SYST-02
PHASE IIIB CLINICAL TRIAL OF NEOADJUVANT CHEMOTHERAPY REVERSING GLIOMA STEM CELLS CHEMORESISTANCE IN NEWLY DIAGNOSED GBM WITH MGMT PROMOTER UNMETHYLATION
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PURPOSE: To evaluate clinical efficacy and safety of combination of nicardipine and valproic acid on temozolomide (TMZ) neoadjuvant chemotherapy targeting on glioma stem cells (GSCs) in newly diagnosed glioblastoma multiforme (GBM) patients with O6-methylguanine-DNA-methyltransferase (MGMT) promoter unmethylation. METHODS: From June 2018 to April 2021, newly diagnosed GBM patients after tumor surgical removal and concurrent radio-chemotherapy with TMZ, with MGMT promoter unmethylation were randomly assigned to two groups. The control group was administered standard TMZ regimen, plus nicardipine(20mg/d) and valproic acid (1.2g/d) as neoadjuvant treatment against GSCs chemoresistance. The relevant treatment data and adverse reactions of the patients were collected, Karnofsky performance status (KPS) score, progression-free survival (PFS) and overall survival (OS) were evaluated during patient follow-up. RESULTS: 33 patients were enrolled in this study, eighteen patients were randomly assigned in the trial group and 15 patients were in the control group. There was no statistical difference in gender composition, age, degree of surgical resection, or KPS score before treatment between the two groups. The median progression-free survival (mPFS) in the trial group was 10.8 months (95%CI 5.81-15.79 month), and the mPFS in the control group was 7.1 months (95%CI 3.12-9.08 month), which was a statistically difference (P < 0.05). The median overall survival (mOS) was increased from 12.1 months (95%CI 9.18-15.00 month) in the control group to 15.7 months (95%CI 7.67-23.73 month) in the trial group (Log-Rank test P = 0.033). There was no statistically significant difference in the incidence of adverse events, such as neurovascular, worsening of KPS, and tumor size reduction between the two groups. CONCLUSIONS: TMZ combined with neoadjuvant of nicardipine and valproic acid against GSCs chemoresistance can prolong the survival time of patients who was newly diagnosed glioblastoma with MGMT promoter unmethylation. The preferred regimen can be applied safely without serious adverse events, which deserved further multi-center clinical investigations.

SYST-03
INCIDENCE AND SURVIVAL OF PATIENTS WITH INTRACRANIAL METASTASES: A RETROSPECTIVE COHORT STUDY
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BACKGROUND: Intracranial metastatic disease (IMD) is a mortality-driving complication of gastrointestinal (GI) cancers. In breast cancer, ERBB2 positivity is associated with shorter overall survival (OS) and chemotherapy resistance. Prior studies have demonstrated that ERBB2 overexpression in breast cancer, no study has directly assessed the relationship of ERBB2 status and IMD in these patients. METHODS: Records for adult patients with GI cancer and IMD, treated with ERBB2-targeted therapy between 2003 and 2018 were retrieved from ICES. Baseline characteristics were compared between subcohorts stratified by ERBB2 and ERBB2+ status. Kaplan-Meier and Cox regression analyses were performed to estimate survival. RESULTS: Records for 99,256 patients with GI cancer and IMD were diagnosed in 2002 patients. The highest IMD incidence rate was among patients with esophageal cancer (5.5%). Among patients with ERBB2+ disease, 306 had gastric (9 IMD), 168 esophageal (13 IMD), and 17 colorectal cancer. Diagnosed with IMD was associated with shorter survival among patients with colorectal cancer (HR 3.0; 95% CI 1.0-9.5, P = .03), gastric cancer (HR 1.7; 95% CI 1.5-1.9), and esophageal cancers (HR 1.2; 95% CI 1.1-1.4). Post-IMD ERBB2-targeted therapy was not associated with OS among patients with ERBB2+ esophageal cancer (HR 0.5; 95% CI 0.3-1.3) or colorectal cancer. Gastrointestinal cancers (HR 0.5; n = 15) or gastric cancer (HR 0.9-0.5; n = 9). CONCLUSION: Our study assessed patients with ERBB2+ GI cancer and IMD. Diagnosis of IMD is associated with shorter survival in gastric, esophageal, and colorectal cancers. Post-IMD ERBB2 therapy was not associated with OS, and IMD diagnosis was associated with prolonged survival of patients with ERBB2+ disease, although interpretation of these results is complicated by small sample size and selection bias. Our results motivate increased reporting and inclusion of patients with ERBB2+ GI cancers in clinical trials.

