Title

ACTR-40. A PHASE 1, MULTICENTER, OPEN-LABEL STUDY OF MARIZOMIB (MRZ) WITH TEMOZOLOMIDE (TMZ) AND RADIOTHERAPY (RT) IN NEWLY DIAGNOSED WHO GRADE IV MALIGNANT GLIOMA (GLIOBLASTOMA, ndGBM): FULL ENROLLMENT RESULTS

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survival than the patients, who were not, 11.0 months and 3.5 months (p=0.0002, Log-rank). BEV could be safely discontinued for the patients, who respond well for the first administration, and the initial response to BEV might be a good prognostic factor at recurrence.

ACTR-38. A PHASE I TRIAL OF AFATINIB AND RADIOTHERAPY (RT) WITH OR WITHOUT TEMOZOLOMIDE (TMZ) IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA (GBM)

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GBM is the most frequent primary CNS tumor. RT + TMZ represents first-line therapy. ErbB pathway dysregulation contributes to GBM pathogenesis; EGFR activation is associated with RT resistance. This 3 + 3 dose-escalation study assessed afatinib, an irreversible ErbB family blocker, with RT ± TMZ in newly diagnosed GBM. Patients with MGMT promoter methylation received afatinib (20, 30, 40 mg/day) + RT + TMZ for 6 weeks (RT period), then afatinib 40 mg/day + TMZ for 6 months, then afatinib 40 mg/day until progression/undue adverse events (AEs; Regimen M). Those with unmethylated MGMT promoter received RT + afatinib then afatinib (Regimen U). Primary endpoint was maximum tolerated dose (MTD) of afatinib + RT ± TMZ; secondary endpoints were safety, pharmacokinetics and antitumor activity. Thirty-six patients were enrolled (M, 20; U, 16). In regimen M, 1/6 (20 mg), 0/6 (30 mg) and 2/5 (40 mg) evaluable patients had dose-limiting toxicities (DLTs) in the RT period (two Grade 4 thrombocytopenia, one Grade 3 vomiting); MTD of afatinib + RT + TMZ was 30 mg/day. In regimen U, 0/3 (20 mg) and 1/6 (40 mg) evaluable patients had DLTs (Grade 3 diarrhea); MTD of afatinib + RT was 40 mg/day. Common treatment-related AEs were diarrhea, rash, fatigue, nausea and thrombocytopenia; 80% and 75% had Grade 3 AEs in M and U. Pharmacokinetic evaluation suggested that afatinib with RT ± TMZ had no influence on afatinib exposure. Five patients in M and one in U had an objective response. Five patients (M, 4; U, 1) were long-term responders to afatinib (>12 months treatment); two had available tumor samples. Both had MGMT promoter methylation; one had a PTPN11 mutation, the other focal EGFR amplification with concomitant EGFRvIII allele amplification. Afatinib + RT ± TMZ appears tolerable; preliminary biomarker analysis may indicate patients likely to have long-term responses.

ACTR-39. TWO-YEAR RESULTS OF THE INTELLANCE 2/EORTC TRIAL 1410 RANDOMIZED PHASE II STUDY ON DEPATUX–M ALONE, DEPATUX-M COMBINED WITH TEMOZOLOMIDE (TMZ) AND EITHER TMZ OR LOMUSTINE IN RECURRENT EGFR AMPLIFIED GLIOBLASTOMA (NCT02343406

