Abstracts

ACTR-08. BENEFICIAL EFFECT OF TUMOR TREATING FIELD THERAPY IN DIFFUSE ASTROCYTOMA WITH GLIOMATOSIS CEREBRI
Nicholas Blondin; Associated Neurologists of Southern Connecticut, Fairfield, CT, USA

BACKGROUND: Gliomatosis Cerebri (GC) in adults is a form of infiltrative glial neoplasia, affecting at least three cerebral lobes. It is recognized as a malignant disease with no clear standard of care for treatment, and a poor prognosis for survival. Due to the large volume of treatment, radiation therapy may cause excessive neurological toxicity without a proven survival benefit. Recent data has suggested temozolomide (TMZ) monotherapy as a safe and effective treatment for all astrocytomas. Tumor Treating Fields (TTFields) delivered via the Optune device in combination with temozolomide has been proven to extend survival in newly diagnosed glioblastoma patients. METHODS: Two newly diagnosed GC patients were treated with continuous Optune therapy and TMZ. RESULTS: Patient 1 is a 50 year old man with GC affecting all supratentorial cerebral lobes. Following diagnostic biopsy (astrocytoma WHO Grade 2, IDH-1 mutated) he was treated with continuous TTFields and 12 conventional cycles of TMZ, with a significant radiographic improvement. TTFields were continued beyond 12 months, and at 15 months TMZ was resumed for another 3 cycles. A radiographic progression occurred and he was then treated with continuous TTFields and lomustine/procarbazine for 4 conventional cycles, again with radiographic improvement. His performance status remains excellent. Patient 2 is a 49 year old woman with GC affecting right hemispheric lobes and left frontal lobe. Following diagnostic biopsy (astrocytoma, WHO Grade 2, IDH-1 mutated) she was treated with continuous TTFields and 6 cycles of TMZ with a significant radiographic improvement. She continued with TTFields therapy for another 6 months, and then opted to suspend therapy due to no active disease. CONCLUSIONS: The combination of TTFields and chemotherapy, with deferred radiation therapy, appears to be an effective treatment strategy for a newly diagnosed adult GC. A clinical trial in this disease state is warranted.

ACTR-09. CLINICAL RESULTS OF THE EORTC RANDOMIZED PHASE II TAVAREC TRIAL ON TEMOZOLOMIDE WITH OR WITHOUT BEVACIZUMAB IN 1ST RECURRENCE OF GRADE II OR III IDH-MUTATED DWT 1P/19Q CO-DELETION

BACKGROUND: The role of bevacizumab in recurrent grade II and III gliomas is unclear. Similar to glioblastoma, uncontrolled studies have shown promising response rates but controlled studies are not available. We conducted a randomized phase II study, in which we investigated the addition of bevacizumab (BEV) to temozolomide (TMZ) in patients with tumours without 1p/19q co-deletion (MDM2/1MG2). METHODS: Eligible were patients with a newly diagnosed grade II or III glioma without 1p/19q co-deletion, with a first and enhancing recurrence treated with TMZ as initial chemotherapy. The primary endpoint was the overall survival rate at 12 months (OS12). An AHERn design was used, 144 patients would have to be randomized to reject the same TMZ regimen in combination with BEV 10 mg/kg every 2 weeks (arm II) or TMZ alone (arm III) with 1p/19q co-deletion, with a first and enhancing recurrence after initial radiotherapy. Prior chemotherapy (either TMZ or PCV regimen) was allowed provided patients were at least 6 months off treatment. Patients were treated with either TMZ day 1-5 200mg/m2 for 12 cycles (arm A), or with the same TMZ regimen in combination with BEV 10mg/kg every 2 weeks (arm B) until progression. Response was evaluated every three months using RANO criteria. Primary endpoint was the overall survival rate at 12 months (OS12). An AHERn design was used, 144 patients would have to be randomized to reject the H0 hypothesis of 50% in favour of the H1 hypothesis of 65%. Analysis of MMGT status and ID4Hunational status is part of the study design (trial nr: NCT01164189). RESULTS: Between Feb 8, 2011 and July 31, 2015 155 patients were enrolled in the TAVAREC trial. Baseline characteristics were similar: Median age was 44 years, 53% were initially diagnosed with a grade II tumor, and 27% of patients had received prior chemotherapy. In August 2016, OS data will be mature and the clinical outcome will be analyzed. CONCLUSION: At the meeting the mature OS results of this randomized phase II trial will be presented.

ACTR-10. PHASE 0 TRIAL OF AZD1775 IN FIRST-RECURRENCE GIOBLASTOMA PATIENTS
Nader Sana1, Jing Li2, Julie Boerner3, Harshil Dhruv4, Michael Berens1 and Patricia Loc Russo5; 1Barrow Neurological Institute, Phoenix, AZ, USA, 2Karmanos Cancer Institute, Detroit, MI, USA, 3TGen, Phoenix, AZ, USA, 4Yale University Cancer Center, New Haven, CT, USA

