C linear and nodular, D normal or hydrocephalus only) presentation. Type I LM is defined by the presence of tumor cells in the cerebrospinal fluid (CSF) (confirmed LM) whereas type II LM is defined by typical clinical and MRI signs (probable or possible LM). Here we explored the clinical utility of these EANO ESMO LM subtypes. PATIENTS AND METHODS: We retrospectively assembled data from 254 patients with newly diagnosed LM from different solid tumors, including as main primary tumors breast cancer (n=98, 45%), lung cancer (n=65, 25.5%) and melanoma (n=51, 13.5%). Survival curves were estimated using the Kaplan-Meier method and compared by Log-rank test. RESULTS: Median age at LM diagnosis was 56.5 years (range 20–82 years). Typical clinical LM symptoms or signs were noted in 225 patients (88.5%); only 13 patients (5%) were clinically asymptomatic. The most common MRI subtype was A seen in 117 patients (46%). Types B (n=33, 13%), C (n=54, 21%) and D (n=50, 19.5%) were less common. Tumor cells were observed in the CSF in 186 patients (73%) whereas the CSF was equivocal in 24 (9.5%) and negative in 44 (17.5%) patients. Patients with confirmed LM had inferior outcome than patients with probable or possible LM (p=0.0063). Type I patients had inferior outcome than type II patients (p=0.0019). Nodular disease was a negative prognostic factor in type II LM, but not in type I LM (p=0.0138). CONCLUSION: The presence of tumor cells in the CSF appears to have a greater prognostic role than the neuroimaging presentation. EANO ESMO LM subtypes are highly prognostic and should be considered in the design of clinical trials.

42. IDENTIFICATION OF BRAIN METASTASIS VULNERABILITIES USING METPLATFORM

Lucía Zhu[1], Natalia Yebra[1], Diana Retana[1], Carmen Blanco-Aparicio[1], Sonia Martínez[1], Riccardo Soffietti[2], Luca Bertero[2], Paola Cassoni[2], Tobias Weiss[3], Javier Muñoz[1], Juan Manuel Sepúlveda[4], Ángel Pérez-Núñez[4], Aurelio Hernández-Laín[4], Óscar Toldos[4], Eduardo Caleiras[1], Carolina Nör[5], Michael D. Taylor[5], Michael Weller[3], Joaquín Pastor[1], and Manuel Valiente[1]; [1]Spanish National Cancer Research Center, Madrid, Spain, [2]University and City of Health and Science Hospital, Turin, Italy, [3]University Hospital Zurich, Zurich, Switzerland, [4]Hospital Universitario Doce de Octubre, Madrid, Spain, [5]The Hospital for Sick Children, Toronto, ON, Canada

The diagnosis of brain metastasis involves high morbidity and mortality and remains an unmet clinical need in spite of being the most common tumor in the brain. Exclusion of these cancer patients from clinical trials is a major cause of their limited therapeutic options. In this study, we report a novel drug-screening platform (METPlatform) based on organotypic cultures which allows identifying effective anti-metastasis agents in the presence of the organ microenvironment. We have applied this approach to clinically relevant stages of brain metastasis using both experimental models and human tumor tissue (by performing patient-derived organotypic cultures). We identified heat shock protein 90 (HSP90) as a promising therapeutic target for brain metastasis. Debio-0932, a blood-brain barrier permeable HSP90 inhibitor, shows high potency against mouse and human brain metastases from melanoma, lung and breast adenocarcinoma with distinct oncogenomic profiles at clinically relevant stages of the disease, including a novel model of local relapse after neurosurgery. Furthermore, we have also used METPlatform to perform unbiased proteomics of brain metastases in situ. By applying this analysis to brain metastases treated with the chaperone inhibitor, we uncovered non-canonical clients of HSP90 as potential novel mediators of brain metastasis and actionable mechanisms of resistance driven by autophagy. Combined therapy using HSP90 and autophagy inhibitors showed synergistic effects compared to sublethal concentrations of each monotherapy, demonstrating the potential of METPlatform to design and test rationale combination therapies to target metastasis more effectively. In conclusion, our work validates METPlatform as a potent resource for metastasis research integrating drug-screening and unbiased omic approaches that is fully compatible with human samples and questions the rationale of excluding patients with brain metastasis from clinical trials. We envision that METPlatform will be established as a clinically relevant strategy to personalize the management of metastatic disease in the brain and elsewhere.

