emtansine, trastuzumab-deruxtecan, 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 receiving chemotherapy (either IT, IV, or as part of an antibody-drug conjugate) concurrently with HER2-TT (N=57) exhibited a median OS (mOS) of 44.0 months, compared to patients treated with targeted anti-HER2 therapies alone (N=52), which exhibited a mOS of 14.5 months (P=0.009, hazard ratio (HR): 0.538, 95% confidence interval (CI): 0.328-0.883). Patients receiving IT trastuzumab (N=83) exhibited a median progression-free survival (mPFS) and mOS of 6.0 and 21.0 months, respectively, while patients concurrently receiving IV trastuzumab (N=14) exhibited a mPFS and mOS of 6.5 and 27.0 months, respectively (PFS: P=0.31, HR: 0.712, 95% CI: 0.331-1.531; 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) exhibited mPFS and mOS of 5.7 and 14.0 months, respectively, while patients concurrently receiving IV chemotherapy (N=10) exhibited a mPFS and mOS 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. IV 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 (*MET*EX14) SKIPPING NSCLC ENROLLED IN VISION

Natasha Leighl[1], Christine Bestvina[2], Jyoti Patel[3], Xiuning Le[4], Remi Veillon[5], Ian Anderson[6], Ingel Demedts[7], Marina Chiara Garassino[8], Julien Mazières[9], Masahiro Morise[10], Egbert Smit[11], S Peter Eggleton[12], Aurora O'Brate[13], Gordon Otto[13], Rolf Bruns[14], Karl Maria Schumacher[15], Paul Paik[16,17]; [1]Princess Margaret Cancer Centre, Department of Medicine, University of Toronto, Toronto, Canada. [2]University of Chicago, Medical Center, Chicago, IL, USA. [3]Lurie Cancer Center, Northwestern University-Feinberg School of Medicine, Chicago, IL, USA. [4]Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. [5]CHU Bordeaux, Service des Maladies Respiratoires, Bordeaux, France. [6]St Joseph Heritage Healthcare, Santa Rosa, CA, USA. [7]Department of Pulmonary Diseases, AZ Delta Hospital, Roeselare, Belgium. [8]Department of Medicine, Section of Hematology/Oncology, Knapp Center for Biomedical Discovery, The University of Chicago, Chicago, IL, USA. [9]CHU de Toulouse, Institut Universitaire du Cancer, Toulouse, France. [10]Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan. [11]Department of Thoracic Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands. [12]Global Clinical Development, Merck Serono Ltd., Feltham, UK, an affiliate of Merck KGaA, Darmstadt, Germany, Darmstadt, Germany. [13]Global Medical Affairs, the healthcare business of Merck KGaA, Darmstadt, Germany, Darmstadt, Germany. [14]Department of Biostatistics, the healthcare business of Merck KGaA, Darmsatdt, Germany, Darmstadt, Germany. [15]Global Clinical Development, the healthcare business of Merck KGaA, Darmstadt, Germany, Darmstadt, Germany. [16]Thoracic Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. [17]Weill Cornell Medical College, New York, NY, USA

