Title

CTNI-08. DB102-01 ENGAGE STUDY: A BIOMARKER-GUIDED, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER PHASE 3 CLINICAL TRIAL OF DB102 IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA (GBM)

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after daily oral trametinib administration for 18 cycles, lasting 28 days each. Secondary objectives include the assessment of progression-free survival, tolerability of trametinib, serum levels of trametinib and quality of life evaluation during treatment. RESULTS: As of February 12 2021, 50 patients have been enrolled (NF1: n=10; KIAA1549-BRAF fusion: n=31; other: n=9 including 5 patients with FGFR1 alterations). Median age is 8.8 years (range 2.4-25.5). Median follow-up is 17.5 months (range 4.7-28.5). Forty-three patients are evaluable. The overall response includes: 4 partial response (PR) (9%), 18 minor response (MR) (42%), 17 stable disease (40%), 4 progressive disease (9%). Median time to response is 5.5 months (range 2.4-13.8). Median duration of response is 6.1 months (range 0.6-26.5). Progression free survival at 12 months is 79.9% (95% CI 68.5-93.6%) and median progression free survival has not yet been reached. Treatment was discontinued for 30 patients: 16 after completing 18 cycles as planned, 5 for progressive disease, 5 for adverse events, 4 for other reasons. A total of 8 patients progressed after discontinuation of treatment including 6 patients (37.5%) that completed 18 cycles. Five of these patients had achieved minor response prior to discontinuation. CONCLUSION: Trametinib is a potentially effective targeted therapy for patients with recurrent/refractory PLGG. Treatment was overall well tolerated. This ongoing trial will continue to gather data on response rate, duration of response and safety of trametinib for PLGG.

CTNI-07. ABTC-1701: PILOT SURGICAL PK STUDY OF BGB324 (BEMCENTINIB) IN RECURRENT GLIOBLASTOMA PATIENTS – RESULTS FROM INTERIM FUTILITY ANALYSIS

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BACKGROUND: Glioblastoma often can relapse as mesenchymal (MES) tumors, indicating a phenotypic shift during clinical progression. Glioma spheres, when they gain MES phenotypes, develop dependence on AXL for their growth both *in vitro* and *in vivo*. The first-in-class orally bioavailable AXL kinase inhibitor bemcentinib has IC_{50} of 14 nM and is > 100-fold selective for AXL over other kinases. Bemcentinib is currently under evaluation as a monotherapy and in combination with other treatments across various PhII trials in several oncology indications. METHODS: This is an open-label, multicenter, intratumoral pharmacokinetic study of bemcentinib in patients with recurrent glioblastoma for whom a surgical resection is medically indicated. All subjects must have had histological confirmation of glioblastoma by either biopsy or resection that is progressive or recurrent following radiation therapy ± chemotherapy. Intratumoral drug levels were analyzed by LC/MS. RESULTS: A planned analysis after the first 5 patients were enrolled with glioblastoma (4 IDH WT and 1 IDH-mutant), (3m, 2f, median age 57, KPS 80). Bemcentinib concentration in contrast enhancing brain tissue ranged from 3.1 to 43.0 uM with a geometric mean concentration of 11.1 uM (% CV, 132.1). The drug concentration in contrast enhancing tumor tissue exceeded the 1.0 uM threshold in all 5 patients, satisfying the criteria of the protocol to enroll an additional 15 patients into the surgical study. Total drug levels were approximately 2-fold greater in contrast enhancing tissue as compared to tissue from a non-enhancing region of the tumor (geometric mean, 5.8 uM; % CV, 187.7). The mean ratio of the drug concentration in brain tissue to plasma was 25.9 (% CV, 92.7) for contrast enhancing tissue and 13.4 (% CV, 126.8) for non-enhancing tissue. CONCLUSIONS: Bemcentinib readily distributes in brain tumor tissue following oral administration. The study continues to complete accrual for the remaining 15 patients.

CTNI-08. DB102-01 ENGAGE STUDY: A BIOMARKER-GUIDED, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER PHASE 3 CLINICAL TRIAL OF DB102 IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA (GBM)

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Precision medicine is vital for treating many cancers. Lack of valid biomarkers might contribute to the failure of drug therapy for GBM. The Denovo Genomic Marker 1 (DGM1), a novel pharmacogenomic biomarker, has been discovered by a genome-wide screen of patients treated with DB102 (enzastaurin) in a trial for lymphoma. Similarly, retrospective analyses showed that DB102 significantly improved outcomes in the biomarker positive GBM patients treated with DB102, regardless of MGMT promoter methylation status. The ENGAGE Study (DB102-01, NCT03776071) is a global Phase 3 clinical trial to confirm clinical benefits in patients with newly diagnosed GBM who are DGM1 biomarker positive. This is a prospective, randomized, double-blind, placebo-controlled, multi-center study. A total of 318 patients with newly diagnosed GBM will be enrolled. After screening, patients will be randomized to receive radiation therapy (RT) and temozolomide (TMZ) plus either DB102 or a matched placebo for 6 weeks in the Concurrent Phase, followed by DB102 or placebo for approximately 5 weeks in the Single-Agent Phase and then TMZ plus DB102 or placebo in the Adjuvant Phase (up to 12 cycles). Thereafter DB102 or placebo may be continued as a single agent for up to 2 years. The primary endpoint is overall survival (OS). The secondary endpoints include progression free survival (PFS), objective response rate (ORR) and drug safety. By April 2021, the safety-run-in part was completed. The study is now open for enrollment in the US and soon in Canada and China.

CTNI-09. TRIDENT PHASE 3 TRIAL (EF-32): FIRST-LINE TUMOR TREATING FIELDS (TTFIELDS; 200 KHZ) CONCOMITANT WITH CHEMO-RADIATION, FOLLOWED BY MAINTENANCE TTFIELDS/ TEMOZOLOMIDE IN NEWLY-DIAGNOSED GLIOBLASTOMA

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INTRODUCTION: Tumor Treating Fields (TTFields; 200 kHz; non-invasive, loco-regional antimitotic treatment) is approved for newly-diagnosed glioblastoma (ndGBM). In the Phase 3 EF-14 trial, post-surgical radiotherapy/temozolomide, followed by maintenance TTFields/ temozolomide significantly increased overall survival (OS) and progression-free survival (PFS) in patients with ndGBM versus TMZ alone. Addition of maintenance TTFields did not increase systemic toxicity; and related adverse events (AEs) were mainly dermatological. In preclinical models, addition of TTFields increased the benefit of radiotherapy. Two pilot studies showed that TTFields concomitant with radiotherapy/temozolomide is feasible and well-tolerated. The benefit of TTFields concomitant with radiotherapy/ temozolomide will be investigated in the TRIDENT trial. METHODS: TRIDENT (EF-32; NCT04471844) is an international, pivotal, phase 3 randomized trial comparing triple-combination of TTFields/radiotherapy/ temozolomide versus standard radiotherapy/temozolomide. Patients in both arms will receive maintenance TTFields/TMZ. Arrays of the Optune® System will be used to deliver TTFields (200 KHz) for ≥18 hours/day concomitant with radiotherapy. TTFields treatment will be continued until second disease progression (RANO) or 24 months, whichever occurs first. Patients with pathologically-confirmed ndGBM, ≥ 18 years of age (≥ 22 years of age; US), KPS ≥ 70, post-surgery/biopsy, and amenable for radiotherapy/temozolomide will be stratified by extent-of-resection and