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 therapeutics to induce tumor kill. Leptomeningeal models were created by engineering MDA-MB-231R breast 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 using 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 survival of the mice were monitored by serial brain computed tomography (CT). RESULTS: Serial BLI showed that intracerebroventricular (ICV) iNSC-TREAT therapy delivered the volume of metastatic tumor burden 99.4% in the brain and 99.8% in the spine within 2 weeks post-infusion and extended survival from 24 to 42 days. Additionally, prophylactic iNSC-TREAT therapy delayed 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-therapy. 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

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BACKGROUND: CSF-CTC testing using the CellSearch® platform is a validated tool for leptomeningeal metastases (LM). CTCs from solid tumors. 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 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 and median CSF-CTCs were 277 and 210, respectively, compared to 44.6 and 0 in the overall cohort; 73/101 had positive (66) or suspicious (7) cytology. CFT-CTCs predicted survival in patients with newly diagnosed LM, with optimal cutoff identified at 61 CSF-CTCs, above which the risk of death doubled (HR=2.09, 95% CI: 1.13–3.87, p=0.02). CONCLUSION: In newly diagnosed LM, with optimal cutoff identified at 61 CSF-CTCs, above which the risk of death doubled (HR=2.09, 95% CI: 1.13–3.87, p=0.02). CSF-CTC measurement can be used as a prognostic tool in patients with CNS metastases.

58. CLINICAL PRESENTATION AND IMAGING CHARACTERISTICS OF LEPTOMENINGEAL CARCINOMATOSIS (LC) IN PATIENTS WITH EGFR MUTATED NON-SMALL CELL LUNG CANCER (NSCLC)

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BACKGROUND: LC is a late and often fatal manifestation of advanced EGFR mutated NSCLC with up to 9% of patients developing LC. Given the higher incidence of LC in EGFR mutated tumors, we hypothesized it may have unique imaging and clinical characteristics. METHODS: We identified 23 patients with EGFR mutated NSCLC and LC treated at a large academic institution between 2016 and 2019. Clinical and treatment characteristics were obtained from the electronic medical record. Radiographic subtype of LC and presence of ventriculomegaly were determined by independent review of available brain and spine MRI imaging. RESULTS: Among 23 eligible patients, 17 years, 96% had nodular LC, 86% had 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 RADIOMICS-BASED MACHINE LEARNING MODEL FOR DISTINGUISHING RADIATION NECROSIS FROM PROGRESSION OF BRAIN METASTASES TREATED WITH STEREOTACTIC RADIOSURGERY (SRS)

Xiaoguang Chen1, Vishwa Parekh1,2, Luke Peng1, Michael Chan1, Michael Soike3, Emory McTyre1, Michael Jacobs1,2, and Lawrence Kleinberg1

BACKGROUND: CSF-CTC testing using the CellSearch® platform is a validated tool for leptomeningeal metastases (LM) from solid tumors. 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 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 and median CSF-CTCs were 277 and 210, respectively, compared to 44.6 and 0 in the overall cohort; 73/101 had positive (66) or suspicious (7) cytology. CFT-CTCs predicted survival in patients with newly diagnosed LM, with optimal cutoff identified at 61 CSF-CTCs, above which the risk of death doubled (HR=2.09, 95% CI: 1.13–3.87, p=0.02). CONCLUSION: In newly diagnosed LM, with optimal cutoff identified at 61 CSF-CTCs, above which the risk of death doubled (HR=2.09, 95% CI: 1.13–3.87, p=0.02). CSF-CTC measurement can be used as a prognostic tool in patients with CNS metastases.

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

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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 in August 2020.
61. EXPRESSION OF ANDROGEN RECEPTOR IN BREAST CANCER BRAIN METASTASIS
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INTRODUCTION: Treatment options for women with breast cancer brain metastases (BrM) are generally limited to surgery and/or radiotherapy because most systemic therapies do not cross the blood-brain barrier. Androgen receptors (ARs) are frequently expressed in breast cancer and anti-androgenic therapies have been shown to penetrate the central nervous system. In this study, we analyzed the expression of AR in breast cancer BrM to identify patients who may benefit from anti-androgenic therapies.

METHODS: Consecutive BrM resected in our institution (July 1999–June 2013) were identified from the Anatomic Pathology departmental database. Cases that were signed out as breast origin given the available immunohistochemical profile and clinical history were included. A tissue microarray was constructed using 1 mm cores in triplicates and stained by immunohistochemistry for AR, ER, PR and HER2 (SP107, SP1, IE2, 4B5; Ventana Medical Systems, Tucson AZ, USA). Immunohistochemistry was used to determine intensity of expression in two subtypes. AR+, AR− = <10% staining.

Among 61 breast cancer BrM with available tissue blocks, AR was expressed in 38 (62%) cases. Among BrMs of luminal A subtype (ER+, PR+/−, HER2−) 50% expressed AR (n=12). Within the luminal B subtype (ER+, PR+, HER2−) 28% expressed AR (100%), while HER2+ was expressed in HER2− BrM: ER− (n=8/16). Among 14 BrM of HER2+ subtype (ER−, PR−, HER2+), 71% expressed AR (n=10/14). Only 30% of triple negative BrM (ER−, PR−, HER2−) were AR+ (n=4/14). CONCLUSION: Almost two-thirds of breast cancer BrM expressed AR. HER2+ luminal B and HER2+ subtypes were most likely to be AR+, while only 30% of triple negative BrM were AR+. Our data suggests that certain subtypes of breast cancer BrM are more likely to be AR+ and could serve as a potential therapeutic target.