BACKGROUND: Brain metastases (BMs) occur in 20–40% of patients with *MET*ex14 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 *MET*ex14 skipping NSCLC patients in the Phase II VISION study (Cohorts A+C; N=275). Here, we report the intracranial activity of tepotinib in VISION. METHODS: Patients with *MET*ex14 skipping NSCLC received oral tepotinib 500 mg QD (450 mg active moiety). Patients with BM (asymptomatic and symptomatic/stable) were eligible. Primary endpoint was systemic ORR (RECIST v1.1); a subgroup analysis in patients with BM was predefined (data cut-off: February 1, 2021). An *ad-hoc* retrospective analysis of brain lesions was conducted by an IRC using RANO-BM criteria. Responses were determined in patients with ≥1 evaluable post-baseline tumor assessment. For those with only non-target lesions (NTLs) per RANO-BM (enhancing and non-enhancing NTLs), disease control was defined as non-complete response (CR)/nonprogressive disease (PD). Data cut-off: July 1, 2020. RESULTS: Fifty-one patients had baseline BM (Cohorts A+C). Systemic efficacy was consistent with the overall population (ORR 52.9% [95% CI: 38.5, 67.1], mDOR 9.0 months [95% CI: 5.6, not estimable]). Fifteen patients were evaluable by RANO-BM (Cohort A); 12 received prior radiotherapy for BM (median 6.4 weeks before treatment). Systemic best objective responses (BORs) were partial response (PR, n=9), stable disease (SD, n=3), and PD (n=3). Seven patients had target CNS lesions per RANO-BM (all with prior radiotherapy); intracranial BORs were PR (n=5), SD (n=1), and PD (n=1). For patients with NTL only (n=8),

one had PD, and seven achieved intracranial disease control with three patients achieving CR of the enhancing NTL. 13/15 patients achieved intracranial disease control. CONCLUSIONS: Tepotinib demonstrated robust systemic activity in patients with *MET*ex14 skipping NSCLC with BM, complemented by intracranial activity in an ad-hoc analysis using RANO-BM.

SYST-07

WINDOW-OF-OPPORTUNITY STUDY OF ONC201 IN PEDIATRIC PATIENTS WITH DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) AND THALAMIC GLIOMA

Yazmin Odia[1], Carl Koschmann[2], Rohinton Tarapore[3], Jeffrey Allen[4], Matthew Hall[1], Doured Daghistani[1], Ziad Khatib[5], Dolly Aguilera[6], Tobey MacDonald[6], Peter de Blank[7], Susan Lynne McGovern[8], Sabine Mueller[9], Cassie Kline[10], Nicholas Vitanza[11], Joshua E. Allen[3], Wafik Zaky[8], Sharon Gardner[4]; [1]Miami Cancer Institute, Miami, FL, USA. [2]University of Michigan, Ann Arbor, MI, USA. [3]Chimerix, Inc., Durham, NC, USA. [4]New York University Grossman School of Medicine, New York City, NY, USA. [5]Nicklaus Children's Hospital, Miami, FL, USA. [6]Children's Healthcare of Atlanta, Emory University, Atlanta, GA, USA. [7]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA. [8]University of Texas MD Anderson Cancer Center, Houston, TX, USA. [9]University of California, San Francisco, San Francisco, CA, USA. [10]Children's Hospital of Philadelphia, Philadelphia, PA, USA. [11]Division of Pediatric Hematology, Oncology, Bone Marrow Transplant, and Cellular Therapy, Department of Pediatrics, University of Washington, Seattle, WA, USA

BACKGROUND: H3 K27M-mutant diffuse midline glioma is a universally fatal malignancy primarily affecting children and young adults; no effective systemic therapy is available. ONC201, a first-in-class imipridone, is an oral, blood-brain barrier penetrating, selective small molecule antagonist of dopamine receptor D2/3 and agonist of the mitochondrial protease ClpP. ONC201 monotherapy demonstrated durable objective responses in adults with recurrent H3 K27M-mutant glioma. This phase 1 trial will evaluate ONC201±radiotherapy (RT) in pediatric patients with H3 K27M-mutant midline glioma DIPG. METHODS: This multicenter, open-label, dose escalation and expansion phase 1 study of ONC201 is comprised of eight arms that will evaluate the recommended phase 2 dose (RP2D) of ONC201, biomarkers, and pharmacokinetics (PK) of ONC201±RT 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 PK and intratumoral ONC201 exposure in biopsy-eligible pediatric tumors (DIPG or contrast-enhancing thalamic glioma). Patients eligible for Arm H will be aged 2-≤19 years, ≥2 weeks from last RT administration, and have a KPS/LPS ≥50; prior 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), with three patients undergoing 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 METASTASIS USING SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER)

