(RP2D) for further study. Toxicity is assessed based on NCI CTCAEv5 and tumor response is assessed by RECIST 1.1. CNS exposure is evaluated in patients via CSF collection with confirmed CNS disease involvement.

TRLS-07. INTRACAVITARY CARRIER-EMBEDDED CS131 BRACHYTHERAPY FOR RECURRENT BRAIN METASTASES: A RANDOMIZED PHASE II STUDY

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BACKGROUND: The salvage treatment of recurrent brain metastases after failed irradiation is a clinical challenge. Adjuvant SRS is standard of care for resected brain metastases in the upfront post-resection setting given a significant local control advantage over surgery alone. However, the role of reirradiation following salvage resection of recurrent post-irradiation metastases is unclear owing to both reduced efficacy of subsequent courses of external beam radiation, and likely increased risk of radiation injury. Intracavitary cesium 131 (Cs131) brachytherapy offers a highly conformal adjunct radiation option that we hypothesize may allow for improved local control while also theoretically conveying a low risk of radiation necrosis. In this randomized controlled study, we aim to define the potential benefits and risks of resection plus permanently implanted, carrier-embedded intracavitary Cs131 brachytherapy versus conventional care (surgery alone). METHODS: This is a single-center randomized controlled study of patients undergoing resection of recurrent, previously-irradiated brain metastases. Exclusion criteria include prior in-field infection, prior radiation >100Gy (in 2Gy fraction equivalents), >5 additional active or untreated CNS lesions, or leptomeningeal carcinomatosis. Subjects are randomized 1:1 to undergo either surgery with placement of Cs131 brachytherapy or surgery alone. The primary endpoint is freedom from treated-site progression at 9 months. Secondary endpoints include wound complications at 3 months and time to local retreatment at the index site, and exploratory objectives include neurocognitive function prior to surgery and at 3 and 12 months postoperatively, with correlative analyses of the previously irradiated brain metastasis tissue. Accrual began on December 24, 2020 and 5 of a planned 76 patients have enrolled. This is the first randomized controlled trial of surgery plus permanently implanted intracavitary Cs131 brachytherapy versus surgery alone for recurrent brain metastases.

ClinicalTrials.gov Identifier: NCT04690348

LEPTOMENINGEAL DISEASE

LMD-01. QUANTIFYING INTRATHECAL DRUG DELIVERY UTILIZING PROGRAMMABLE VENTRICULOPERITONEAL SHUNTS

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BACKGROUND: Programmable ventriculoperitoneal shunts (pVP shunts) are increasingly utilized for intraventricular chemotherapy, radioimmunotherapy, and/or cellular therapy. Shunt adjustments allow optimization of thecal space drug concentrations with minimization in the peritoneum. Drug delivery quantification using several types of pVP shunts has not been reported. METHODS: We performed a retrospective analysis on patients with CNS tumors and pVP shunts at Memorial Sloan Kettering Cancer Center from 2003–2020, noting shunt model. CSF flow through the pVP shunt was evaluated using In-111-DTPA scintigraphy at approximately 4 and 24 hours after injection. pVP shunts were calibrated pre-injection to minimize peritoneal flow and re-calibrated to baseline setting 4–5 hours following injection. Scintigraphy studies quantified ventricular-thecal and peritoneal drug activity at these 2 time points. RESULTS: Twenty-one CSF flow studies were administered to 15 patients, ages 1–27 years. Diagnoses included medulloblastoma (N=10), metastatic neuroblastoma (N=3), pineoblastoma (N=1), and choroid plexus carcinoma (N=1). Models of pVP shunts included Aesculap Miethke proGAV (N=3), Aesculap Miethke proGAV2.0 (N=3), Codman HAKIM (N=2), Codman Certas Plus (N=1), Medtronic STRATA (N= 5), and Sophysa Polaris (N= 1). All 21 studies (100%) demonstrated ventriculo-thecal drug activity. 29% (6 of 21) of the studies had no peritoneal uptake visible by imaging. 73% (16 of 21) of the studies had minimal peritoneal uptake (<12%), and 24% (5 of 21) demonstrated moderate peritoneal uptake (12–37%). Models of pVP shunts measuring minimal to no peritoneal uptake included: Aesculap Miethke proGAV (N=2), Aesculap Miethke proGAV2.0 (N=3), Codman HAKIM (N=2), Codman Certas Plus (N=1), Medtronic STRATA (N= 3), and Sophysa Polaris (N= 1). CONCLUSIONS: pVP shunts successfully deliver drugs to the ventriculothecal space with 80% of studies having minimal (<12%) peritoneal drug activity. Though efficacy varies by shunt model, low numbers preclude conclusions regarding model superiority. CSF flow scintigraphy studies reliably assess drug distribution.

