PTCH1, BCOR, CLIC6, TLL2, COL1A1, PTPRK). Notably, mutations in *BCOR* and *PTCH1* have been previously implicated in both systemic neuroendocrine tumors as well as primary tumors of the pituitary gland, while *MYO18A, FGF4, and PTPRK* mutations had not been reported in systemic neuroendocrine tumors but have been implicated in tumor migration and pituitary adenoma progression. In summary, these data demonstrated an expected mutational pattern indicating a systemic lung neuroendocrine origin but also revealed new mutations previously implicated in primary pituitary pathologies that may have evolutionarily drove divergence from the primary tumor. Further genome studies of these rare lesions may yield further insight into the genetic alterations underlying metastasis to the sellar region.

29. ROLE OF AGE AND CNS MYELOID CELLS ON BREAST CANCER BRAIN METASTASIS

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Women diagnosed with breast cancer at a younger age (typically defined as < 40 years old) often have a poorer prognosis and an increased risk of brain metastasis compared to their older counterparts. Multivariate analyses accounting for differences in tumor characteristics have shown that age is an independent predictor of worse outcome. We therefore hypothesized that rather than intrinsic tumor properties, extrinsic microenvironmental factors contribute to age-related differences in aggressiveness. The effect of age was examined by injecting brain-selected breast cancer cells into young (2 – 6 months) and older (>12 months) mice. In four brain metastasis models examined, young mice developed 2- to 16-fold ($p < 0.05$) more brain metastases compared to older mice. The effect of age was not observed in mouse breast cancer models that metastasize to liver and lungs, suggesting that this is an organ-specific phenomenon. Flow cytometry-based immune-profiling of mouse brains showed that T-cells (CD4+, CD8+, and FOXP3+CD25+ regulatory T-cells), monocytes and neutrophils were elevated in brains with metastases, but the abundance of these populations did not vary dramatically with age. Furthermore, antibody-based depletion of T-cells, monocytes and neutrophils did not significantly alter brain metastasis development. Microglia, which are resident CNS myeloid cells, were 1.5-fold more abundant in young brains compared to older brains. Depletion of CNS myeloid cells using the colony stimulating factor-1-receptor inhibitor PLX3397 reduced brain metastatic tumor burden in young mice by 2.1-fold ($p < 0.001$). Importantly, loss of CNS myeloid cells/microglia, which are normally more activated in aged mice and thus may protect the older brain against metastasis, did not augment brain metastasis formation in older mice. These results suggest that the younger brain is more permissive for breast cancer metastasis and that targeting resident CNS myeloid cells may be an effective strategy to prevent brain metastasis development in younger patients.

30. RADIOSURGERY FOLLOWED BY TUMOR TREATING FIELDS FOR BRAIN METASTASES (1–10) FROM NSCLC IN THE PHASE 3 METIS TRIAL

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BACKGROUND: Tumor Treating Fields (TTFields) are non-invasive, loco-regional, anti-mitotic treatment modality comprising alternating electric fields. TTFields have demonstrated efficacy in preclinical non-small cell lung cancer (NSCLC) models. TTFields treatment to the brain was safe and extended overall survival in newly-diagnosed glioblastoma. The objective of the METIS study [NCT02831959] is evaluation of the efficacy and safety of TTFields in NSCLC patients with brain metastases. METHODS: NSCLC patients (N=270) with 1–10 brain metastases were randomized 1:1 to stereotactic radio surgery (SRS) followed by continuous TTFields ((150 kHz, > 18 hours/day) within 7 days of SRS or supportive care. The portable device delivered TTFields to the brain using 4 transducer arrays, while patients received the best standard-of-care for systemic disease. Patients were followed every two months until second intracranial progression. Key inclusion criteria: KPS ≥70, new diagnosis of 1 inoperable or 2–10 supra- and/or infratentorial brain metastases from NSCLC amenable to SRS; and optimal therapy for extracranial disease. Prior WBRT, surgical resection of metastases, or recurrent brain metastases were exclusionary. Primary endpoint was time to 1st intracranial progression. Secondary endpoints included time to neurocognitive failure (HVLT, COWAT and TMT), overall survival, radiological response rate (RANO-BM and RECIST V1.1); quality-of-life; adverse events; time to first/second intracranial progression for patients with 1–4 and 5–10 brain metastases; bi-monthly intracranial progression rate from 2–12 months; and time to second intracranial and distant progression. The sample size (N=270) was calculated using a log-rank test (Lakatos 1988 and 2002) with 80% power at two sided alpha of 0.05 to detect a hazard ratio of 0.57. On September, 2019, an independent Data Monitoring Committee (DMC) reviewed METIS trial data collected to that point. The DMC concluded that no unexpected safety issues had emerged and recommended continuation of the METIS study as planned.

