pts and 8 melanoma pts without LMDz were studied. All but 1 LMDz pts (92%) had CSF-CTCs (avg: 2148.60; range 23 - 3055 CTCs/ml). In contrast, 3/8 (37%) melanoma Brain Mets pts without LMDz had CSF-CTCs but fewer of them (avg: 0.31; range 0.13 - 0.6 CTCs/ml CSF). *CSF-CTCs Profile:* These had BrafV600E (83%), and GNAQ Q209P & NRAS Q61R in 1 pt each. *Ex-vivo culture of CSF-CTCs and PDX model:* After lengthy optimization of conditions we successfully expanded CSF-CTCs *in-vitro* (~25% of pts), and *in-vivo* in immunodeficient mice from 1 pt (~10% of samples). Ceritinib, used as a FAK inhibitor, with MEKi was effective *in-vitro* (p=3.17e^{-6}) and prolonged survival *in-vivo* in LMDz (median survival: >32 days vs control: 18 days; p=7.81e^{-5}). CONCLUSIONS: Though the sample size is small, this is the first report of the successful *in-vitro* & *in-vivo* culture of CSF-CTCs from pts with LMDz. Single cell analysis to determine how representative these models are and further *in-vivo* testing are in progress.

LPTO-04. GENERATION AND CHARACTERIZATION OF PATIENT-DERIVED PRECLINICAL MODELS FROM TUMOR CELLS ISOLATED FROM CEREBROSPINAL FLUID

Michael Offin, <u>Morana Vojnic</u>, Zebing Liu, Allan Lui, Evan Siau, Eric Gladstone, Marissa Mattar, Inna Khodos, Alexander Drilon, Adrienne Boire, Charles Rudin, Elisa De Stanchina, Marc Ladanyi, and Romel Somwar; Memorial Sloan-Kettering Cancer Center, New York, NY, USA

BACKGROUND: CNS metastases occur in 20–50% of lung cancer patients during their disease; leptomeningeal disease (LMD) representing 5–8%, classically carries a poor prognosis with a median overall survival ranging from 1–11 months. There is a paucity of patient-derived preclinical disease models using tumor cells isolated from the CSF. Models that faithfully recapitulate the biology of CNS tumors would offer new insights into the biology of the disease as well as provide the basis for developing more effective therapy. METHODS: To create more representative preclinical models to study LMD we isolated tumor cells from CSF of 5 patients with cytologically proven LMD and implanted the cells into the subcutaneous flank of immune-compromised mice. Where possible, cell lines were also generated from PDX tissues. Models were characterized by next generation sequencing (NGS), growth rates, expression of driver oncogenes and sensitivity to small molecule inhibitors. RESULTS: To date, one PDX (LUAD-0048A) and cell line model were successfully derived from CSF samples (NSCLC patient with *MET* amplification) and 4 are pending. *MET* amplification and mRNA over-expression were confirmed by quantitative PCR in the PDX tissue and the cell line. Western blot analysis indicated that over-expressed MET was phosphorylated in both PDX tissue and cell line. These results were confirmed by immunohistochemistry. Growth of LUAD-0048A cells were unaffected by 3 MET inhibitors (crizotinib, cabozantinib, glesatinib). Similarly, MET inhibitors did not induce apoptosis in the cells. CONCLUSION: LMD represents an aggressive metastatic event in lung cancer patients. Here we were able to successfully establish a PDX from the CSF of a patient with LMD and trial targeted therapies *in vivo*. Translational collaborations where patients with clinical suspicion of LMD undergo CSF sampling, NGS/ctDNA analysis, and PDX modeling are crucial in improving our understanding of this metastatic compartment and investigating novel treatment paradigms.

LPTO-05. FACTORS INFLUENCING RISK OF LEPTOMENINGEAL METASTASIS IN BREAST CANCER PATIENTS RECEIVING STEREOTACTIC RADIOSURGERY FOR LIMITED BRAIN METASTASES

<u>Michael Zhang</u>[1], Jason Chan[1], Chelsea Xu[2], August Anderson[1], Ann Lazar[3], Javier Villanueva-Meyer[4], Mike McDermott[5], Michelle Melisko[6], Penny Sneed[1], Olivier Morin[1], and Steve Braunstein[1]; [1]University of California, San Francisco, Department of Radiation Oncology, San Francisco, CA, USA, [2]University of California, San Francisco, Department of Medicine, San Francisco, CA, USA, [3]University of California, San Francisco, Department of Epidemiology and Biostatistics, San Francisco, CA, USA, [4]University of California, San Francisco, Department of Radiology, San Francisco, CA, USA, [5]University of California, San Francisco, Department of Neurological Surgery, San Francisco, CA, USA, [6]University of California, San Francisco, Department of Medicine, Division of Hematology/Oncology, San Francisco, CA, USA

Leptomeningeal metastasis (LM) is a late stage manifestation of advanced breast cancer frequently managed with whole brain radiotherapy (WBRT) and/or intrathecal chemotherapy. A subset of breast cancer patients who undergo stereotactic radiosurgery (SRS) for limited brain metastases (BM) ultimately develop LM. We hypothesized that this subset of high-risk patients may be identified by patient, disease, and/or treatment parameters. Clinical records from 135 consecutive breast cancer patients from a single institution who underwent SRS for BM between February 2010 and March 2018 were retrospectively analyzed. Diagnosis of LM was determined radiographically and/or by cerebrospinal fluid analysis. Demographic data, clinical history, histopathology, BM features, systemic disease burden, and prior treatments were

