparib (300 mg QD) prior to planned resection at 3-5 or 8-12 hours following the last dose. Tumor tissue (enhancing and nonenhancing regions), cerebrospinal fluid (CSF), and plasma were collected. Total and unbound niraparib concentrations were measured using validated LC-MS/MS methods. A PK 'trigger' determined eligibility for the therapeutic expansion phase and was defined as unbound [niraparib] > 5-fold biochemical IC50 (i.e., 19 nM) in non-enhancing tumor. PARP inhibition was assessed by quantification of PAR induction after 10 Gy *ex vivo* irradiation in surgical tissue compared to non-irradiated control tissue. Patients with unmethylated MGMT tumors exceeding the PK threshold were eligible for expansion phase dosing of niraparib plus radiotherapy followed by a maintenance phase of niraparib. RESULTS: Nineteen patients were enrolled into the Phase 0 study; all tumors met the study's PK threshold and five unmethylated patients continued onto the expansion phase. One expansion phase patient experienced treatment-related Grade 3 serious adverse event (ALT and AST elevation) and four remain on treatment (median 4.2 months). In nonenhancing regions, the mean unbound concentrations of niraparib were 353.4 nM and 331.9 nM in the 3-5 hr cohort (n= 17) and the 8-12 hr (n = 3) cohort, respectively. The suppression of PAR levels after *ex vivo* radiation was observed in 69% of the patients (11/16). CONCLUSIONS: Niraparib achieves pharmacologically-relevant concentrations in non-enhancing, newly-diagnosed GBM tissue in excess of any other studied PARP inhibitor.

CTNI-15. REGORAFENIB IN COMBINATION WITH TEMOZOLOMIDE WITH OR WITHOUT RADIOTHERAPY IN PATIENTS WITH NEWLY DIAGNOSED MGMT-METHYLATED, IDH WILDTYPE GLIOBLASTOMA: A PHASE I DOSE-FINDING STUDY (REGOMA-2)

Marta Padovan[1], Gian Luca De Salvo[2], Antonio D'Avolio[3], Mario Caccese[1], Vittorina Zagonel[1], and Giuseppe Lombardi[1]; [1]Department of Oncology, Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy, Padua, Italy, [2]Clinical Research Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy, Padua, Italy, [3]Laboratory of Clinical Pharmacology and Pharmacogenetics, Amedeo di Savoia Hospital, Department of Medical Sciences, University of Turin, Italy, Turin, Italy

Glioblastoma (GBM) has activation of multiple signaling pathways in the tumor microenvironment, including the receptor tyrosine kinases, VEGFR, FGFR and PDGFR. The potential response to anti-angiogenic agents makes GBM an attractive target for regorafenib (REG). Antitumor activity of REG in recurrent GBM patients was shown in the REGOMA trial. Interestingly, in "in vivo" studies, beneficial effects were observed with the combination of REG and temozolomide (TMZ) in subcutaneously xenografts. This phase I open-label multicentric study will evaluate the addition of REG to standard of care treatment with TMZ as adjuvant therapy (cohort A), and in combination with TMZ+RT as concomitant therapy (cohort B), in newly diagnosed MGMT-methylated, IDH wildtype GBM patients. Primary objectives are: to determine the safety and tolerability of REG and to establish the maximum tolerated dose (MTD) of REG in those two cohorts. Secondary objectives are: assessment of pharmacokinetics of REG, TMZ and possible pharmacokinetic interactions between TMZ and REG (cohort A); assessment of preliminary antitumor activity; evaluation of quality of life during the treatment. The dose escalation will be explored according to a "3 + 3" design, starting from cohort A and following 3 dose levels of REG [80 mg, 120 mg and 160 mg; level -1 40 mg will be evaluated in case of Dose-Limiting Toxicity (DLT) during REG 80 mg]. After finding the MTD in cohort A, the cohort B dose escalation will start, exploring escalating oral doses of REG in combination with concomitant TMZ+RT (60 Gy/30 fractions); in the adjuvant phase of cohort B, REG will be given (in association to TMZ) at MTD shown in the prior adjuvant phase dose escalation.The DLT evaluation period will be two cycles from the start of cycle 1 of adjuvant or from day 1 to last day of the concomitant phase. Approximately 36 subjects will be enrolled.