LMD-02. CEREBROSPINAL FLUID DIVERSION FOR METASTATIC LEPTOMENINGEAL CARCINOMATOSIS: PALLIATIVE, PROCEDURAL AND ONCOLOGIC OUTCOMES

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BACKGROUND: Leptomeningeal disease (LMD) occurs in 3–5% of patients with solid metastatic tumors and often portends a severe prognosis including symptomatic hydrocephalus and intracranial hypertension. Cerebrospinal fluid (CSF) shunting can provide symptomatic relief in this patient subset; however, few studies have examined the role of shunting in the palliation, prognosis and overall oncologic care of these patients. OBJECTIVE: To identify and evaluate risk factors associated with prognosis after CSF diversion and assess surgical, symptomatic and oncologic outcomes in this population. METHODS: A retrospective study was conducted on patients with solid-malignancy LMD treated with a shunt at an NCI-designated Comprehensive Cancer Center between 2010–2019. RESULTS: One hundred and ninety patients with metastatic LMD underwent CSF diversion. Overall survival was 4.14 months from LMD diagnosis (95%CI:3.29–4.70) and 2.43 months (95%CI:2.01–3.09) from shunting. KPS at time of shunting and BrM number at LMD diagnosis demonstrated significant associations with survival (HR=0.66; 95%CI[0.51–0.86], p=0.002; HR=1.40; 95%CI[1.01–1.93] per 10 BrM, p=0.04, respectively). Eighty-three percent of patients experienced symptomatic relief, and 79% were discharged home or to rehabilitation facilities post-shunting. Post-shunt, 56% of patients received additional systemic therapy or started or completed WBRT. Complications included infection (5%), symptomatic subdural hygroma/hematoma (6.3%), and shunt externalization/removal/repair (8%). Abdominal seeding was not identified. CONCLUSIONS: CSF diversion for LMD with hydrocephalus and intracranial hypertension secondary to metastasis can achieve symptomatic relief, hospital discharge, and return to further oncologic therapy, with a complication profile unique to this pathophysiology. However, decision-making in this population must incorporate end-of-life goals of care given limited prognosis.

LMD-03. SINGLE CELL ANALYSIS REVEALS HOW THERAPY REMODELS THE TUMOR MICROENVIRONMENT IN MELANOMA CNS METASTASES AND UNCOVERS A NOVEL PREDICTOR OF IMPROVED SURVIVAL

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We interrogated the microenvironment of 43 clinical samples from melanoma skin, brain (MBM) and leptomeningeal metastases (LMM) using single-cell RNA-seq analysis to determine how therapeutic intervention shaped the immune environment and affected patient survival. LMM is a poorly-characterized, devastating complication of late-stage disease, typically refractory to treatment and associated with dismal survival time. Analysis of serial specimens over the course of therapy demonstrated reductions in melanoma cells and macrophages, coupled with increased levels of T cells and dendritic cells in the CSF of a rare extraordinary responder, whereas typical poor survivors showed no improvement in T cell responses. In MBM patients, both targeted therapy and immunotherapy was associated with increased immune infiltrate. Treatment with targeted therapy was associated with an enrichment of CD8 T cells, while immunotherapy was associated with a more diverse lymphocyte landscape and higher numbers of antibody-producing cells. These findings were confirmed by multiplex-IF staining of patient specimens and using an immune-competent mouse model of MBM. Interestingly, a history of prior radiation therapy was associated with a diminished myeloid compartment. Although immune infiltrate was significantly lower in the brain compared to skin tumors, the phenotypic make-up of the lymphocyte compartment was quite similar, suggesting that the immune cells may have trafficked from the periphery to the brain post-therapy. Correlation analysis across the entire immune landscape identified the presence of a rare, novel population of dendritic cells (DC3s) to be correlated with increased overall survival, regardless of disease site/treatment. The presence of DC3s positively regulated the immune environment of both patient samples and preclinical

melanoma models through modulation of activated T cells and MHC expression in the tumor. Overall, we present the first ever comprehensive single-cell atlas of the tumor microenvironment in melanoma CNS metastases in response to therapy.

