an important mediator of breast cancer stem cells (BCSC); however, FDA-approved therapies targeting smoothened have demonstrated limited clinical efficacy in breast cancer. Despite advances made in understanding BCSC, it is still challenging to effectively target BCSC, underscoring the need to identify and inhibit novel mediators of BCSC for treating BCBM patients. Our laboratory recently reported that truncated glialia-associated oncogene homolog 1 (tGLI1) promotes preferential metastasis to the brain in breast cancer by recruiting BCSC and astrocytes in the tumor microenvironment (Onconege 39:64–78, 2020); tGLI1 was discovered in our laboratory as an alternatively spliced GLI1 that functions as a tumor-specific gain-of-function transcription factor and terminal effector of the hedgehog pathway. We found that tGLI1 knockdown ablated BCBM, providing the rationale to therapeutically target tGLI1. Cell-based optical screens followed by validations demonstrated that ketoconazole, an FDA-approved azole antifungal, specifically inhibits tGLI1 leading to suppression of BCSC in vitro and BCBM in vivo. Based on these data, we opened a window-of-opportunity study in patients with BCBM to define if ketoconazole penetrates the blood-brain barrier (BBB) and alters tGLI1 signaling in humans (NCT03796273). Preliminary sample analysis has confirmed tGLI1 expression in collected BCBM samples. To help identify more effective tGLI1 inhibitors, we screened 63azole compounds for tGLI1-selectivity and identified four additional compounds as potential tGLI1 inhibitors. Animal studies were performed to compare the efficacy of these four compounds with ketoconazole in suppressing BCBM. Collectively, these data establish tGLI1 as an actionable target for BCBM.

55. A RANDOMIZED, MULTICENTER PHASE III TRIAL OF SURGERY PLUS STEREOTACTIC RADIOSURGERY (SRS) COMPARED WITH SURGERY PLUS PERMANENTLY IMPLANTED COLLAGEN TILE BRACHYTHERAPY (CTB) FOR RESECTABLE METASTATIC BRAIN TUMORS-PROTOCOL IN PROGRESS

Jeffrey Weinberg, MD,1 Mary Frances McAulier, MD, PhD,2 Hussein Tawbi, MD, PhD,3 and Frederick Lang, MD1.1The University of Texas MD Anderson Cancer Center, Dept of Neurosurgery, Houston, TX, USA, 2The University of Texas MD Anderson Cancer Center, Dept of Radiation Oncology, Houston, TX, USA, 3The University of Texas MD Anderson Cancer Center, Dept of Melanoma Medical Oncology, Houston, TX, USA

BACKGROUND: Resection (R) followed by single or multi-fraction stereotactic radiosurgery (SRS) lowers resection bed recurrence compared to R alone. Nevertheless for larger brain metastasis (>2.5 cm) 12-month recurrence rates after R+SRS can exceed 20–30%. Aiming to improve outcomes, a permanently implanted collagen tile brachytherapy (CTB) device (GammaTile, GT Medical Technologies, Tempe AZ) utilizing Cs-131 was developed, hypothesizing that immediate adjuvant radiotherapy (RT) and/or RT dose intensification could improve outcomes. The device received FDA clearance for this indication, based on a single-arm pre-commercial study and in early commercial use due to the excellent safety and local control of R+CTB. It is hypothesized that R+CTB will increase the time to post-R+CTB progression compared to R+SRS by prolonging survival and reducing the impact on functional and neurocognitive status compared to R+SRS. STUDY DESIGN: Multicenter, randomized, comparison trial. Patients with resectable, previously untreated “index” brain metastases measuring ≥2.5–5 cm and ≥5 cm, respectively, and resectable isolated brain metastases were randomized 1:1 to receive R+SRS or R+CTB to the index lesion; untreated tumors in both groups will receive SRS. Planned sample size is 160 to ~5 sites; accrual to start in Q3-2020. Primary endpoint is surgical bed-recurrence free survival. Secondary endpoints include overall survival, quality of life (Functional Assessment of Cancer Therapy-Brain), time to new intervention, neurocognition (Hopkins Verbal Learning Test, Trail Making Tests, Mini-Mental Status Exam, Controlled Oral Word Association), functional decline (Karnofsky Performance Scale, Barthel-ADL), and adverse events. Follow-up will be at 1, 3, 6, and 9, and months, then 6 months through 5 years. CONCLUSIONS: This will be the first randomized trial comparing R+SRS vs R+CTB delivered by Cs-131 sources in permanently implanted resorbable collagen tile carriers. Primary outcome measures will be captured to elucidate the potential risks and benefits of these two differing approaches for patients with metastatic brain tumors.