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BACKGROUND: Depatux-M is an antibody-drug-conjugate consisting of an antibody (ABT-806) specific to the activated conformation of EGFR bound to the toxin monomethylauristatin-F. In the primary analysis on EORTC 1410 we reported a trend (p = 0.06) towards improved overall survival (OS) in patients with EGFR-amplified (amp) recurrent glioblastoma treated with Depatux-M in combination with temozolomide. METHODS: Eligible were patients with centrally confirmed EGFRamp glioblastoma at 1st recurrence after temozolomide chemo-irradiation. Patients were randomized to either a) Depatux-M 1.0 mg/kg every 2 weeks intravenously, or b) the same treatment combined with temozolomide 150–200 mg/m2 day 1–5 every 4 weeks, or c) either lomustine or temozolomide (TMZ/LOM) depending on the time of relapse. Primary endpoint was OS. Pharmacokinetic sampling was part of the study design, all samples were used to calculate the Depatux-M average concentration during course 1 (CavgC1). The level of EGFRamp was re-analysed using next generation sequencing. RESULTS: In February 2018, an updated OS comparison performed after 220 observed deaths of Depatux-M in combination with TMZ versus TMZ/LOM using log-rank test and cox models stratified by stratification factors at randomization showed a HR of 0.68 (95%CI [0.48, 0.95]; p = 0.024) and 1-year OS rates of 40% versus 28%. In multivariate analysis CavgC1 was a significant predictor for OS (HR 0.96, 95% CI [0.93, 0.98], p = 0.0013). In Depatux-M treated patients, EGFR status (high vs low level amplification) did not correlate with OS. At the meeting the follow-up from Aug 2018 will be presented, obtained more than 24 months after the end of accrual. CONCLUSION: This updated OS analysis of Depatux-M in combination with temozolomide confirmed the OS improvement in EGFRamp recurrent glioblastoma. In Depatux-M treated patients, higher drug levels during course 1 were associated with improved OS, but high levels of EGFR amplification at first diagnosis were not.

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Proteasome inhibition sensitizes glioma cells to TMZ and RT, providing a novel therapeutic strategy for ndGBM. MRZ, an irreversible, brain-penetrant, pan-proteasome inhibitor with anti-glioma activity was combined with standard-of-care (SOC) concomitant TMZ/RT followed by adjuvant TMZ in ndGBM (NCT02903069), to determine the recommended dose (RD). Patients were enrolled in separate concomitant (TMZ/RT+MRZ, N=15) and adjuvant (TMZ+MRZ, N=18) cohorts in dose-escalation (3 + 3 design), followed by dose-expansion (N=20) at RD (0.8 mg/m2) in concomitant followed by adjuvant treatment. MRZ infused IV (10 min) at increasing dose levels (0.55, 0.7, 0.8, and 1.0 mg/m2): Concomitant days 1, 8, 15, 29, 36; Adjuvant days 1, 8, 15 (28-day cycle). RESULTS (as of 02May2018): Mean age 55 years, 68% male. Most common treatment-emergent adverse events (TEAEs, 20% patients, all grades): fatigue, nausea, vomiting, hallucination, ataxia, headache. Dose-limiting toxicities (DLTs): 1 (fatigue) at 0.7 mg/m2 adjuvant cohort, 3 (ataxia/diarrhea; ataxia/confusion; myocardial infarction) in concomitant and 2 (delirium/ataxia; ataxia/fatigue) in adjuvant cohorts at 1.0 mg/m2. Grade 3 TEAEs in 11 of 12 patients at 1.0 mg/m2 including one Grade 4 and one Grade 5 TEAE; at 0.8 mg/m2 MRZ, Grade 3 TEAEs in 9 of 21 patients. MRZ demonstrated a steep dose-response with TEAEs/DLTs predominately CNS AEs (ataxia, hallucinations) which were dose-related, short-lasting, reversible and ameliorated by early dose reductions, allowing patients to remain on treatment. Currently 8 dose-escalation patients remain active in Cycle 10–23. Median OS for dose-expansion not yet estimated; 7 patients remain active, 1 death, median follow-up 4.1 months. MRZ at the RD with adjuvant TMZ+Tumor Treating Fields (Optune) is currently enrolling. An international Phase 3 trial (EORTC #1709-BTG, NCT03345095) has been launched in 2018 to assess the overall survival benefit of MRZ added to SOC in ndGBM.

ACTR-42. THE USE OF ADVANCED DIFFUSION MRI PARAMETERS IN THE ASSESSMENT OF TREATMENT RESPONSE IN GLIOBLASTOMA USING MULTI-B VALUE ACQUISITION AND A HISTOGRAM-BASED APPROACH

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