Abstracts

Progression of patients undergoing surgical resection of melanoma brain metastases. METHODS: This retro-
spective, single-center study included patients undergoing first-time surgical resection of a brain metastasis. A multivariate Cox proportional model was used to estimate the association of patient and treatment factors with OS and CNS progression. RESULTS: 85 patients underwent first-time resection of 97 melanoma brain metastases with a median follow-up of 9.5 months. In 71% of cases, patients required a second or additional tumor resection due to local disease progression. Intra-axial lesions (P< 0.001), extra-axial lesions (P< 0.005), and lesions involving >15 brain metastases (P=0.001) were significant predictors of OS. Checkpoint inhibitor treatment was associ-
ated with longer OS from surgery (median 3 vs 0.5 yrs, log-rank p=0.004). However, patients who underwent craniotomy after prior checkpoint in-
hibitor treatment had poorer OS (median 0.56 yrs). Prior radiotherapy was also associated with poorer OS (median 0.53 yrs). CONCLUSIONS: While checkpoint inhibitor treatment was associated with improved survival in this surgical cohort of melanoma brain metastases, patients who require surgery after checkpoint inhibitor treatment or radiotherapy are poor surgical candidates.

13. MANAGEMENT OF BRAIN METASTASES FROM SMALL CELL LUNG CANCER USING SRS

Daniel Koffler1, Sirisha Viswanatha1, Fatemeh Fekrmandi2, Zaker Rana3, Michael Schuler1, and Anuj Goenka1; 1Northwell Health Cancer Institute, Lake Success, NY, USA, 2Princess Margaret Cancer Center, Toronto, ON, Canada

PURPOSE/OBJECTIVE(S): The management of brain metastases in pa-
tients with SCLC has become controversial in the MRI era. We examine our institutional experience treating patients with SCLC with stereotactic radiosurgery. We hypothesize that an SRS strategy in well-selected patients with close MRI surveillance will result in acceptable tumor control, and without disproportionate future neurological symptoms associated with intracranial disease. MATERIALS/METHODS: Patients with a diagnosis of high grade neuroendocrine lung cancer who had undergone SRS between 2013 and 2019 were identified and divided into two groups: SRS-primary and SRS-salvage. SRS-primary was defined as patients who, at time of SRS, had not received previous PCI or WBRT. SRS-salvage was defined as patients who had received previous PCI or WBRT. Primary outcome was intracranial progression free survival. Secondary outcomes included overall survival and neurologic symptom free survival (N-SFS), defined as time to development of neurologic symptoms attributed disease. RESULTS: Twenty patients were identified with median follow-up of 14.1 months. 11 patients were identified as SRS-primary, 9 as SRS-salvage. Among SRS-primary, median PFS and OS were 6.1 months (range 0.9 – 14.5 months) and 15.3 months (4.1 – 43.3) respectively. N-SFS was 11.2 months (range 3.6 – 40.0); 3 of 11 patients developed neurosensory neurological symptoms attributable to disease. In SRS-
salvage salvage SRS and 2 salvage WBRT. None died from intracranial disease. Among SRS-salvage, median PFS following PCI/WBRT was 9.8 months (range 1.8 – 23.6 months) and OS following salvage SRS 5.5 months (range 1.1 – 27.8 months). 3 of 9 patients developed further brain metastases post-
SRS. 1 patient died from intracranial disease. CONCLUSION: Among well-
selected patients followed with MRI surveillance, our data suggest SRS as primary management of brain metastases from SCLC may be reasonable. Symptomatic intracranial disease was uncommon after SRS, and no patients undergoing upfront SRS died from intracranial disease. Prospective data are required to validate these results.

