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

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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

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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

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VAL-083 is a novel bi-functional DNA targeting agent that induces interstrand 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

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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 CD3ζ 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.