LMD-04. FLAIR HYPERINTENSITY ALONG THE BRAINSTEM SURFACE IN LEPTOMENINGEAL METASTASES: A CASE SERIES AND LITERATURE REVIEW

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BACKGROUND: The incidence of leptomeningeal metastasis (LM) is underestimated because of its non-specific signs and the low sensitivity of clinical diagnostic modalities. Cerebrospinal magnetic resonance (MR) imaging with and without contrast enhancement (CE) is a gold standard for the neuroradiological assessment of patients with suspected LM. Previous studies suggested that some LM cases show changes of the brainstem surface on non-contrast MR images without or before the appearance of abnormalities on CE images. We assessed the features of this non-contrast MR finding in a cohort of LM patients in this retrospective single-institution study. METHODS: We reviewed head MR images and clinical data of 142 consecutive patients in whom the final diagnosis was LM. RESULTS: We found that 11 of these 142 patients (7.7%) with LM had band-like hyperintensity on the brainstem surface on non-enhanced FLAIR images, which looked like bloomy rind on cheese. Three of seven patients who were examined using diffusion-weighted imaging showed restricted diffusion in the corresponding lesion site. The above-mentioned 11 patients included 10 women and 1 man, with a median age of 61 years. All 11 patients had primary lung adenocarcinoma. Seven patients had symptomatic hydrocephalus. Ten patients had EGFR-mutated and one had ALK-rearrangement adenocarcinomas. Before the diagnosis of LM, 10 patients had undergone systemic therapy with EGFR-TKI or pemetrexed, and 1 patient with ALK inhibitor and bevacizumab. CONCLUSIONS: We present a series of patients with bloomy rind sign that is non-enhancing LM reliably detected by FLAIR hyperintensity on the brainstem surface. This finding is rare, but may reflect the spread of cancer cells in both the leptomeningeal membrane and the surface of the brain parenchyma specifically in patients with lung adenocarcinomas. Further study is needed to determine the clinical significance of this sign.

LMD-05. PHASE 1B STUDY OF AVELUMAB AND WHOLE BRAIN RADIOTHERAPY (WBRT) IN PATIENTS WITH LEPTOMENINGEAL DISEASE (LMD): PRELIMINARY RESULTS.

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BACKGROUND: LMD has a dismal prognosis with median survivals of 8–10 weeks. Recently the first phase 2 trial of PD-1 inhibitor monotherapy in solid tumor LMD showed median overall survival (OS) 3.6 months. We aimed to determine the safety/efficacy of avelumab with WBRT in patients with LMD from solid malignancies (NCT0371768). This combination can treat tumor directly and increase the permeability of the blood-brain-barrier with increased egress of activated T cells into the meninges/CSF and facilitated Avelumab entry into the CSF. HYPOTHESIS: Combination radioimmunotherapy will produce an activated immunocyte/cytokine profile in CSF. METHODS: Patients received concurrent Avelumab 800mg IV q2weeks x≤5 cycles with WBRT 3000cGy, 10 fractions. Primary endpoints: Safety/DLTs and OS at 3 months. Secondary endpoints: CSF T-cell/cytokine profiles (scRNAseq/phosophoproteomics) and clinical outcomes, to be performed when all 15 patients are accrued to minimize batch effects. RESULTS: Ten patients (5 breast, 4 lung & 1 undifferentiated sinonasal carcinoma) were enrolled (n=8 females, n=2 males, ages 32–79); n=1 patient did not complete WBRT. Patients who received anti-PD-1/PD-1L/PD-L2/CD137/CTLA-4 therapy within 6 months prior to enrollment were excluded. 30% had grade 3 AEs at least possibly related to treatment (n=3 diarrhea, lymphopenia, decreased WBC count). There were no grade 4–5 toxicities. Six patients (66.7%) were alive at 3 months. The estimated median follow up in 9 patients (regardless whether patients failed or not) is 10.49 months (range, 0.95–19.82 months, 95% CI) and the estimated median follow up survival was 19.8 months assessed using the reverse Kaplan-Meier method. Median PFS is 4.27 months (range, 0.30–16.73 months, 95% CI). CONCLUSIONS: In this pilot study, combination of Avelumab and WBRT is safe, and demonstrates encouraging activity in patients with solid tumor LMD. Multiple platform interrogation of CSF may determine mechanisms of LMD therapeutic effects and differentiate responders from non-responders.