14. DELAYED MRI RESPONSE TO LITT IN PATIENTS UNDERGOING IMMUNOTHERAPY

Christopher Hong and Veronica Chiang; Yale University, New Haven, CT, USA

Laser interstitial thermal therapy (LITT) is an effective treatment for re-
growing lesions after previous radiosurgery to brain metastases, typically resulting in decreased perilesional edema within weeks followed by delayed reduction in lesion size. We have anecdotally observed that patients on immunotherapy (IT) at time of LITT may exhibit a delayed lesion response to LITT may exhibit a delayed lesion response to laser ablation. Post-operative imaging for cases of LITT, performed by the senior author from June 2012-July 2019, for regrowing lesions after prior radiosurgery for brain metastases were retrospectively reviewed. The LITT procedure was defined as any patient receiving IT treatment within 3 months of LITT. Post-operative MRIs obtained at serial time points after surgery (2 weeks, 6 weeks, 3 months, 6 months, and 12 months) were reviewed for treatment response to LITT, defined as change in surrounding edema on T2 FLAIR and change of lesion size on T1-weighted post-contrast images. 22 were in the IT and 38 were in the non-IT groups. There were no differences in distribution of original cancer pathology (IT: 9 melanoma, 8 lung, 5 other, non-IT: 6 melanoma, 20 lung, 12 other; p=0.05). Time to lesion size response on T1-weighted post-contrast imaging after LITT was shorter in the IT group compared to the non-IT group (median: 25 days vs 129 days, Log-Rank 0.01). As expected, the median OS for patients in the IT group was shorter compared to the non-IT group (p=0.04), respectively. However, time to reduction of perilesional edema on T2-weighted MRI was significantly longer in the IT group, compared to the non-IT group: median 25 days vs 15 months (p=0.003). Delayed response to LITT may lead to delayed edema reduction on MRI after LITT. We hypothesize IT may enhance normal immune-mediated mechanisms thus increasing perilesional inflammation after LITT. Further studies are needed to corroborate our observations and explore the underlying pathophysiology.
versus 7.0 months [95% CI: 6.1–8.3]; p<0.0003) and patients with <5 BM versus ≥5 BM [12.49 months [95% CI: 10.52–16.03] versus 5.48 months [95% CI: 4.2–6.8]; p<0.0001]. Prognostic multivariable modeling significantly associated shortened OS independently with leptomeningeal dissemination (p<0.0001), ≥5 BM at diagnosis (p<0.0001), MBM diagnosis year 2010–2014 (p=0.0007), immunotherapy treatment prior to BM diagnosis (p=0.02), and extracranial disease presence (p<0.03). CNS-directed treatment schedules associated with BM were associated with shorter OS for specific symptoms, diagnosis year, and extracranial disease presence. Multivariable analysis demonstrated improved survival for patients that underwent craniotomy (p<0.01). CONCLUSIONS: MBM prognosis has improved in the period following targeted and immunotherapy introduction, and even within the last 5 years of this study. Improving survival reflects and may influence the willingness to use aggressive multimodality treatment for MBM.

19. PLEKHA5 REGULATES TUMOR GROWTH IN METASTATIC MELANOMA

Victor Oriol1, Hongyi Zhang1,2, Huafang Zhu1,3, Gang Deng4,5, Christopher Zito1,4, Chetan Kane1, Shengi Zhang2, Sarah Weiss1, Huyen Tran1, Adamewole Adeniran2, Fanfan Zhang1, Jiangbing Zhou1, Yiuval Kluger2, Marcus Rosenberg2, Harriet Kluger1, and Luca Jilaveanu1,

1Department of Medical Oncology, Yale University, New Haven, CT, USA,
2Department of Microbiology and Immunology, Jinan University, Guangzhou, Guangdong, China,
3Cancer Research Center, Chongqing Medical University, Chongqing, China,
4Department of Neurosurgery, Yale University, New Haven, CT, USA,
5Department of Neurosurgery, Renmin Hospital of Wuhan University, Wuhan, Hubei, China,
6Department of Biology, University of Saint Joseph, West Hartford, CT, USA,
7Department of Pathology, Yale University, New Haven, CT, USA,
8Department of Dermatology, Yale University, New Haven, CT, USA.