62. PRESENCE OF EXTRACRANIAL TUMORS INFLUENCES RESPONSE TO IMMUNE CHECKPOINT INHIBITORS IN A PRE-CLINICAL MODEL OF MELANOMA BRAIN METASTASIS
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Up to 75% of patients with melanoma develop brain metastases. While immune checkpoint inhibitors (ICI) targeting PD-1 and CTLA4 have revolutionized the treatment of metastatic melanoma, responses within the immune-specialized microenvironment of the brain are not well understood and there is a paucity of animal models to investigate the effect of ICI intracranially. We characterized responses to checkpoint inhibitors in a syngeneic mouse model of melanoma brain metastasis with concurrent intracranial and subcutaneous melanoma. D1UV3 cells (obtained from David Fisher’s laboratory) were derived using UVB irradiation from D4M.3A melanoma cell line and implanted into the striatum using stereotactic injection or subcutaneously injected into the flank of C57BL/6 mice. Mice were then treated with anti-PD-1 antibody, anti-CTLA4 antibody, a combination of anti-PD-1 and anti-CTLA4, or isotype controls. While mice with intracranial melanoma alone had no response to monotherapy with anti-PD-1 or anti-CTLA4 antibody (p=1 and 0.1, respectively), and only a slight response to combination therapy (p=0.04), mice with concurrent subcutaneous tumors had significantly improved responses to anti-PD-1, anti-CTLA4 and combination treatment (p=0.002, 0.01 and 0.01 respectively compared to mice with intracranial tumors alone with equivalent treatment). These results demonstrate the presence of extracranial tumors to result in an effective antitumor response to ICI in pre-clinical mouse models of melanoma brain metastasis. We have therefore established a pre-clinical model with concurrent intracranial and extracranial tumors to better recapitulate the clinically observed context of melanoma brain metastases and lead to a better understanding of the setting in which ICI are effective for patients with this devastating complication.

64. AN ENDT-DEPENDENT, CELL-PENETRATING, AND DNA-DAMAGING LUPUS AUTOANTIBODY CROSSES THE BLOOD-BRAIN BARRIER TO TARGET BRAIN TUMORS
Zahra Rattray1, Gang Deng3, Shengli Zhang4, Anupama Shiralil1, Christopher May3, Jun Liu1, Pan Zou1, Benedette Cuffari2, Nicholas Rattray1, Caroline Johnson2, Valentina Dublijev1, James Campbell1, Anuta Hutter1, Joachim Baehringer1, Jiangbing Zhou1, 2, and James Hansen1.1Yale School of Medicine, New Haven, CT, USA, 2Patrys Ltd, Melbourne, Australia

The blood-brain barrier (BBB) limits conventional antibody-based approaches to brain tumors. ENT2, an equilibrative nucleoside transporter, facilitates penetration of autoantibodies into live cells and is expressed in the BBB. PAT-DX1 (also known as Deoxymab-1 or DX1) is an ENT2-dependent, cell-penetrating, and DNA-damaging lupus autoantibody that is synthetically lethal to cancer cells with defects in the DNA damage response. PTEN loss renders sensitivity to DX1 and is common in primary and metastatic brain tumors. We show that DX1 is toxic to spheres derived from primary PTEN-deficient glioblastoma (GBM), and crosses the BBB to suppress the growth of orthotopic GBM and breast cancer brain metastases. Mechanistically, we find the ENT2 inhibitor dipridamole blocks DX1 penetration into brain endothelial cells and transport across the BBB in vitro and in vivo, consistent with ENT2-mediated uptake of DX1 into brain tumors. Autoantibodies that hijack nucleoside transporters to cross cell membranes may open new frontiers in brain tumor therapy.

65. INVASIVE HISTOPATHOLOGY DRIVES POOR OUTCOMES IN SURGICALLY RESECTED BRAIN METASTASES
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BACKGROUND: Brain metastasis (BrM) patients treated with surgery and radiotherapy frequently experience local recurrence (LR), leptomenigeal metastasis (LM), and poor overall survival (OS). We sought to correlate the presence of invasive or circumscribed histopathological growth pattern, observed in the BrM lesion and surrounding brain, with these outcomes, and to study molecular mediators of parenchymal invasion. METHODS: We assessed the HGP of HE&E-stained slides from 164 surgically resected BrM from 147 patients. HGP was correlated with incidence of LR, LM and OS. Single-cell RNA sequencing (scRNAseq) was performed on three invasive HGP patients, sampling the metastasis center (MC) and surrounding brain (SB) outside of the contrast-enhancing region. Orthotopic patient-derived xenograft models (OPDX) were established from NS30 brain metastasis via intracranial propagation. RESULTS: 56/164 BrM specimens (34%) showed a circumscribed growth pattern between the tumor and adjacent brain (cHGP) while 108/164 (66%) showed significant invasion of tumor lobules or single cells into the brain parenchyma (iHGP). iHGP was associated with LR, LM and shortened OS in BrM patients. OPDX models of BrM exhibited features of patient BrM, including HGP. scRNAseq identified abundant cancer cells in SB that overexpressed a number of genes involved in cell survival, invasion and metastasis compared to matched cancers in MC. Validation of these targets with immunohistochemistry in patient and OPDX derived xenografts identified three promising targets: CIRBP, patataxin, and HOXD11. CONCLUSION: iHGP is a poor prognostic indicator in patients with surgically resected BrM, establishing HGP as an clinical parameter.