CTNI-16. NRG-RTOG 9802 OBSERVATION ARM - LONG TERM RESULT

Fabio Iwamoto[1], Mei-Yin Polley[2], Edward Shaw[3], Jan Buckner[4], Geoffrey Barger[5], Stephen Coons[6], Peter Ricci[7], Mark Gilbert[8], Paul Brown[9], Keith Stelzer[10], C. Leland Rogers[11], John Suh[12], Christopher Schultz[13], Steven Howard[14], Barbara Fisher[15], Michelle Kim[16], Jiayi Huang[17], Michael Haddock[4], Minhee Won[18], and Minesh Mehta[19]; [1]Division of Neuro-Oncology, New York-Presbyterian/Columbia University Medical Center, New York, NY, USA, [2]NRG Oncology, Chicago, IL, USA, [3]Wake Forest, Winston-Salem, NC, USA, [4]Mayo Clinic, Rochester, USA, [5]Wayne State, Detroit, MI, USA, [6]Barrow Neurological Institute, Phoenix, USA, [7]Radiology Imaging Associates, ENglewood, USA, [8]Neuro-Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA, [9]Department of Radiation Oncology, Mayo Clinic, Rochester, MN, USA, [10]Radiation Oncologists - The Dalles, The Dalles, USA, [11]Gamma West, West Jordan, USA, [12]Cleveland Clinic, Cleveland, USA, [13]Medical College of Wisconsin, Milwaukee, WI, USA, [14]University of Wisconsin, Madison, USA, [15]University of Western Ontario, London, USA, [16]University of Michigan, Ann Arbor, USA, [17]Washington University, St. Louis, USA, [18]NRG Oncology, Philadelphia, PA, USA, [19]Baptist Health South Florida, Miami, FL, USA

BACKGROUND: Radiation Therapy Oncology Group 9802 was a phase III trial for patients with centrally confirmed LGG (WHO grade II). Participants ³ 40 years or those with neurosurgeon defined less than gross total resection (GTR) were randomized to radiotherapy (RT) +/- PCV. In a separate cohort, adults age < 40 years with neurosurgeon defined GTR were observed by MRI every 6 months without adjuvant therapy. At last report, outcome for the observation cohort was immature with median follow-up of only 4.4 years. Here, we present mature outcomes for the observation arm. METHODS: Eligible adults (as above) were observed by MRI every 6 months. OS and PFS were estimated by Kaplan-Meier method and estimated hazard ratios to characterize the prognostic variables. RESULTS: There were 111 eligible patients (median age 30; median KPS = 100). Median follow-up was 16.1 years with 71 (64%) alive at the last follow-up. 79 patients (71%) had progressed with median PFS of 6.9 years. 5, 10, and 15 year-PFS and OS rates were 54%, 39%, 28% and 94%, 77%, and 65%. 1p19q status was codeleted in 32%, IDH1/2 mutant in 78% and MGMT promoter methylated in 39% of tested cases. Multivariate Cox analyses showed that preoperative tumor size ³ 4 cm (HR = 2.43 for PFS, p = 0.001; HR = 2.58 for death, p = 0.016) and residual disease on imaging ³ 1 cm (HR = 2.97 for PFS, P < 0.001; HR = 2.02 for death, p = 0.05) were associated with worse outcomes. Analyses based on molecular results will be presented. CONCLUSION: A subset of low-grade gliomas can be observed after the initial resection based on younger age, smaller tumor size, and no residual disease on neuroimaging. This can likely be further refined by prognostic molecular markers. Patients with the most favorable prognostic factors can avoid or delay the acute and long-term side effects of RT and chemotherapy for several years.

CTNI-17. A MULTI-INSTITUTIONAL RANDOMIZED CLINICAL TRIAL COMPARING ASSAY - GUIDED CHEMOTHERAPY WITH PHYSICIAN-CHOICE TREATMENT FOR RECURRENT HIGH-GRADE GLIOMA (NCT03632135)

Tulika Ranjan[1], Soma Sengupta[2], Michael Glantz[3], Richard Green[4], Alexander Yu[5], Dawit Aregawi[6], Rekha Chaudary[7], Ricky Chen[8], Mario Zuccarello[9], Christine Lu-Emerson[10], Hugh Moulding[11], Neil Belman[12], Jon Glass[13], Aaron Mammoser[14], Mark Anderson[15], Nicholas Marko[16], Jason Schroeder[17], Steven Jubelirer[18], Frances Chow[19], Anthony Alberico[20], Candace Howard[15], Seth Lirette[15], Krista Denning[20],