Understanding the mechanisms behind melanoma brain metastasis, a diagnostic hallmark that we need to understand, is crucial to develop novel and effective therapies. PLEKHA5, a gene involved in brain development, was recently associated with melanoma brain metastasis. Our findings highlight the significance of PLEKHA5 as a possible regulator in melanoma brain metastasis. Our aim was to further characterize the function of this protein in brain-tropic melanoma. We established stable PLEKHA5 knockdown and knockin cell lines to explore the underlying mechanisms of PLEKHA5-mediated tumor growth. The effect of PLEKHA5 expression silencing on proliferation and tumor growth was assessed using both in vitro systems and xenograft models of brain-tropic melanomas, respectively. The clinical relevance of PLEKHA5 dysregulation in brain metastasis was also investigated in two unique cohorts of melanoma patients with cerebrotropic disease and included analysis of matched cranial and extra-cranial specimens. Knock-down of PLEKHA5 in brain-tropic melanoma cell lines negatively regulated cell proliferation by inhibiting G1 to S cell cycle transition. This coincided with up-regulation of PDCD4, p21, and p27, as well as the down-regulation of pRb protein, involved in the regulation of cell cycle. Conversely, the ectopic over-expression of PLEKHA5 had an inverse effect. Secreted PLEKHA5 knockdown xenograft injection in nude mice significantly inhibited tumor growth, while its overexpression upregulated the growth of tumors. This reduction in tumor growth in vivo might be attributable to decreased phosphorylation of Akt (S473) and mTOR (S2448), key mediators for tumor growth and survival. Our findings demonstrate the role of PLEKHA5 as a mediator of melanoma brain metastasis.

Our findings highlight the significance of PLEKHA5 as a possible regulator of cell cycle transition via crosstalk with the ubiquitin-proteasome and PI3K/AKT/mTOR signaling pathways, driving the proliferation and growth of brain-tropic melanomas. Our studies suggest that PLEKHA5 targeting should be further investigated for melanoma brain metastasis patient population.

20. MELANOMA CELL INTRINSIC GABA A RECEPTOR ENHANCEMENT POTENTIATES RADIATION AND IMMUNE CHECKPOINT INHIBITOR RESPONSE BY PROMOTING DIRECT AND T CELL-MEDIATED ANTI-TUMOR ACTIVITY

Soma Sengupta1, Tahseen Nazri2, Milota Kaluzova1, Laura Kallay1, Johannes Melms1, Benjamin Izmir1, Malcolm Xu1, Debjanij Bhattacharya1, Andre Burnham1, Guanqun Li3, Taukir Ahmed4, David Lawson4, Jeanne Kowalski5, James Cook5, Mario Medvedovic5, Andrew Jenkins5, Mohammad Khan1, and Daniel Pomeranz Krummel1,

1University of Cincinnati, Cincinnati, OH, USA,
2Emory University, Atlanta, GA, USA,
3University of Cincinnati, Cincinnati, OH, USA,
4Columbia University, New York, NY, USA,
5Johns Hopkins, Baltimore, MD, USA,
6University of Wisconsin, Milwaukee, WI, USA,
7University of Texas, Austin, TX, USA.

Most metastatic melanoma patients exhibit poor and variable response to radiotherapy and targeted therapies, including immune checkpoint inhibitors. There is a need for therapeutics that can potentiate existing treatments, including radiotherapy and targeted therapies, including immune checkpoint inhibitors. Using whole-brain cell patch clamp electrophysiology, we find that melanoma cells possess GABAARs that control membrane permeability to anions. Select benzodiazepines, by enhancing GABAAR-mediated anion transport, depolarize cell mitochondria and increase potential anion entry in vitro. Using a syngeneic melanoma mouse model, we find that a benzodiazepine promotes reduction in tumor volume when administered alone and potentiated radiation or immune checkpoint inhibitor α-PD-L1. When a benzodiazepine is combined with concurrent α-PD-L1 and a sub-therapeutic dose of chemotherapy, there is near complete loss of tumor, beyond what is observed for benzodiazepine with radiation or α-PD-L1. Mechanistically, benzodiazepine with radiation or α-PD-L1 results in ipsilateral and an ipsilateral tumor volume reduction commensurate with enhanced infiltration into the tumor milieu of polyfunctional CD8 T-cells. There is also an increased expression of genes with roles in the cytokine-cytokine receptor and p53 signaling pathways. This study provides evidence for melanoma cell GABAARs as a therapeutic vulnerability with benzodiazepines promoting both direct and immune-mediated anti-tumor activity.