LMD-06. A NSCLC PATIENT WITH LEPTOMENINGEAL METASTASIS HARBORING RARE EGFR MUTATIONS G719S AND L861Q BENEFITED FROM DOUBLING DOSAGE OF OSIMERTINIB: A CASE REPORT

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Leptomeningeal metastasis (LM) is a rare but lethal complication of advanced non-small cell lung cancer (NSCLC) that has a devastating impact on patient survival and quality of life. Osimertinib, an irreversible tyrosine kinase inhibitor, is approved as a therapy for advanced NSCLC with epidermal growth factor receptor (EGFR) mutation. However, the efficacy and optimal dosage of osimertinib in the treatment of NSCLC patients with LM who harbor uncommon *EGFR* mutations have yet to be fully investigated. Herein, we report a case of an advanced NSCLC patient with LM carrying *EGFR* G719S and L861Q, who was successfully treated by osimertinib at 160 mg. The patient initially presented with clear cell renal carcinoma and renal metastatic adenocarcinoma, and underwent right nephrectomy. At 2 months after nephrectomy, He developed a disturbance of consciousness and was subsequently diagnosed with NSCLC with LM by meningeal biopsy pathology and cerebrospinal fluid (CSF) cytology. Next-generation sequencing detected the rare *EGFR* mutations G719S and L861R in the meningeal biopsy tissues. The patient was then administered osimertinib at 80 mg quaque die (QD); after 1 month of treatment, his symptoms were alleviated. However, two months later, he experienced epileptic episode. Subsequently, the osimertinib dosage was doubled to 160 mg QD. After 1 month of treatment, the patient achieved central nervous system (CNS) response, and at the time of this manuscript's submission, he had maintained stable disease (SD) for more than 1 year. To our knowledge, this study provides the first clinical evidence that the administration of osimertinib at 160 mg once daily can achieve an encouraging, durable response in an NSCLC patients with LM carrying *EGFR* G719S and L861Q. Aslo, it is recommended to consider performing leptomeningeal biopsy for precision treatment in NSCLC paiernts with leptomeningeal metastasis.

LMD-07. *IN VITRO* AND *IN VIVO* CULTURE OF PATIENT DERIVED-CEREBRAL SPINAL FLUID-CIRCULATING TUMOR CELLS (PD-CSF-CTCS) IN LEPTOMENINGEAL DISEASE (LMD) FROM MELANOMA TO IDENTIFY NOVEL TREATMENT STRATEGIES

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BACKGROUND: Approximately 5% of melanoma patients (pts) will develop LMD. Currently there is no effective treatments for this disease. A significant barrier to the development of effective therapies has been the inability to culture CSF-CTCs for functional analysis. For the first time, we were able to successfully expand CSF-CTCs *in vitro* and *in vivo*. We assessed gene signatures of PD-CSF-CTCs to determine novel targets for therapy. As a proof of concept, we tested the efficacy of combining ceritinib (cer), an IGF-1R inhibitor and trametinib (tra), a MEK inhibitor, against LMD. METHODS: CSF from 11 pts were collected from various sources (ie: LPs, Ommayas, rapid autopsies). PD-CSF-CTCs were expanded *in vitro* in conditioned media and *in vivo* using cell line-derived xenograft model. Single-cell RNA-sequencing (scRNAseq) analysis was performed to assess transcriptional profiles of PD-CSF-CTCs. RESULTS: Of the total 61 PD-CSF-CTCs collected from 11 pts (avg: 4.07 CSF collections/patient), we successfully cultured PD-CSF-CTCs from 3 pts (20%) and were able to grow them *in vivo* from 2 pts (18%). scRNAseq identified IGF-1R, Sox9, ErbB3 and MLANA were among the enriched genes for PD-CSF-CTCs. IGF-1R inhibition by cer and depletion by CRISPR suppressed cell growth. We evaluated the responses of cer + tra treatment *in vitro* and found that combining these agents produced drug synergy against PD-CSF-CTCs and resensitized BRAF inhibitor-resistant melanoma cell line, WM164R. *In vivo* LMD xenograft model showed cer + tra treatment significantly prolonged median survival of PD-CSF-CTCs LMD (control: 27 days vs treatment: 38.5 days; P value < 0.032) and WM164R LMD (control: 35 days vs treatment: MS not reached; P value < 0.047). CONCLUSIONS: Though the sample size is small, this is the first report of the successful *in vitro* and *in vivo* culture of CSF-CTCs from pts with LMD.