BACKGROUND: AZD1775 is a first-in-class Weel inhibitor with dual-function as a DNA damage sensitizer and cytotoxic agent. A Phase I trial for solid tumors suggested CNS activity, but a preclinical study indicated limited blood-brain-barrier penetration in mice. To resolve this controversy, we examined the pharmacokinetic (PK) and pharmacodynamics (PD) of AZD1775 in first-recurrence glioblastoma (GBM) patients. METHOD: Four adult patients received a single dose of AZD1775 (100/200/400mg) and tumor was resected at 4h, 8h, or 24h post-dosing. Sparse blood sampling was performed and tumor samples were collected intraoperatively. AZD1775 concentrations in plasma and cerebrospinal fluid (CSF) were determined by validated LC-MS/MS methods. PD endpoints were compared to matched archival tissue. RESULTS: AZD1775 plasma exposure increased with increasing dose and exhibited an absorption rate constant (Ka) of 0.84 h⁻¹, an elimination rate constant (K) of 0.11 h⁻¹ and apparent oral clearance (CL/F) of 417 L/h, with interindividual variability (IIV) of 98%, 28% and 52%, respectively. Glomerular filtration rate was a significant covariate on CL/F, explaining 25% of the IV of CL/F. Total and unbound brain tumor-to-plasma ratios appeared dose- and time-independent, with mean values of 9.1 (3.8–4.0) and 3.2 (1.3–2.4), respectively. 1 to 24h after a 400mg dose, unbound concentrations in tumor ranged from 18–315 ng/g, with the mean (±58 ng/g) above the in vitro IC50 (42 ng/mL) for Weel inhibition. Following drug exposure, Weel suppression was inferred by double-strand DNA breakage (phosphorylated H2AX, p<0.005), cell-cycle re-entry (phosphorylated pRb, p<0.037), and apoptosis (capase-3, p<0.028). CONCLUSIONS: Within 6 months of study activation, we obtained data to justify Phase II study of AZD1775 in GBM. Unlike preclinical models, our findings show adequate tumor penetration in patients, provide the first evidence of biological activity in human GBM, and confirm the utility of Phase 0 trials as part of an accelerated paradigm for drug development in glioma patients.

ACTR-11. PHASE II STUDY OF SINGLE AGENT BUPARLISIB IN RECURRENT/REFRACTORY PRIMARY (PCNSL) AND SECONDARY CNS LYMPHOMA (SCNSL)
Christian Grommes1, Elena Pentsova2, Craig Nolan3, Julie Wolfe4, Ingo Mellinghoff5, and Lisa DeAngelis5; Memorial Sloan-Kettering Cancer Center, New York, NY, USA

PCNSL is an aggressive primary brain tumor. Outcome and treatment options are poor for recurrent/refractory (r/r) patients with response rates between 30–60% and progression free survival (PFS) of 2–6 months. PI3K inhibition has shown promising response in some B-cell malignancies. This phase II trial investigates Buparlisib in patients with r/r PCNSL and SCNSL. Eligible patients had r/r PCNSL and received Buparlisib 840mg PO daily for 21 days. Primary endpoint was investigator-assessed PFS. Secondary endpoints included safety, unrestricted number of prior therapies. Systemic disease needed to be absent in SCNSL patients. Patients received Buparlisib 100mg daily. The trial was closed prematurely due to limited clinical response. Four patients were enrolled (55, 60, 68, 79 y.o), resected respectively, 3 were men; 50% had PCNSL. All had parenchymal disease. Median prior CNS directed treatment was 2 (range 1–3); all methotrexate regimens. Two grade 4 toxicities (lymphopenia, neutropenia) were observed that resolved after drug was held. Most common toxicities were hyperglycemia, hypocromia, and lymphopenia. Overall response rate was 25% with one partial response. This patient developed psychiatric symptoms within 8 weeks of treatment and drug was discontinued. Three patients developed neurological symptoms at a median of 37 days after trial drug initiation all due to (CNS) progression. Median progression free survival was 39 days. Median overall survival was 196 days. Buparlisib concentrations were assessed 2h after treatment initiation on day 15 in plasma and CSF. Mean plasma concentration was 1104ng/ml (range: 844–1610); mean CSF concentration 139.5ng/ml (82.9–205). CSF concentration in the trial population (medium: 340nM; range: 202–499) was below the IC50 observed to induce cell death in lymphoma cells in vitro(≥500nM). CD79B mutations were found in 3/4 patients. Patients with CNS lymphoma tolerate drug with acceptable toxicities. Treatment did not result in clinical response possibly due to CNS concentration below a meaningful IC50. Additionally, Buparlisib might not have single agent activity.

ACTR-12. PHASE III STUDY OF SINGLE AGENT IBRUTINIB IN RECURRENT/REFRACTORY PRIMARY (PCNSL) AND SECONDARY CNS LYMPHOMA (SCNSL)
Christian Grommes1, Igor Gorvilovic1, Thomas Kaley2, Craig Nolan3, Antonio Omuro4, Julie Wolfe2, Elena Pentsova2, Vaios Hatzoglou5, Ingo Mellinghoff1 and Lisa DeAngelis5; Memorial Sloan-Kettering Cancer Center, New York, NY, USA, 1Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Ibrutinib has shown promising clinical response in some B-cell malignancies. This trial investigates Ibrutinib in patients with r/r PCNSL/SCNSL. Eligible patients had r/r PCNSL/SCNSL, age>18, B-cell lymphoma, with interstitial number of CNS directed prior therapies. Systemic disease needed to be absent in SCNSL patients. Twenty patients were enrolled (3 at 560mg; 17 at 840mg). Median age: 69 (range 21–83); 12 were women. Median