SYST-04
PRELIMINARY REPORT OF A CLINICAL TRIAL EVALUATING THE SAFETY AND EFFICACY OF INTRACRANIAL CAMELZUMAB AND APATINIB IN RECURRENT HGG WITH ERBB2 OVEREXPRESSION: A PHASE I CLINICAL TRIAL
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High-grade glioma is the most common malignant primary brain tumor in the central nervous system. Multiple strategies such as surgery, radiotherapy, and chemotherapy have been used, but the prognosis of patients with high-grade glioma remains poor. No standard treatment exists for recurrent gliomas; however, combination therapies of programmed cell death protein 1 blockades with antangiogenic agents have demonstrated promising effects in different solid tumors. We have initiated a clinical trial designed to evaluate the safety and efficacy of neoadjuvant chemotherapy using camrelizumab and apatinib in patients with recurrent high-grade gliomas. In this prospective, Phase II, single-arm study, patients with recurrent high-grade gliomas will receive single-dose intravenous injection of camrelizumab (200 mg) and daily oral administration of apatinib (250 mg/day for 7 days) 14 days before surgery for recurrent tumor. Sequential therapy will begin 2 weeks after surgery with the biweekly injection of camrelizumab and 4 weeks after surgery with the daily administration of apatinib. Treatment of camrelizumab and apatinib will be continued until disease progression or unacceptable toxicity or death. The trial is planned to enroll 30 patients. Up-to-date (March 31, 2022), 12 patients have been enrolled, in which, 9 were GBM. Three patients died, while 4 cases on trial more than 6 months, the longest already 1 year. Although an evaluation is still impossible to be conducted yet, some patients have shown a promising outcome. We will present updated results on the meeting. These preliminary data suggest that this study is worthwhile. This study was approved by the Ethics Committee of Sun Yatsen University Cancer Center (Guangzhou, China; approval No. SL202014901). This study was registered with ClinicalTrials.gov under identifier NCT04588987.

SYST-05
OPTIMIZING HER2-TARGETED THERAPIES (TT) FOR BREAST CANCER (BC) LEPTOMENINGEAL METASTASES (LM): A SYSTEMATIC REVIEW AND META-ANALYSIS
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INTRODUCTION: LM is a debilitating condition associated with metastatic cancers, including BC. When oncogenic drivers are identified, targeted therapies can be applied safely without serious adverse events, which deserved further multi-center clinical investigations.
entametas, trastuzumab-deuxtecan, and lapatinib. Primary outcome was overall survival (OS). RESULTS: Of 7780 abstracts screened, 91 publications and a total of 109 patients were included in the final analysis. Patients received chemotherapy (either IT, IV, or both) and an anti-HER2 drug con- jugate concurrently with HER2-TT (N=57) or estimated a median OS of 44.4 months, compared to patients treated with targeted anti-HER2 therapies alone (N=52), which exhibited a median OS of 14.3 months (P=0.009, hazard ratio (HR): 0.51, 95% confidence interval (CI): 0.329-0.826). Among patients receiving IT trastuzumab (N=83) estimated a median progression-free survival (mPFS) and OS of 6.0 and 21.0 months, respectively, while patients receiving IV trastuzumab (N=14) estimated a mPFS and OS of 6.5 and 21.0 months, respectively (PFS, HR: 0.712, 95% CI: 0.431-1.531; OS: P=0.68, HR: 1.154, 95% CI: 0.587-2.266). In the subgroup of patients receiving IT trastuzumab (N=58), those who concurrently received IT chemotherapy (N=48) estimated a mPFS and OS of 5.7 and 14.0 months, respectively, while patients concurrently receiving IV chemotherapy (N=10) estimated a mPFS and OS of 6.0 and 27.0 months, respectively (PFS: P=0.45, HR: 1.360, 95% CI: 0.602-3.073; OS: P=0.29, HR: 1.821, 95% CI: 0.630-5.260). CONCLUSIONS: HER2-TT is an effective therapeutic strategy for BCLM. Patients with BCLM receiving concurrent cytotoxic chemotherapy alongside HER2-TT experience prolonged mOS and IT trastuzumab are similarly effective. Univariate and multivariate analyses will be presented.