Caleb Stahl[1], Angel Baroz[1], Debarati Bhanja[1], Hannah Wilding[1], Alireza Mansouri[2]; [1]Penn State College of Medicine, Hershey, PA, USA. [2]Department of Neurosurgery, Penn State College of Medicine, Hershey, PA, USA

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 cohort. METHODS: Data were collected from the Surveillance, Epidemiology and End Results (SEER) database, version 8.3.4 (22 March 2017). Three cohorts were created based on the FDA approval date of IT: ipilimumab (2011), nivolumab (2014), and nivolumab plus ipilimumab (2015) for use in metastatic melanomas. Respectively, the cohorts are defined as the pre-IT era cohort (2010), early-IT era cohort (2011-2015) and late-IT era cohort (2016-2018). One-year overall survival (OS), 2-year OS, and median OS were assessed using a Kaplan-Meier analysis and log rank tests. RESULTS:

1,893 patients were included in this analysis (190 in the pre-IT era, 1,021 in the early-IT era, and 682 in the late-IT era) that had histologically confirmed melanoma with secondary BM at diagnosis. Median OS was significantly increased across the pre-, early-, and late-IT era cohorts, respectively, with the largest increase occurring between the early-IT and late-IT eras (1-year OS: 20.6% vs. 17.0% vs. 38.2%, 2-year OS: 10.5% vs. 14.2% vs. 27.1%, and median OS: 5 vs. 6 vs. 8 months, p < 0.001 by log-rank test). CONCLUSION: The introduction of IT for malignant melanomas has significantly improved the survival outcomes of melanoma patients with brain metastasis. Novel treatment paradigms involving IT with other adjuvant therapies need to be explored to further improve intracranial activity in melanoma patients.

SYST-09

IMPACT OF END-STAGE RENAL DISEASE AND CONCOMITANT DIALYSIS ON THE EFFICACY OF IMMUNOTHERAPY IN BRAIN METASTASES PATIENTS: A PROPENSITY-MATCHED SURVIVAL ANALYSIS

Angel Baroz[1], Debarati Bhanja[1], Caleb Stahl[1], Hannah Wilding[1], Alireza Mansouri[2]; [1]Penn State College of Medicine, Hershey, PA, USA. [2]Department of Neurosurgery, Penn State College of Medicine, Hershey, PA, USA

INTRODUCTION: Mounting evidence demonstrates the therapeutic promise of immunotherapies (ITs) for brain metastases (BM). However, there is concern that stringent eligibility criteria in these clinical studies have selected against patients with comorbid conditions. As a result, it remains unclear if these results are truly applicable to the general population, particularly in individuals with end-stage renal disease (ESRD) on dialysis. Therefore, we sought to determine the impact of concomitant dialysis treatment and IT on overall survival (OS) of patients with BM. METHODS: Data were collected from TriNetX (TriNetX, Inc., Cambridge, MA), a global research network that aggregates clinical data from 92 healthcare organizations. Independent variables included 'secondary malignant neoplasm of brain', 'ipilimumab', 'pembrolizumab', 'ESRD', 'dependence on renal dialysis', and 'dialysis services and procedures'. Patients with BM receiving IT were dichotomized by dialysis use. Cohorts were propensity matched on age, gender, and race. Kaplan-Meier analyses and log rank tests were conducted to assess overall survival (OS) and survival probability over a five-year period. RESULTS: Of the 14,368 confirmed BM patients treated with IT, 95 (0.6%) began dialysis within three months of IT initiation. Propensity matching established 95 patients in each cohort. The dialyzed cohort had a median OS of 277 days with a survival probability of 11.6%, compared to the non-dialyzed group with a median OS of 419 days and survival probability of 40.29% (p=0.109; hazard ratio 1.422, 95% confidence interval, 0.923-2.191, p=0.891). A separate comparison cohort was created to compare ESRD diagnosis with or without dialysis (n=56 and n=106 respectively). The comparison cohorts did not show a difference in median OS and survival probability (p=0.49). CONCLUSION: Despite their health complexities, individuals with ESRD, with or without dependence on dialysis, may nonetheless derive a similar survival benefit from ITs. Therefore, we advocate for greater inclusion of patients with advanced comorbidities in clinical trials to assess for real-world safety and efficacy outcomes.