56. TUMOR-HOMING STEM CELL THERAPY INHIBITS THE PROGRESSION OF BREAST CANCER LEPTOMENINGEAL CARCINOMATOSIS

Wulin Jiang1, Alain Valdivia2, Alison Mercer-Smith1, Carey Anders1, and Shawn Hinglent2.1University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 2Duke University, Durham, NC, USA

INTRODUCTION: Leptomeningeal carcinomatosis remains one of the most lethal forms of central nervous system metastasis, with a median survival of only 4 months. Effective and distant metastatic effective therapies are urgently needed to treat this highly aggressive cancer. In this study, we used models of both prophylactic
lactic and established leptomeningeal disease to investigate the efficacy of engineered tumor-homing neural stem cells (NSCs) therapy for breast cancer leptomeningeal carcinomatosis. METHODS: Personalized NSC carriers were created using Sox2 overexpression to transdifferentiate human fibroblasts into induced NSCs (iNSCs) that home to cancer cells and carry therapeutic agents to induce tumor kill. Leptomeningeal models were created by engineering MDA-MB231-Br human breast cancer cells with fluorescent and bioluminescent reporters, then using intracranial injection to inoculate nude mice with the tumor cells. iNSC therapy was evaluated by infusing iNSCs releasing the pro-apoptotic agent TRAIL into the lateral ventricle of mice either 1 week prior to or 3 days after tumor inoculation for prophylactic or established tumor treatment respectively. Tumor progression in the brain and spinal cord was monitored by serial brain MRI. RESULTS: Serial BLI showed that intracerebroventricular (ICV) iNSC-TRAIL therapy delivered the volume of metastatic tumor burden 99.49% in the brain and 99.80% in the spine within 2 weeks post-infusion and extended survival from 24 to 42 days. Additionally, prophylactic iNSC-TRAIL therapy delivered ICV markedly delayed tumor development, with tumors in the brain remaining >1000-fold smaller than control through 1-month post-treatment, below the limit of detection in the spinal cord through 1 month, and eliminating mortality through 50 days post-treatment. CONCLUSION: These data suggest that iNSC therapy could be a promising treatment option for breast cancer patients with leptomeningeal carcinomatosis.

57. CIRCULATING TUMOR CELLS (CTC) IN CEREBROSPINAL FLUID (CSF) AS A PREDICTOR OF SURVIVAL IN CNS METASTASES Maria Djar1, Priya Singh2, Ivan Kotekova1, Anna Skakodub1, Anne Reiner1, Katherine Panagias1, Lakshmi Ramanathan1, and Ellen Pentzwala1, 1Department of Neurosurgery, Sloan Kettering Cancer Center, New York, NY, USA, 2Hunter College/Macaulay Honors College, New York, USA

BACKGROUND: CSF-CTC testing using the CellSearch® platform is a useful tool for leptomeningeal metastases (LM) from solid tumors. CSF-CTCs can also be detected in patients with brain metastases (BM), but their significance is unclear. Our objective was to evaluate the utility of CSF-CTC measurement in predicting outcomes in CNS metastases. METHODS: We conducted a retrospective single-institution review of patients who underwent CSF-CTC testing from 2016–2019. Information on neuroaxis imaging, CSF results, systemic cancer status, tumor molecular profile and survival was collected. LM was diagnosed by unequivocal MRI findings and/or positive or suspicious CSF cytology. Survival analyses were performed using Cox proportional hazards modeling, and CSF-CTC splits associated with survival were identified through recursive partitioning analysis. RESULTS: A total of 407 patients (38% lung primary, 34% breast, 28% other tumor types) were included; of these, 144 had LM and 233 had BM diagnosed before or around the time of CSF analysis (97 had both). We identified a subgroup of newly diagnosed CNS metastases, comprising 144 patients with LM, BM, or both diagnosed within 30 days of CSF sampling: 70 patients with LM, 43 with BM, and 31 with both. For 101 patients with newly diagnosed LM, mean age was 57 years, 96% had advanced NSCLC at diagnosis and of available brain and spine MRI imaging. RESULTS: Among 23 eligible patients aged 18–77 years, 96% had advanced NSCLC at diagnosis and 61% had EGFR exon 19 deletion. Median time from NSCLC diagnosis to LC development was 23 months (95% CI:13–33), with only 17% of patients presenting with LC in the absence of parenchymal brain metastases. Of the 91% of patients with radiographic evidence of LC, equal numbers had nodular or linear LC (22% each) and 39% had a mixed presentation. Additionally, 30% of patients had evidence of spinal LC. Ventriculomegaly was present in 52% of patients, with 48% developing clinical symptoms of hydrocephalus and 13% receiving shunt placement. Median overall survival (OS) from time of LC diagnosis was 3.9 months (95% CI:2.7–10.0), which is consistent with published studies. Patients with nodular LC and absence of ventriculomegaly fared better with a median OS of 6.5 months and 5.7 months respectively. CONCLUSIONS: OS is poor in patients with LC associated with EGFR mutated NSCLC, although appears better in patients with nodular LC. The high incidence of hydrocephalus emphasizes the need for its early recognition and further studies are needed to identify promising treatment strategies and to determine factors associated with improved OS in this population.