SYST-06 INTRACRANIAL ACTIVITY OF TEPOTINIB IN PATIENTS WITH MET EXON 14 (METEX14) SKIPPING NSCLC ENROLLED IN VISION

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BACKGROUND: Brain metastases (BMs) occur in 20–40% of patients with METex14 skipping NSCLC. Tepotinib, a highly selective MET inhibitor, demonstrated an objective response rate (ORR) of 49.1% and median duration of response (mDOR) of 13.8 months in METex14 skipping NSCLC patients 18 years of age or older with BM who had measurable BM. The goal of this study was to validate these findings in a large population consisting of eight arms that will evaluate the recommended phase 2 dose (RP2D) of ONC201, biomarkers, and pharmacokinetics (PK) of ONC201 in various treatment settings (NCT03416530). Arm G previously defined the RP2D for twice-weekly ONC201 on consecutive days. Arm H, for which enrollment is ongoing, will estimate the influence of tumor location and blood-brain barrier integrity on intracranial BM exposure in biopsy-eligible pediatric tumors (DIPG or contrast-enhancing thalamic glioma). Patients eligible for Arm H will be aged 2–19 years, with at least one BM and a KPS at least 70; pre-confirmation of H3 K27M mutation is not required. In Arm H, single-agent ONC201 administration will occur twice-weekly on consecutive days during each 21-day cycle at the RP2D defined in Arm G. Arm H has a planned enrollment of 27 patients (DIPG, n=15; thalamic glioma, n=12). Patients will receive a single biopsy at each of the following time points: 1–3 h post-first dose, 22–26 h post-second dose, 1–3 h post-first dose, 6–10 h post-second dose, and 22–26 h post-second dose. The 22–26 h post-first dose biopsy in thalamic glioma was previously collected and will not be assessed in this treatment arm. Plasma for PK analysis will be collected from all patients.

SYST-08 SURVIVAL ANALYSIS OF METASTATIC MELANOMA PATIENTS WITH BRAIN METASTASES USING SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) DATABASE

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INTRODUCTION: Melanoma brain metastases (BM) are common and are historically associated with poor prognosis. In the early 2010s, the treatment paradigm for malignant metastatic melanoma shifted with the introduction of immunotherapy (IT). Recent studies suggest that IT provides survival benefits for patients with BM from melanoma primary. The goal of this study was to validate these findings in a large population consisting of eight arms that will evaluate the recommended phase 2 dose (RP2D) of ONC201, biomarkers, and pharmacokinetics (PK) of ONC201 in various treatment settings (NCT03416530). Arm G previously defined the RP2D for twice-weekly ONC201 on consecutive days. Arm H, for which enrollment is ongoing, will estimate the influence of tumor location and blood-brain barrier integrity on intracranial BM exposure in biopsy-eligible pediatric tumors (DIPG or contrast-enhancing thalamic glioma). Patients eligible for Arm H will be aged 2–19 years, with at least one BM and a KPS at least 70; pre-confirmation of H3 K27M mutation is not required. In Arm H, single-agent ONC201 administration will occur twice-weekly on consecutive days during each 21-day cycle at the RP2D defined in Arm G. Arm H has a planned enrollment of 27 patients (DIPG, n=15; thalamic glioma, n=12). Patients will receive a single biopsy at each of the following time points: 1–3 h post-first dose, 22–26 h post-second dose, 1–3 h post-first dose, 6–10 h post-second dose, and 22–26 h post-second dose. The 22–26 h post-first dose biopsy in thalamic glioma was previously collected and will not be assessed in this treatment arm. Plasma for PK analysis will be collected from all patients.