

utilized to determine differences in OS and the Chi-square test was utilized to determine differences in PD-L1 expression. RESULTS: In 109 patients where both KRAS and PD-L1 status were known, KRAS mutations had greater PD-L1 expression (80.1% vs 61.9% positive, $p=0.04$). There was no difference in OS between KRAS mutant vs KRAS wild-type patients treated with immunotherapy. Median survival from the start of immunotherapy was 15.6 vs 15.5 months respectively ($p=0.7$), after adjusting for age, KPS, lesion number and extra-cranial metastasis (HR = .91, $p=.7$). Patients with KRAS mutations treated with immunotherapy versus those who received chemotherapy had a 1-year OS from the diagnosis of brain metastasis of 60.9% vs 38.7% respectively (trending towards significance, $p=0.05$). KRAS wild-type patients treated with immunotherapy versus those who did not receive immunotherapy had a 1-year OS from the diagnosis of brain metastasis of 61.9% vs 62.5% ($p=0.85$), respectively. DISCUSSION: KRAS mutations are associated with increased PD-L1 expression. Use of immunotherapy negates the poor outcomes seen traditionally in patients with NSCLCBM and KRAS mutations and it improves survival compared to use of chemotherapy. Our experience supports the use of immunotherapy in these patients.

TH10. IMPACT OF BRAF MUTATIONAL STATUS ON THE EFFICACY OF IMMUNOTHERAPY FOR MELANOMA BRAIN METASTASES

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BACKGROUND: BRAF mutations occur in 50% of melanoma patients. Targeted agents – BRAF and MEK inhibitors and immunotherapy improve survival of melanoma patients with BRAF mutations. These agents have intracranial efficacy as shown in clinical trials. However, the efficacy of immunotherapies (immune checkpoint blockade) in melanoma brain metastases and the correlation with BRAF status is not as well characterized. **METHODS:** We reviewed 351 patients with melanoma brain metastases treated at our tertiary care center between 2000 and 2018, 75 of which received immunotherapy with known BRAF mutational status. Two-year, 5-year, and median overall survival (OS) was calculated from the start of immunotherapy to compare the efficacy of immunotherapy in BRAF mutant and BRAF wild type patients using the log-rank test. **RESULTS:** At the time of diagnosis of brain metastasis, the median age was 61 (23–87) years, median KPS was 80 (50–100), number of intracranial lesions was 2 (1–15), and 79% had extra-cranial metastases. Sixty-three patients were treated with stereotactic radiosurgery (SRS), 27 underwent whole brain radiation (WBRT) and 21 underwent surgery. When treated with immunotherapy, BRAF mutant and BRAF wild type median survival was 15.7 months (95% CI=9.4 – 42.4) and 6.9 (95% CI=4.1– 26.7) months (p -value=0.205), respectively. Two-year BRAF mutant and BRAF wild type survival was 35% (95% CI=21 – 58) and 28% (95% CI=16 – 51), and 5-year survival was 22% (95% CI=10 – 46) and 23% (95% CI=11 – 47), respectively. **CONCLUSIONS:** Twenty percent of patients with BRAF mutant and BRAF wild-type patients treated with immunotherapy derive a long-term benefit from immunotherapy and multimodality treatment and are alive 5 years from diagnosis of brain metastases. This was rarely seen in the pre-immunotherapy era in melanoma brain metastases. There was no difference in outcome based on the BRAF mutational status with use of immunotherapy in melanoma brain metastases.

TH11. PEPTIDE-MEDIATED PERMEABILIZATION OF THE BLOOD-BRAIN BARRIER IMPROVES DRUG DELIVERY TO BRAIN METASTASIS

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BACKGROUND: Melanoma patients have a high risk of developing brain metastases, which is associated with a poor prognosis. The blood-brain barrier (BBB) inhibits sufficient drug delivery into metastatic lesions. We investigated the ability of a synthetic peptide (K16ApoE) to permeabilize the BBB for more effective drug treatment. **METHODS:** DCE-MRI was performed to study the therapeutic window of BBB opening facilitated by K16ApoE. *In vivo* and *in vitro* assays were used to determine K16ApoE toxicity and also to obtain mechanistic insight into its action on the BBB. The therapeutic impact of K16ApoE on melanoma metastases was determined together with dabrafenib, which is otherwise known not to cross an intact

BBB. **RESULTS:** DCE-MRI exhibited an effective K16ApoE-mediated BBB opening for up to 1h. Mechanistic studies displayed a dose-dependent effect of K16ApoE caused by induction of endocytosis. At higher concentrations, the peptide also showed unspecific disturbances on plasma membranes. Combined treatment with K16ApoE and dabrafenib reduced the brain metastatic burden in mice compared to dabrafenib. We also showed by PET/CT that the peptide facilitated the delivery of compounds up to 150 kDa into the brain. **CONCLUSIONS:** We demonstrate a transient opening of the BBB, caused by K16ApoE, that facilitates improved drug-delivery into the brain. This improves the efficacy of drugs that otherwise do not cross the intact BBB.