31. RADIATION NECROSIS IN STEREOTACTIC RADIOSURGERY AND CHECKPOINTS INHIBITORS FOR BRAIN METASTASES FROM LUNG ADENOCARCINOMA

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PURPOSE: Treatment with stereotactic radiosurgery (SRS) and immune checkpoint inhibitors (ICI) is increasingly common for brain metastases (BM) from lung adenocarcinoma. Rates of radiation necrosis (RN) with SRS in the setting of ICIs is an ongoing area of research. We investigated rates of RN in patients with BM from lung adenocarcinoma treated with SRS with or without concurrent ICIs. METHODS: We identified 39 patients at a single institution who underwent SRS treatment for BM from lung adenocarcinoma. Of these, 19 (49%) received SRS without ICIs and 20 (51%) patients received ICIs within a month of SRS. The rate of RN, defined by MRI features and histology when available, was compared between each group using multivariate analysis. Kaplan Meier survival estimates were calculated based on overall survival and compared to median survival predicted by the graded prognostic assessment. RESULTS: Overall survival for all patients from diagnosis of brain metastases was 16.6 months (range 3.6–45.9) and median survival predicted by the graded prognostic assessment was 13.7 months (range 6.9–26.5). In total 11 (28%) patients developed MRI and/or histologic evidence for RN during the follow-up period; 5 of 20 (25%) from the SRS with ICI group and 6 of 19 (31%) from the SRS without ICI group. In multivariate analysis, ICI treatment had no significant impact on rates of RN between groups (OR 0.72 [95% CI: 0.17–2.93]; p=0.65) while bevacizumab treatment was associated with a decreased RN risk (OR 0.88 [95% CI: 0.43–0.99]; p=0.02). CONCLUSION: Retrospective analysis of patients with BM from lung adenocarcinoma treated with SRS suggested that administration of ICIs does not increase risk for development of RN. Further, concomitant treatment with bevacizumab may decrease risk of RN. These findings suggest that patients with BM from lung adenocarcinoma can be treated with combination therapy without increased risk of neurologic toxicity.

32. TREATMENT MONITORING OF IMMUNOTHERAPY AND TARGETED THERAPY USING AMINO ACID PET IN PATIENTS WITH BRAIN METASTASES

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PURPOSE: Recently, the RANO group has analyzed the additional diagnostic value of amino acid PET in patients with primary and secondary brain tumors and recommended the use of this imaging technique in addition to conventional MRI. Here, we investigated the value of PET using the radiolabled amino acid O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) for treatment monitoring of immune checkpoint inhibition (ICI) or targeted therapy (TT) alone or in combination with radiotherapy in patients with brain metastases (BM) since contrast-enhanced MRI often remains inconclusive. METHODS: We retrospectively identified 40 patients with 107 BM secondary to melanoma (n=29 with 75 BM) or non-small cell lung cancer (n=11 with 32 BM) treated with ICI or TT who had FET PET (n=60 scans) for treatment monitoring from 2015–2019. The majority of patients (n=37; 92.5%) had radiotherapy during the course of disease. In 27 patients, FET PET was used for the differentiation of treatment-related changes from BM relapse following ICI or TT. In 13 patients, FET PET was performed for response assessment to ICI or TT using baseline and follow-up scans (median time between scans, 4.2 months). In all lesions, static and dynamic FET PET