SYST-10

CSNO2012001 STUDY: A PHASE III TRIAL ON ADJUVANT TEMOZOLOMIDE CHEMOTHERAPY WITH OR WITHOUT INTERFERON-ALPHA IN NEWLY DIAGNOSED HIGH-GRADE GLIOMAS

Zhongping Chen, Chengcheng Guo; SYSUCC, Guangzhou, China

PURPOSE: The therapeutic efficacy and toxicity of the combination of temozolomide (TMZ) with interferon-alpha (IFN-α) and TMZ alone were compared in newly diagnosed high-grade glioma (HGG) patients. PATIENTS AND METHODS: Following surgery, patients with newly diagnosed HGG were eligible and randomized into two groups. All the patients received standard radiotherapy concurrent with TMZ. After a 4-week break, patients in group A received standard TMZ (200mg/m2 for 5 days) combined with interferon-α (3mIU, subcutaneous, d1, d3, and d5) every 28 days. Patients in group B received standard TMZ. RESULTS: A total of 199 HGG patients were enrolled, with a median follow-up time of 77.9 months. The median overall survival (OS) of patients in the TMZ+IFN group was significantly longer than that in the standard group (TMZ+IFN: 26.67 months, TMZ: 18.83 months, P=0.005), although the progression-free survival (PFS) of both groups was similar (TMZ+IFN:14.83 months, TMZ:12.90months, P=0.114). In grade 3 gliomas, the median OS was 39.57 months in the TMZ+IFN group versus 29.40 months in TMZ alone (P=0.043). The median PFS was also longer in the TMZ+IFN group (24.33 months) than that in the TMZ group (14.13 months) (P=0.046). In grade 4 gliomas, the difference in PFS survival between TMZ+IFN and TMZ group showed no significant difference (TMZ+IFN:12.00 months, TMZ:12.83 months, P=0.582). However, the TMZ+IFN group had a

longer OS than that of the TMZ alone group (TMZ+IFN:20.53 months, TMZ:17.70 months, P=0.044). TMZ+IFN also significantly improved the OS in O6-methylguanine-DNA methyltransferase (MGMT) unmethylation patients. The incidence of toxic effects such as neutropenia, thrombocytopenia, anemia, increased transaminase, skin reactions, fatigue, nausea, or vomiting, and skin reactions were similar in both groups. CONCLUSIONS: Compared with the standard regimen, TMZ+IFN combination treatment could prolong the survival time of HGG patients, especially MGMT promoter unmethylated patients, and the toxicity remained tolerable.

