Abstracts

SYST-13
PHASE II STUDY OF THE COMBINATION OF LIPOSOMAL IRINOCUZUMAB AND PEMBROLIZUMAB FOR TRIPLE-NEGATIVE BREAST CANCER (TNBC) WITH BRAIN METASTASES (BM) IN PATIENTS WITH MUTANT DIFFUSE MIDLINE GLIOMA (DMG) (T13-001)

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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 4.4-7.3 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. Nat-IRI is an intravenous 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 prolonging survival in preclinical TNBC BM models. Additionally, Nat-IRI has demonstrated promising anti-tumor activity in patients with TNBC-BM in a phase-1 trial (NCT01770353). Pembrolizumab is a humanized anti-CD1 delivery monoclonal antibody which has shown efficacy in TNBC. The purpose of this study is to evaluate whether the combination of Nat-IRI and pembrolizumab 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 nat-IRI in combination with pembrolizumab (400mg IV Q6W). Simon’s 2-stage design is used, lead-in to evaluate the efficacy of nal-IRI (50-70mg/m2 IV Q2W) in combination with pembrolizumab (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. Key eligibility includes histologically confirmed TNBC with new or progressive BM; prior immunotherapy is allowed but not prior nat-IRI/irinotecan; prior sacituzumab-govitecan is permitted if disease stable for ≥16-week while on therapy and ≥24-week washout prior to starting trial; measurable disease; and ≤5 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: NCT05253666)

SYST-14
CLINICAL EFFICACY OF OXACITIN IN RECURRENCE H3 K27M-MUTANT TREATMENT MIDLINE GLIOMA (DMG) PATIENTS

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No standardized treatments exist for patients with treatment-refractory brain metastases, 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. In a xenograft model expressing BTICs, 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 TKI in patients having brain metastases. In 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 90 U.S. healthcare organizations. Three cohorts were established, consisting of patients with BMLC treated with 1) Osimertinib, 2) Afatinib, or 3) Neatatinib. Results: At a 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 ONC021 by investigator assessment. CONCLUSIONS: ONC021 monotherapy exhibits durable and clinically meaningful efficacy in recurrent H3 K27M-mutant DMG.

SYST-16
PROGRESSION-MATCHED SURVIVAL ANALYSIS OF SECOND AND THIRD GENERATION TYROSINE KINASE INHIBITORS IN THE TREATMENT OF BRAIN METASTASES FROM LUNG CANCER PRIMARY 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 TKI in patients having brain metastases. In 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 90 U.S. healthcare organizations. Three cohorts were established, consisting of patients with BMLC treated with 1) Osimertinib, 2) Afatinib, or 3) Neatatinib. 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-LGG and/or RANO-HGG. 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 a median follow-up of 18.8 months, median