TH12. PRECLINICAL EVALUATION OF NERATINIB PLUS T-DM1 IN ORTHOTOPIC PDX MODELS OF HER2-POSITIVE BREAST CANCER BRAIN METASTASES

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Breast cancer brain metastases (BCBM) are a major cause of morbidity and mortality, despite multimodal management including surgery, radiotherapy, and systemic therapies. There is an urgent need to develop novel, efficacious alternatives. Neratinib is an orally bioavailable, irreversible pan-HER tyrosine kinase inhibitor that is FDA-approved in the extended adjuvant treatment setting for HER2-positive, early breast cancer (NCT00878709). Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate with reported single-agent activity against HER2-positive BCBM. Here, we used HER2-positive orthotopic patient derived xenograft (PDX) models of BCBM to test if combining neratinib with T-DM1 could improve tumor response. PDX cells are labelled with luciferase to allow tumor growth measurement *in vivo*. We found that neratinib is able to reduce phosphorylated HER2 in an orthotopic PDX tumor derived from HER2-positive BCBM, indicating that neratinib can cross the BBB and inhibit HER2 activation in BCBM PDX tissues. However, in both HER2-positive DF-BM354 and DF-BM355 PDX models, single agent neratinib did not block orthotopic tumor growth compared to vehicle control as monitored by bioluminescence measurements. In contrast, combined treatment of neratinib with T-DM1 significantly reduced tumor growth compared to single agent treatment with neratinib or T-DM1 at earlier time points in both models. At later time points, the combined treatment is comparable to T-DM1 alone in DF-BM354 model, but significantly prolong the survival of mice bearing DF-BM355 tumors. These data warrant further testing of neratinib alone and in combination with T-DM1 in additional BCBM PDX models to better understand drivers of resistance and susceptibility to HER2-inhibitors in HER2-positive BCBMs. Furthermore, they support the launch of a prospective clinical trial (NCT01494662) to test the efficacy and tolerability of T-DM1 in combination with neratinib in patients with progressive HER2-positive BCBM.

TH13. IMMUNOTHERAPY VERSUS STANDARD OF CARE IN MELANOMA BRAIN METASTASES WITH KNOWN BRAF STATUS

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BACKGROUND: A mutation of the BRAF protein is seen in approximately 50% of melanoma patients. Immune checkpoint inhibitors (ICI) are standard therapy in melanoma patients independent of a patient's BRAF status. The primary objective of this study is to investigate the impact of BRAF status in patients treated with ICI compared to non-ICI systemic therapy on overall survival (OS) in patients with melanoma brain metastasis (MBM). **METHODS:** We reviewed 351 patients with MBM treated at our tertiary care center between 2000 and 2018. Of these, 144 had known BRAF status, 71 of which were BRAF mutant and 73 were BRAF wild-type. OS was calculated from the date of diagnosis of brain metastasis to compare the efficacy of ICI to other systemic therapies. Many of these patients received multiple lines of treatment including targeted therapies at some point during their care. The log-rank test and Cox proportional hazard model was utilized to determine differences in OS. **RESULTS:** Eighty-four percent of patients received local therapy that included either surgery, stereotactic radiosurgery or whole brain radiation therapy. In BRAF wild-type patients, 40 received ICI and 33 underwent non-ICI systemic therapy with a median survival (5.6 vs 7.1 months) and 2-year survival (28% vs 32%), respectively ($p=0.64$). Of the BRAF mutant patients, 33 received ICI and 38 did not with a median survival (17.1 vs 9.0 months) and 2-year survival (36% and 19%), respectively ($p=0.014$). When controlling for age, KPS, ECM, and number of lesions, BRAF mutant MBM patients treated with ICI compared to non-ICI had an OS hazard ratio, HR=0.4 (95% CI=0.21 – 0.78, $p=0.0069$). **CONCLUSIONS:** ICI therapy in BRAF mutant MBM patients results in improved OS compared to those with non-ICI systemic therapy. No such difference was observed in the BRAF wild-type cohort.