SYST-11

PHASE 2 STUDY OF VAL-083 AND RADIOTHERAPY IN NEWLY DIAGNOSED MGMT-UNMETHYLATED GBM

Zhongping Chen, Chengcheng Guo; SYSUCC, Guangzhou, China

VAL-083 is a novel bi-functional DNA targeting agent that induces inter-strand DNA cross-links at N7-guanine, leading to DNA double-strand breaks and cell death. In vitro and in vivo studies have demonstrated VAL-083 circumvents MGMT-mediated chemoresistance and differentiates it from other therapies used in the treatment of GBM, including temozolomide (TMZ). VAL-083 also acts as a radiosensitizer against GBM cancer stem cells in vitro. A Phase 2 study was conducted to evaluate the safety and tolerability of VAL-083 when administered concurrently with radiation therapy (RT) in newly diagnosed MGMT unmethylated GBM. Stage 1 was a dose-escalation phase to confirm the dose of VAL-083 in this setting. Patients received VAL-083 at 20, 30, or 40 mg/m2/day x 3 days every 21 days in combination with standard radiation treatment (RT) (2 Gy/day, 5 days/week for 6 weeks). Stage 2 was an expansion phase to enroll up to 20 additional patients at the 30 mg/m2/day of VAL-083 with RT. A total of 29 patients were enrolled in the study and completed treatment, with 25 patients receiving 30 mg/m2/day VAL-083. The median number of cycles completed by all patients was 9 (range 2-13). Consistent with our prior experience, myelosuppression was the most common adverse event. Pharmacokinetics (Cmax and AUC) of VAL-083 were broadly linear with respect to dose, and drug half-life was 0.8 hrs. In a sub-group of patients, levels of VAL-083 in CSF were found to be at least as high as those in plasma. The median progression free survival (PFS) for all patients enrolled was 9.3 (95%CI: 6.4-12.0) months. Eighteen (18/29; 62.1%) patients have died, and median overall survival for all patients enrolled was 19.6 (95%CI: 14.0-22.4) months. These results support the potential benefit of VAL-083 as a treatment alternative against GBM tumors with MGMT-mediated resistance to TMZ. Clinicaltrials.gov: NCT03050736.

SYST-12

D2C7 CAR: A NOVEL CAR T CELL THAT SIMULTANEOUSLY TARGETS WILDTYPE EGFR AND ITS MUTANT ISOFORM EGFRVIII FOR TREATMENT OF GLIOMA AND BRAIN METASTASES

Daniel Wilkinson, Katherine Ryan, Joseph Wilson, Vidyalakshmi Chandramohan, Darell Bigner, Peter Fecci; Duke University, Durham, NC, USA

INTRODUCTION: Chimeric antigen receptor (CAR) T-cells represent a revolutionary class of immunotherapy, achieving considerable success in hematological cancers but generally failing to control solid tumors, including gliomas, partly due to the lack of a ubiquitously-expressed target antigen. In this study, we engineered a novel CAR T-cell consisting of the D2C7scfv targeting moiety that binds a shared epitope between EGFR and EGFRvIII. EGFR is the most homogeneous antigen on glial brain tumors, and the mutant EGFR variant, EGFRvIII, is present on a considerable subset of high grade gliomas. CAR T-cells targeting EGFRvIII alone fail to treat tumors possessing as few as 5-10% EGFRvIII-negative cell. Thus, D2C7 CAR is expected to be superior to the EGFRvIII CAR. METHODS: We retrovirally transduced T-cells with a vector encoding the D2C7scFv in tandem with intracellular signaling domains of CD28, 4-1BB, and CD3 to generate D2C7 CAR. We co-cultured D2C7 CAR or control CAR with fluorescently-tagged tumor cells expressing either EGFRwt or EGFRvIII to validate efficacy and specificity by flow cytometry. To determine in vivo efficacy, EGFRwt or EGFRvIII-expressing tumors were implanted intracranially in immunodeficient NSG mice. 48 hours later, D2C7 CAR, VIII CAR, or Mock CAR were administered intracranially and mice were monitored for survival. RESULTS: D2C7 CAR specifically killed tumor cells that expressed either EGFRwt or EGFRvIII, but not cells that lacked EGFR. Intracranial D2C7 CAR administration resulted in significantly prolonged survival of mice bearing EGFRwt or EGFRvIII tumors compared to Mock CAR controls. Importantly, D2C7 CAR significantly benefitted mice bearing a heterogeneous mix of EGFRwt and EGFRvIII tumor cells, a model of tumor heterogeneity. CONCLUSIONS: D2C7 CAR is efficacious against EGFRwt/EGFRvIII heterogeneous tumors. Intracranial administration of D2C7 CAR is predicted to safely and effectively treat a large cohort of patients due to the relatively high prevalence of EGFR and/or EGFRvIII-expressing brain tumors.