43. DELAYS IN ADJUVANT STEREOTACTIC RADIOSURGERY REDUCE LOCAL CONTROL FOR RESECTED BRAIN METASTASES

Diana Roth O'Brien, Phillip Poppas, Sydney Kaye, Sean Mahase, Anjile An, Paul Christos, Benjamin Liechty, David Pisapia, Rohan Ramakrishna, A. Gabriella Wernicke, Jonathan Knisely, Susan Pannullo, and Theodore Schwartz; Weill Cornell Medicine/New York Presbyterian Hospital, New York, NY, USA

OBJECTIVE: For resected brain metastases (BM), stereotactic radiosurgery (SRS) is often offered to minimize local recurrence (LR). Although the aim is to deliver SRS within a few weeks of surgery, a variety of socioeconomic, medical, and procedural issues can cause delays. We evaluated the relationship between timing of postoperative SRS and LR. METHODS: We retrospectively identified a consecutive series of BM patients managed with resection and adjuvant SRS, recommended within two weeks of surgery, at our institution from 2012–2018. We assessed the correlation between time to SRS, as well as other demographic, disease, and treatment variables, and LR, distant recurrence (DR), and overall survival (OS). RESULTS: 133 patients met inclusion criteria. Median age was 64.5 years. Approximately half of patients had a single BM, and median BM size was 2.9 cm. Gross total resection was achieved in 111 (83.6%) patients, and >90% received fractionated SRS. Median time to adjuvant SRS was 37.0 days and LR rate was 16.4%. The factor most predictive of LR was time from surgery to SRS. Median time from surgery to SRS was 34.0 days for patients without LR, versus 61.0 days for those with LR (p<0.01). LR was 2.3% with SRS administered ≤4 weeks postoperatively, compared to 23.6% if delayed >4 weeks (p<0.01). Local recurrence-free survival (LRFS) was also improved for patients who had SRS at ≤4 weeks (p=0.02). Delayed SRS was also predictive of DR (p=0.02), but not OS. CONCLUSIONS: We demonstrate that the strongest predictor of failure of postoperative SRS for BM is the delay to SRS. A cut-off of 4 weeks is a reliable predictor of increased LR. Every effort should be made to perform SRS within 4 weeks of surgery, and if this cannot be achieved, other RT modalities, such as brachytherapy or preoperative SRS, should be strongly considered.

44. EFFECT OF STEREOTACTIC RADIOSURGERY ON NON-SMALL CELL LUNG CANCER BRAIN METASTASIS: CONTINUED CORRELATIVE RADIOBIOLOGIC ANALYSIS OF DNA AND RNA GENOMIC PROFILES FROM PHASE-II CLINICAL TRIAL NCT03398694

Mario Henriquez[1], Wei Huff[2], Jack Shireman[3], Gina Monaco[2], Namita Agrawal[2], Choel Hong Park[3], Miranda Saathoff[3], Gordon Watson[2], Atique Ahmed[3], and Mahua Dey[1]; [1]University of Wisconsin School of Public Health and Medicine, Madison, WI, USA, [2]Indiana University School of Medicine, Indianapolis, IN, USA, [3]Northwestern University Feinberg School of Medicine, Chicago, IL, USA

BACKGROUND: Stereotactic radiosurgery (SRS) is an increasingly common modality used with or without surgery for the treatment of brain metastases (BM). However, the effects of SRS on tumors *in vivo* is unknown. METHODS: Patients were treated with SRS prior to surgery as per clinical trial NCT03398694. Resected tumor was divided into two groups: 'center' and 'periphery' with respect to SRS treatment. Tissue were analyzed by DNA and RNA sequencing and compared between the two and to non-radiated tumor. RESULTS: DNA analysis showed at the individual level, matched comparison of SRS samples from the center or periphery of the same tumor had mutational burden differences. RNA analysis revealed no differentially expressed genes between center and periphery, but there were 62 and 192 differentially expressed genes between the center or periphery and non-radiated control, respectively. At an individual level, matched center and periphery tumor had an average of 16641 differentially expressed genes. Comparing total number of up- and downregulated genes with SNP and Indel mutations of matched patient samples, in patients with higher mutational burdens in peripheral tumors as compared to center there was a higher number of upregulated genes. Reciprocally, when mutation burden was higher in center tumor, total number of genes that were either up- or downregulated were about the same. Pooled analysis revealed significant downregulation of oncogenes, such as TP63 and RECQL4, in the SRS group. DO enrichment analysis also revealed pathways related to NSCLC and lung carcinoma significantly altered in radiation cohort. CONCLUSION: In summary, this study demonstrates that SRS alters the molecular and genomic profile of NSCLC BM. It results in downregulation of oncogenes and pathways related to lung cancer. Additionally, by sampling the tumor at the center and periphery, there are differential effects of the dose gradient on the cellular and molecular response to ionizing radiation.