21. A PHASE II TRIAL OF COMPREHENSIVE TREATMENT BASED ON RADIOTHERAPY IN LEPTOMENINGEAL METASTASIS

Siran Yang, Qingfeng Liu, Jianping Xiao, Hongmei Zhang, Nan Bi, Ye Zhang, Yuchao Ma, Kai Wang, Xuesong Chen, Ruizhi Zhao, Xi Wu, Junling Li, Junlin Yi, Shilian Wang, and Yexiong Wang; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Capital Academy of Medical Sciences and Peking Union Medical College, Beijing, China.

OBJECTIVES: To investigate the efficacy and security prospectively for patients with leptomeningeal metastases (LM) of comprehensive treatment based on radiotherapy. METHODS: From 2014 to 2017, 93 patients diagnosed with LM admitted to our hospital who underwent whole brain radiotherapy (WBRT) or craniospinal irradiation (CSI) with or without simultaneously boost were enrolled. The dynamic changes of enhanced magnetic resonance imaging, clinical signs and symptoms, cerebrospinal fluid cytology and liquid biopsy detection were recorded. The primary endpoint was overall survival (OS), the secondary endpoints were local control (LC), intracranial progress-free survival (IFPS), brain metastasis specific survival (BMSS) and toxicity. RESULTS: The major primary diagnosis was non-small cell lung cancer. Subjects received WBRT with boost (40 Gy in 20 fractions for WBRT and 60 Gy in 20 for boost), focal radiation to LM, WBRT and CSI (40 Gy in 20 for CSI and 35 Gy in 25 for WBRT and 36 Gy in 20 for CSI), 20 patients were found tumor cells were administered intrathecal chemotherapy. 63 patients used target therapy. The median follow-up time was 33.8 months. OS/LC/IFPS at 1 year were 62.4%/77.2% and 52.6%, respectively. The median survival time was 15.9 months, and the 1-year survival rate was 70.2%. Treatment-related grade 3–4 adverse events were rare and included eight grade 3 hematological toxicity. CONCLUSION: Reasonable comprehensive treatment including precise radiotherapy, intracranial chemotherapy and targeted agents may help to extend the survival time of LM patients compared with historical controls. KEY WORDS: Leptomeningeal Metastasis; Tomotherapy; Comprehensive treatment

22. COMPARATIVE EFFICACY OF ALK-INHIBITORS IN ALK INHIBITOR-NAIVE ALK+ LUNG CANCER BRAIN METASTASES: A NETWORK META-ANALYSIS

Philip Haddad, Dalia Hammoud, and Kevin Gallagher; LSUHSC-SC/Overton Brooks VAMC, Shreveport, LA, USA.

BACKGROUND: Lung cancer has been the leading cause of cancer death in the world, and worse for non-smokers. Non-small cell lung cancer (NSCLC) displays an array of molecular abnormalities most commonly involving ALK and EGFR pathways. NSCLC with ALK rearrangements comprises around 5% of cases. Over the years, several ALK inhibitors (ALKI) have been approved with notable activity in brain metastases. However, there have been limited comparative studies exploring their relative efficacies. This analysis was conducted to compare the relative efficacy of ALKIs against ALK1-naive ALK+ lung cancer brain metastases. METHODOLOGY: A review of the medical literature was conducted using online databases. Inclusion criteria consisted of English language; diagnosis of ALK1-naive ALK+ lung cancer trials with brain metastases; treatment with Crizotinib (CRZ), Alectinib (ALC), Brigatinib (BRG), and Ceritinib (CER); and comparative studies reporting brain metastases specific responses/events. A Bayesian and a frequentists network meta-analysis were conducted using netmeta package and the random-effects model. RESULTS: Eight studies