SYST-13
PHASE II STUDY OF THE COMBINATION OF LIPOSOMAL IRINOTECAN AND PEBRIMOZULAM FOR TRIPLE-NEGATIVE BREAST CANCER (TNBC) WITH BRAIN METASTASIS (BM)
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BACKGROUND: Breast cancer is one of the most common cancers associated with brain metastases (BM). Up to 50% of patients with metastatic triple-negative breast cancer (TNBC) develop BM which portends a poor prognosis, with a median survival of 4.4-7.5 months. There is a lack of effective systemic therapy. Irinotecan is a topoisomerase-1 inhibitor with a response rate of 5-23% in advanced breast cancer. NaI-RH is an intra-venous liposomal formulation of irinotecan, with greater efficacy in tumor growth inhibition and the ability to cross the blood brain barrier (BBB) than irinotecan, resulting in a prolonged survival in preclinical TNBC BM models. Additionally, NaI-RH has demonstrated promising anti-tumor activity in patients with TNBC- BM in a phase-I trial (NCT01770353). Pebromozulam is a humanized anti-PI-1 monoclonal antibody which has shown efficacy in TNBC. The purpose of this study is to evaluate whether the combination of NaI-RH and pebromozulam can provide a synergic effect to control the CNS disease and prolong survival in TNBC with progressive BM. METHODS: This is a phase II, single arm trial with a safety lead-in to evaluate the efficacy of NaI-RH (80mg/m2 IV Q2W) in combin-ation with pebromozulam (400mg IV Q6W). Simon's 2-stage design is used, with 18 patients in the 1st stage and additional 24 at 2nd stage for a total of 42. The first 6 patients will serve as a safety lead-in. Keyeligibilities include: histologically/cytologically confirmed TNBC with new or progressive BM; patients with 18 patients in the 1st stage and additional 24 at 2nd stage for a total of 42. The first 6 patients will serve as a safety lead-in. Key eligibilities include: histologically/cytologically confirmed TNBC with new or progressive BM; patients with ≤4 prior lines of therapy in the metastatic setting. The primary endpoint is CNS disease control rate (DCR) at 6 months using RANO-BM criteria. Secondary endpoints include CNS and non-CNS ORR, PFS and OS.

(ClinicalTrials.gov: NCT03523666)

SYST-14
CLINICAL EFFICACY OF ONC201 IN RECURRENT H3 K27M-MUTANT TDG-6 MIDLINE GLIOMA (DMG) PATIENTS
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No standardized treatments exist for patients with treatment-refractory brain metastasis, glioblastoma and other recurrent brain tumours. Given the aggressive nature of these diseases and difficulty in modelling tumour recurrence, minimal efforts have been made to design rational therapies against them. Neurodevelopmental pathways are often hijacked and go awry in the progression of these cancers. The roundabout guidance receptor 1 (ROBO1) protein is involved in axonal guidance during neurodevelopment, and we have shown that aberrant ROBO signalling promotes invasiveness and tumour growth in glioblastoma. Likewise, this signalling may contribute to the metastasis and growth of metastatic brain tumours, making the ROBO1-expressing tumour cell population an attractive and functionally relevant therapeutic target. Here, we present that ROBO1 is highly expressed on the surface of malignant and treatment-refractory brain tumour initiating cells (BTICs), prompting the development of an anti-ROBO1 CAR-T cell therapy. Using the binding region of a single-domain antibody targeting ROBO1, we developed second-generation anti-ROBO1 CAR-T cells specific and effective against malignant brain cancers, upregulating markers of activation and degranulation (ROBO1- expressing CAR-T cells). In preclinical studies, orthotopic patient-derived xenograft models of malignant brain tumours treated with anti-ROBO1 CAR-T cells had a reduced tumour burden and prolonged survival, demonstrating therapeutic potential for treating brain malignancies.

SYST-15
TARGETING AXONAL GUIDANCE WITH ANTI-ROBO1 CAR T PRIMARY NEW THERAPEUTIC STRATEGY FOR MALIGNANT BRAIN CANCER
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INTRODUCTION: Brain metastases from lung cancer (BMLC) are common and represent an aggressive form of disease. Numerous ongoing clinical trials are investigating targeted molecular therapies against epidermal growth factor receptor (EGFR), which have demonstrated blood-brain-barrier permeability and intracranial activity. However, there is limited real-world efficacy data on second and third-generation EGFR tyrosine kinase inhibitors (TKI) Afatinib and Osimertinib for the treatment of BMLC. This study provides a real-world assessment to evaluate the impact of these agents on overall survival (OS) at the population-level. METHODS: This retrospective cohort study queried data from TriNetX, a multi-institutional de-identified database, aggregating data from 12 healthcare organizations in 6 countries. Patients with BMLC treated with 1) Osimertinib, 2) Afatinib, or 3) Neither Osimertinib nor Afatinib. Cohorts 1 and 3, as well as cohorts 2 and 3, were propensity matched on demographics and comorbidities. Median endpoints were assessed by dual-reader blinded independent central review. Data cutoff was May 31, 2021. RESULTS: ORR was 20.0% (95% CI, 10.0–33.7) by RANO-HGG criteria. Median duration of response was 11.2 months (95% CI, 3.8–not reached) and median time to response was 8.3 months (range, 1.9–15.9). PFS at 6 months was 35.1% (95% CI, 21.2–49.3). The ORR was 26.0% (95% CI, 14.6–40.3) by RANO-LGG criteria. Fifteen patients (30.0%; 95% CI, 17.9–44.6) achieved an objective response by RANO-HGG and/or RANO-LGG. Of 15 patients receiving ≥4 mg daily dexamethasone at baseline, 7 (46.7%; 95% CI, 21.3–73.4) achieved ≥50% confirmed reduction in dose. Of 34 patients with baseline KPS/LPS ≤80, 7 (20.6%; 95% CI, 8.7–37.9) achieved a confirmed performance status improvement with 1 median follow-up of 18.8 months, median OS was 11.7 months (95% CI, 8.0–20.3) and OS at 24 months was 34.7% (95% CI, 20.7–49.2). Twenty-five patients had serious adverse events with one possibly related to ONC201 by investigator assessment. CONCLUSSIONS: ONC201 monotherapy exhibits durable and clinically meaningful efficacy in recurrent H3 K27M-mutant DMG.

SYST-16
TARGETING AXONAL GUIDANCE WITH ANTI-ROBO1 CAR T PRIMARY NEW THERAPEUTIC STRATEGY FOR MALIGNANT BRAIN CANCER
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