45. DELAY OR FAILURE TO ADMINISTER STEREOTACTIC RADIOSURGERY TO THE CAVITY AFTER SURGERY FOR BRAIN METASTASES. AN INTENTION-TO-TREAT ANALYSIS

Diana Roth O'Brien, Sydney Kaye, Phillip Poppas, Sean Mahase, Anjile An, Paul Christos, Benjamin Liechty, David Pisapia, Rohan Ramakrishna, A. Gabriella Wernicke, Jonathan Knisely, Susan Pannullo, and Theodore Schwartz; Weill Cornell Medical College/New York Presbyterian Hospital, New York, NY, USA

BACKGROUND: Data regarding the efficacy of adjuvant stereotactic radiosurgery (SRS) for resected brain metastases (BM) is often limited to patients completing SRS within a specified timeframe. We performed an intention-to-treat analysis to determine local recurrence (LR) for all BM patients referred for SRS. METHODS: We retrospectively identified resected BM patients referred for SRS between 2012 and 2018. Patients were divided based on delay to SRS into four categories: 1) ≤4 weeks, 2) >4–8 weeks, 3) >8 weeks, and 4) never received. We investigated the relationship between

delay to SRS and LR, local recurrence-free survival (LRFS), and overall survival, as well as the predictors of and reason for delays. RESULTS: In our cohort of 159 patients, median age was 64.0 years, 56.5% patients were female, median tumor diameter was 2.9 cm, and gross total resection was achieved in 83.0%. On intention-to-treat analysis, LR was 22.6%. Delays to SRS correlated with LR: 2.3% with SRS ≤4 weeks postoperatively, 14.5% with SRS at >4–8 weeks (p=0.03), 48.5% with SRS at >8 weeks (p<0.001). No LR difference was observed with SRS delayed by >8 weeks, vs. never completed, 48.5% vs. 50.0% (p=0.91). 53 (33.3%) patients comprised these latter two categories. A similar relationship emerged between delay to SRS and LRFS (p<0.01). Non-small cell lung cancer pathology (p=0.04) and earlier year of treatment (p<0.01) were predictive of delays. Common reasons for delays included logistics, management of systemic disease, complications, or comorbidities. CONCLUSION: A significant number of patients referred for SRS never receive it, or are treated with a delay >8 weeks, conferring equivalent LR risk. Accordingly, the actual efficacy of adjuvant SRS may need reassessment. Reasons for delays and mechanisms for reducing them are discussed. For patients likely to experience significant delays, other techniques, such as preoperative SRS or intraoperative brachytherapy, may be considered.

