CTNI-20. RESULTS OF A PHASE 1/2 CLINICAL TRIAL OF BLOOD-BRAIN BARRIER (BBB) OPENING WITH THE SONOCLOUD-9 IMPLANTABLE ULTRASOUND DEVICE IN RECURRENT GLIOBLASTOMA PATIENTS RECEIVING IV CARBOPLATIN

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Low intensity pulsed ultrasound in combination with microbubbles can be used to temporarily disrupt the blood-brain barrier (BBB). A phase 1/2 clinical study (NCT03744026) was initiated to demonstrate the safety and efficacy of BBB disruption using an implantable ultrasound system (SonoCloud-9) in patients with recurrent glioblastoma receiving carboplatin chemotherapy. The SonoCloud-9 device, which contains nine, 1-MHz, 10-mm diameter ultrasound emitters (Carthera, Paris, France) was placed at the end of tumor resection and replaced the bone flap. The device was activated 9-14 days after surgery for a duration of 270 seconds every four weeks until progression or treatment completion, concomitantly with IV DEFINITY microbubbles (10 ml/kg, Lantheus, Billerica, US). The Phase 1 cohort consisted of an escalation of BBB disruption volume by activation of 3 (n = 3), 6 (n = 3), then 9 (n = 3) emitters of the device. Dose limiting toxicity (DLT) was assessed during the first two weeks after the 1st sonication. A subsequent expansion cohort consisted of patients treated with nine emitters in which the primary endpoint was assessment of BBB opening on MRI using gadolinium (< 1 hr after sonication). All patients received carboplatin either after (n = 21) or before (n = 12) device activation to disrupt the BBB. In addition, a sub-study was performed to investigate carboplatin concentration enhancement in the peritumoral region with sonication at time of device implantation. Study accrual is complete with 33 patients having been implanted and received at least one sonication. A total of 101 sonications were performed (range = 1-10 sonication sessions/patient). No DLTs were observed. Five serious adverse events (all resolved) were considered as possibly related to the study procedure. BBB disruption was confirmed by gadolinium enhancement after sonication. In three patients who underwent intraoperative sonication and carboplatin administration, a 7.58-fold increase in brain/plasma drug levels was demonstrated. Updated survival results will be presented.

CTNI-21. TROTABRESIB (CC-90010) IN COMBINATION WITH CONCOMITANT TEMOZOLOMIDE PLUS RADIOTHERAPY AND ADJUVANT TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA: UPDATED RESULTS FROM A PHASE 1B/2 STUDY

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Trotabresib, a novel bromodomain and extraterminal protein inhibitor, has demonstrated antitumor activity and blood–brain barrier penetration in patients with high-grade gliomas, and enhanced the antiproliferative effects of temozolomide in preclinical models. CC-90010-GBM-002 (NCT04324840) is a phase 1b/2 study investigating the addition of trotabresib to standard-of-care (SOC) concomitant temozolomide plus radiotherapy and adjuvant temozolomide, followed by maintenance trotabresib, in patients with newly diagnosed glioblastoma. The design of the dose escalation (part A) has been described previously (Vieito M, et al. SNO 2021. Abstract CTNI-51). Primary objectives of part A were to establish the safety, tolerability, and maximum tolerated dose/recommended phase 2 dose (RP2D) of trotabresib. In part A, addition of trotabresib to SOC was safe and well tolerated in the concomitant (N = 14) and adjuvant (N = 18) cohorts; the most frequent grade 3/4 treatment-related adverse event was thrombocytopenia (7/14 and 9/18 patients, respectively). The RP2D for trotabresib was 30 mg/day 4 days on/24 days off in both settings. At data cutoff (February 20, 2022), median duration of treatment was 34 weeks (concomitant cohort) and 33 weeks (adjuvant cohort); progression-free survival data are not yet mature. Trotabresib plasma pharmacokinetics and pharmacodynamics were consistent with monotherapy. At last follow-up, 6 and 5 patients remained on treatment in the concomitant and adjuvant dose-escalation cohorts, respectively, including 1 patient in cycle 20 with ongoing complete response. The ongoing randomized phase 2 dose expansion (part B; planned N = 162) is comparing concomitant trotabresib at the RP2D + SOC followed by adjuvant trotabresib at the RP2D + SOC, followed by maintenance trotabresib 45 mg/day 4 days on/24 days off, versus SOC alone in patients with newly diagnosed *IDH*–wild-type glioblastoma. Key objectives are to compare progression-free and overall survival, safety, and tolerability. Longer follow-up from part A and the first disclosure of data from part B will be presented.

CTNI-23. PRELIMINARY SAFETY AND PHARMACOKINETICS DATA FOR A PHASE 1B TRIAL OF TELAGLENASTAT IN COMBINATION WITH RADIATION THERAPY AND TEMOZOLOMIDE IN PATIENTS WITH IDH-MUTANT GRADE 2/3 ASTROCYTOMA (NCI-10218)

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IDH mutant gliomas depend on glutaminase for glutamate/glutathione generation from glutamine because R-2-hydroxyglutarate inhibits branched chain amino acid transaminase mediated glutamate biosynthesis. Telaglenastat (CB-839 HCl) is a potent glutaminase-1 specific inhibitor which depletes tumor glutamate in orthotopic IDH mutant glioma PDX models and extends survival in these orthotopic models when added to radiation/temozolomide. NCI-10218 (NCT03528642) is a phase I clinical trial investigating the safety and tolerability of telaglenastat administered orally concurrently with standard doses of radiation (50.4 Gy, grade 2; 59.4 Gy, grade 3) and temozolomide (75 mg/m2 orally daily) in patients (age 16+) with previously untreated IDH mutant grade 2/3 astrocytoma. Telaglenastat dose was escalated in cohorts (400-800 mg twice daily) based on a standard 3 + 3 design to determine the recommended phase 2 dose (RP2D). Toxicities were graded per CTCAE v5.0. An expansion cohort additionally incorporated a seven-day run-in of telaglenastat monotherapy at RP2D prior to radiation to evaluate the pharmacodynamic impact of telaglenastat on plasma and tumor metabolites. 23 patients with IDH mutant astrocytoma (WHO grade 2, n = 5; WHO grade 3, n = 18) were accrued between December 2018 and January 2022 (Dose Escalation: 16; Dose Expansion: 7). Median age was 32 years (range 23-69 years). 61% were male and 70% were ECOG 0. No dose-limiting toxicities were observed. Grade 3/4 adverse events (independent of attribution) included: lymphopenia (3), neutropenia (2), leukocytosis (2), alanine transaminase elevation (2), thrombocytopenia (1), leukopenia (1), maculopapular rash (1), hyperglycemia (1), hyponatremia (1). The RP2D of concurrent telaglenastat was defined as 800 mg twice daily. Following peak absorption on Day 15 at RP2D, the mean (%CV) terminal elimination half-life in the plasma was 4.2 (53.5%) hours (range 2.1-7.1 hours). The Cmax, Tmax, oral clearance, and AUC were 1496 ng/mL, 4.0 hr, 93.6 L/hr/m2, and 7430 ng/mL*hr, respectively.

CTNI-24. SINGLE CENTER EXPERIENCE OF DOPAMINE ANTAGONIST ONC-201 FOR RECURRENT H3K27M-MUTANT GLIOBLASTOMA IN ADULTS

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