analyzed with Cox proportional hazards regression. In our cohort, 22 (16.3%) patients ultimately developed LM. With a median follow up of 18.9 (IQR 8.6–38.7) months after diagnosis of BM, the actuarial rate of LM at 18 months was 14.5% (95% CI, 7.0–21.4%). Median OS after diagnosis of LM was 7.3 (95% CI, 3.1–15.4) months. There was significantly increased risk of LM with ≥5 vs < 5 BM at BM diagnosis (33.0% vs 7.5% [18-month actuarial risk], HR 3.5, p=0.0045), and ≥7 vs < 7 cumulative number of BM treated (21.9% vs 11.1% [18-month actuarial risk], HR 2.7, p=0.023). Variables not significantly associated with the risk of LM included tumor receptor status (ER, PR, HER2, triple negative), graded prognostic assessment, KPS, extracranial metastases, total BM volume, prior WBRT, or prior surgical resection. In conclusion, patients with a larger number of brain metastases at BM diagnosis or ≥7 cumulative number of brain metastases treated appear to be at higher risk of developing LM and may benefit from stronger consideration of WBRT, intrathecal chemotherapy, and/or brain-penetrating systemic therapy.

LPTO-06. A NOVEL BRAIN-PERMEANT CHEMOTHERAPEUTIC AGENT FOR THE TREATMENT OF BREAST CANCER LEPTOMENINGEAL METASTASIS

<u>Jiaojiao Deng</u>[1], Sophia Chernikova[1], Wolf-Nicolas Fischer[2], Kerry Koller[2], Bernd Jandeleit[2], Gordon Ringold[2], and Melanie Gephart[1]; [1]Stanford University, Stanford, CA, USA, [2]Quadriga BioSciences, Los Altos, CA, USA

Leptomeningeal metastasis (LM), a spread of cancer to the cerebrospinal fluid and meninges, is universally and rapidly fatal due to poor detection and no effective treatment. Breast cancers account for a majority of LMs from solid tumors, with triple-negative breast cancers (TNBCs) having the highest propensity to metastasize to LM. The treatment of LM is challenged by poor drug penetration into CNS and neurotoxicity. Therefore, there is an urgent need for new modalities and targeted therapies able to overcome the limitations of current treatment options. Quadriga has discovered a novel, brain-permeant chemotherapeutic agent that is currently in development as a potential treatment for glioblastoma (GBM). The compound is active in suppressing the growth of GBM tumor cell lines implanted into the brain. Radiolabel distribution studies have shown significant tumor accumulation in intracranial brain tumors while sparing the adjacent normal brain tissue. Recently, we have demonstrated dose-dependent *in vitro* and *in vivo* anti-tumor activity with various breast cancer cell lines including the human TNBC cell line MDA-MB-231. To evaluate the *in vivo* antitumor activity of the compound on LM, we used the mouse model of LM based on the internal carotid injection of luciferase-expressing MDA-MB-231-BR3 cells. Once the bioluminescence signal intensity from the metastatic spread reached (0.2 - 0.5) x 10^6 photons/sec, mice were dosed i.p. twice a week with either 4 or 8 mg/kg for nine weeks. Tumor growth was monitored by bioluminescence. The compound was well tolerated and caused a significant delay in metastatic growth resulting in significant extension of survival. Tumors regressed completely in ~ 28 % of treated animals. Given that current treatments for LM are palliative with only few studies reporting a survival benefit, Quadriga's new agent could be effective as a therapeutic for both primary and metastatic brain tumors such as LM. REF: https://onlinelibrary.wiley.com/doi/full/10.1002/pro6.43

LPTO-07. CARCINOEMBRYONIC ANTIGEN OF CEREBROSPINAL FLUID PREDICT PROGNOSIS OF LEPTOMENINGEAL METASTASIS FROM NON-SMALL CELL LUNG CANCER

<u>Junjie Zhen</u>, Lei Wen, Shaoqun Li, Mingyao Lai, Cheng Zhou, and Linbo Cai; Guangdong Sanjiu Brain Hospital, Guangzhou, China

BACKGROUND: Leptomeningeal metastasis (LM) is a detrimental complication of patients with non-small cell lung cancer (NSCLC) and its incidence has increased due to recent improvements in survival. The aim of this study was to identify the clinicolpathological features and prognostic factors related to overall survival in NSCLC patients with LM. METHODS: Seventy-four consecutive patients diagnosed with LM from NSCLC between 2009 and 2018 in Guangdong Sanjiu Brain Hospital were retrospectively reviewed. RESULTS: Median KPS at diagnosis of LM were 60 (range, 20–90). Forty-seven (63.5%) patients harboring epidermal growth factor receptor (EGFR) or anaplasticlymphoma kinase (ALK) mutation while other twenty-seven patients (36.5%) were wild type or unknown status. Local treatment for LM consisted of whole-brain radiotherapy (WBRT) (52.7%), ventriculoperitoneal (VP) shunt (6.8%) and external drainage (6.8%). Systematic therapy for LM included EGFR or ALK tyrosine kinase inhibitors (TKI) (59.5%), chemotherapy (40.5%) and bevacizumab (8.1%). The median overall survival from diagnosis of LM to death was 8.1 months (95% confidence interval: 5.2 to 11.0). Patients with high Cerebrospinal Fluid (CSF) carcinoembryonic antigen (CEA) level (>50ng/ml) had worse prognosis compared with those low CSF CEA level (≤50ng/ml) ones (p=0.02). However, there was no significant difference in survival between patients with high serum CEA and those with low serum CEA (p=0.645). EGFR/ALK mutation and EGFR/ALK TKI after LM were also identified as variables that had prognostic influence on survival, while KPS, concurrent brain metastasis, WBRT and chemotherapy had no prognostic value for survival.