46. PAN-CANCER ANALYSIS OF ORTHOTOPIC PATIENT DERIVED XENOGRAFTS FROM BRAIN METASTASES

Yu Zeng[1,2], Kristine Pelton[1], Smitha Yerrum[3], Pei-Lun Kao[3], Claire Sinai[3], Tony Tran[3], Rileen Sinha[4], Aniket Shetty[3], Michael Y. Tolstorukov[4], Aliya Jaber[3], Dylan E. Freitas[3], William Pisano[1], Sigitas J. Verselis[5], Zach T. Herbert[6], Nancy U. Lin[7], Jean J. Zhao[8], David M. Weinstock[7], Ugonma N. Chukwueke[7], Ayal A. Aizer[9], E. Antonio Chiocca[10], Wenya Linda Bi[10], Patrick Y. Wen[7], Eudocia Q. Lee[7], Lakshmi Nayak[7], David M. Meredith[11], Sandro Santagata[11], Kin-Hoe Chow[1,3], and Keith L. Ligon[1,3]; [1]Department of Oncologic Pathology, Dana-Farber Cancer Institute, Boston, MA, USA, [2]Department of Neurosurgery, Xiangya Hospital, Central South University, Changsha, China, [3]Center for Patient Derived Models, Dana-Farber Cancer Institute, Boston, MA, USA, [4]Bioinformatics and Data Science Group, Informatics and Analytics Department, Dana-Farber Cancer Institute, Boston, MA, USA, [5]Molecular Diagnostics Laboratory, Dana-Farber Cancer Institute, Boston, MA, USA, [6]The Molecular Biology Core Facilities, Dana-Farber Cancer Institute, Boston, MA, USA, [7]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Boston, MA, USA, [8]Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, MA, USA, [9]Department of Radiation Oncology, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA, USA, [10]Department of Neurosurgery, Brigham and Women's Hospital, Boston, MA, USA, [11]Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA

Brain metastases (BM) are a leading cause of cancer death and prognosis remains poor despite treatment advances at other sites. Models are central to therapeutic development, but few orthotopic patient-derived xenograft (PDX) models of BM exist. To represent diversity across BM types, we established a program to create orthotopic PDX at scale from all BM patients. To date BM were received from 100 patients and PDX attempted by direct brain injection (PDX, n=89) or injection of low passage patient-derived cell lines (PDCLX, n=11). We created 65 successful BM PDX from 13 cancers: 17 lung (55% take), 15 breast (68%), 6 melanoma (75%), 5 CNS lymphoma (83%), 3 gastrointestinal (75%), 2 esophageal (40%), 2 ovarian (67%), 1 sarcoma (100%), 1 laryngeal (100%), 1 prostate (100%), 1 pancreatic (100%), 1 uterine adenosarcoma (100%), and 1 yolk sac tumor (100%). Take rate was similar for models derived from patients with prior chemotherapy-only versus immune/targeted therapy-only (63 vs 58%). Fifteen patients had live tumor and matching PBMCs archived for modeling in vitro immunotherapy responses. Mean time to moribund among different cancer types ranged from 27 days (yolk sac tumor) to 177.5 days (ovarian). BM PDX had a favorable timeline for preclinical study (90% moribund at 180 days). All PDX matched the patient driver SNVs and copy aberrations, even at >P4. No significant differences noted by immunodeficient strain (SCID versus NSG) or injection site (orthotopic versus heterotopic). Explants from BM PDX were able to generate long-term cell lines (60%) or short-term cultures with qualitative concordance of model-to-patient responses to targeted therapy (Osimertinib, EGFRi) and immunotherapy (Pembrolizumab, PD1i). Genomic and clinical data were used to create the DFCI BM PDX cBioPortal for public release and models distribution will be available through the DFCI Center for Patient Derived Models.

47. UNCOVERING A NOVEL ROLE FOR HLA-G IN BRAIN METASTASES

Blessing Bassey-Archibong[1], Nikoo Aghaei[1], Chirayu Chokshi[1], Agata Kieliszek[1], Nazanin Tatari[1], Dillon Mckenna[1], Mohini Singh[2], Minomi Subapanditha[1], Tomas Tokar[1], Igor Jurisica[3], Fred Lam[1], Yu Lu[1], Chitra Venugopal[1], and Sheila Singh[1]; [1]McMaster University, Hamilton, ON, Canada, [2]Harvard University, Cambridge, MA, USA, [3]University of Toronto, Toronto, ON, Canada