59. A RADIOMIC-BASED MACHINE LEARNING MODEL FOR DISTINGUISHING RADIATION NECROSIS FROM PROGRESSION OF BRAIN METASTASES TREATED WITH STEREOTACTIC RADIOTHERAPY (SRS)

Xuqiang Chen1, Vishva Parekh1,2, Luke Peng3, Michael Chan4, Michael Soike3, Emory McTye5, Michael Jacobs6,7, and Lawrence Kleinberg2, 1Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2Department of Computer Science, Johns Hopkins University, Baltimore, MD, USA, 3Russell H, Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD, USA, 4Department of Radiation Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, Boston, MA, USA, 5Department of Radiation Oncology, Wake Forest School of Medicine, Winston-Salem, NC, USA, 6Sidney Kimmel Comprehensive Cancer Center, IRAT Core, Johns Hopkins University School of Medicine, Baltimore, MD, USA

PURPOSE: This study aims to test whether MRI radiomic signatures can distinguish radiation necrosis (RN) from tumor progression (TP) in a multi-institutional dataset using machine learning. METHODS: Brain metastases treated with SRS were followed by serial MRI, and those showing evidence of RN or TP underwent pathologic confirmation. Radiomic features were extracted from T1 post-contrast (T1c) and T2 fluid attenuated inversion recovery (T2 FLAIR) MRI. High dimensional radiomic feature space was visualized in a two-dimensional space using t-distributed stochastic neighbor embedding (t-SNE). Cases from 2 institutions were combined and randomly assigned to training (2/3) and testing (1/3) cohorts. Backward elimination was used for feature selection, followed by random forest algorithm for predictive modeling. RESULTS: A total of 135 individual lesions (37 RN and 98 TP) were included. The majority (72.6%) received single-fraction SRS to a median dose of 18 Gy. Clear clustering of cases around the institutional origin was observed on t-SNE analysis. 21 T1c and 4 FLAIR features were excluded due to significance testing with the institutional origin. Backward elimination yielded 6 T1c and 6 FLAIR features used for model construction. A random forest model based on the 6 FLAIR features (cluster shade, neighborhood gray tone difference matrix NGLD, texture strength, GNTLZ, run percentage, and short run high gray-level emphasis) achieved sensitivity of 76% and specificity of 70% on the training cohort (AUC 0.74, 95% CI 0.60–0.88), and sensitivity and specificity of 83% on the testing cohort (AUC 0.75, 95% CI 0.59–0.93). Addition of the T1c features resulted in overfitting of the training cohort (AUC 1.00), but did not improve model performance on the testing cohort (AUC 0.69, 95% CI 0.51–0.87). CONCLUSION: MRI radiomics based machine learning can distinguish RN from TP after brain SRS in a heterogeneous image dataset.

60. IDEAL TREATMENT REGIMES FOR PATIENTS WITH ≥2 BRAIN METASTASIS FROM PRIMARY NON-SMALL CELL LUNG CANCER (NSCLC) – A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Karabiri Bhar1, Yosef Ellenbogen2, Behnam Sadeghirad1, Jiawen Deng2, Winston Hou3, Xiaoxin Wang2, Shervin Taslimi2, and Alireza Mansouri4, 1Faculty of Medicine, University of Toronto, Toronto, ON, Canada, 2Division of Neurosurgery, University of Toronto, Toronto, ON, Canada, 3Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada, 4Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada, 5McMaster University, Hamilton, ON, Canada, 6Department of Neurosurgery, Penn State Health, PA, USA

BACKGROUND: Brain metastases (BM) are common in non-small cell lung cancer (NSCLC). The aim of this study was to assess the comparative effectiveness of treatments for BM from NSCLC. METHODS: We searched MEDLINE, EMBASE, Web of Science, ClinicalTrials.gov, CENTRAL and references of key studies for randomized controlled trials (RCTs) published...