Brain metastases (BM) are the most common brain tumour in adults and are ten times more likely to develop than primary brain tumours. More than 20% of patients with cancer will develop BM with the three most common sources being primary cancers of the lung, breast, and melanoma. Unfortunately, current treatment options for BM do not effectively eradicate BM, with a mere median overall survival time of 12 months in treated patients. This indicates the need for better and more effective therapies against BM. Using patient-derived cell lines established from surgically removed brain metastatic tumours of lung-, breast- and melanoma-BM patients, we generated patient-derived orthotopic murine xenograft (PDX) models of lung-, breast-, and melanoma-BM. From these PDX models, we isolated a rare population of stem-like brain metastasis initiating cells (BMICs) we termed "pre-metastatic", that had traveled from their primary/orthotopic tumours and lodged in the brain but had not yet developed into mature BM. Transcriptomic analyses performed on pre-metastatic and non-pre-metastatic BMICs from lung, breast and melanoma PDX models of BM, identified a set of deregulated genes exclusive only to pre-metastatic BMICs. Further analysis revealed *HLA-G* as being commonly up-regulated only during the pre-metastatic stage of the lung-, breast-, and melanoma-BM cascade. *In vitro* and *in vivo* analyses demonstrated that HLA-G knock-down reduced the proliferation and survival of BMICs from all BM cohorts, and attenuated the establishment of mature brain metastatic tumours, implying a crucial role for HLA-G in the formation of BM. Developing a therapeutic strategy that targets HLA-G in BM may prove effective at completely eliminating brain metastatic cells at an early stage of the BM cascade, thereby turning a fatal disease into an eminently more treatable one.

48. DEVELOPING TUMOR-HOMING CYTOTOXIC HUMAN INDUCED NEURAL STEM CELLS AS AN ADJUVANT TREATMENT FOR RADIATION THERAPY OF BRAIN METASTASES

Alison Mercer-Smith[1], Wulin Jiang[1], Alain Valdivia[1], Juli Bago[2], Scott Floyd[3], and Shawn Hingtgen[1]; [1]University of North Carolina, Chapel Hill, NC, USA, [2]University of Ostrava, Ostrava, Czech Republic, [3]Duke University, Durham, NC, USA

INTRODUCTION: Non-small cell lung cancer (NSCLC) is the most common primary cancer to metastasize to the brain. Radiation is first-line for multifocal brain metastases, but recurrence is observed in 40% of patients. An adjuvant treatment to radiation is needed to effectively treat post-radiation tumor. Genetically engineered neural stem cells (NSCs) have the unique ability to seek out tumors and deliver therapeutic payloads that significantly reduce tumor burden. Here we have transdifferentiated human fibroblasts into induced neural stem cells (hiNSC) and explored the efficacy of hiNSCs therapy for NSCLC brain metastases. METHODS: hiNSCs were infused intracerebroventricularly (ICV) into mice with bilateral intracranial H460 NSCLC tumors. Bioluminescent imaging (BLI) was used to determine hiNSCs persistence while fluorescent analysis of brain sections characterized tumor-homing migration. *In vitro* co-culture assays and isobologram analysis were used to determine the synergistic effect of the cytotoxic protein TRAIL and radiation therapy on NSCLC tumor cells. To determine efficacy *in vivo*, H460 cells were implanted in the brains of mice and treated with either hiNSC-TRAIL alone or in combination with 2 Gy radiation. Tumor volumes were then tracked via BLI. RESULTS/CONCLUSION: hiNSCs persisted in the brain >1 week after ICV injection, and hiNSCs were found to co-localize with both bilateral tumor foci. Isobologram analysis showed a combination index of 0.64, suggesting radiation and TRAIL have a synergistic cytotoxic effect on NSCLC tumors. *In vivo*, radiation and hiNSC-TRAIL therapy reduced tumor volumes 90% compared to control-treated animals, while each therapy alone only reduced tumors 21% and 52%, respectively. While neither monotherapy significantly impacted survival, combination therapy demonstrated a 40% extension in survival, with treated mice surviving a median of 28 days while controls animals only survived 20 days. Together, these results demonstrate the therapeutic potential of hiNSC-TRAIL as an adjuvant to radiation for treatment of NSCLC brain metastases.

49. CORRELATES AND PREDICTORS OF HEALTH-RELATED QUALITY OF LIFE IN METASTATIC BRAIN CANCER

Dario Marotta[1,2], Emily Hayward[1], Zachary Tucker[1], Adam Gerstenecker[1], Meredith Gammon[1], Matthew Mason[1,2], Gabrielle Willhelm[1], Helen Bae[1], and Kristen Triebel[1]; [1]University of Alabama at Birmingham, Birmingham, AL, USA, [2]Alabama College of Osteopathic Medicine, Dothan, AL, USA

PURPOSE: Neurocognitive functioning (NCF), mood disturbances, physical functioning, and social support all share a relationship with health-related quality of life (HRQOL). However, a characterization of these