multiple ErbB receptors has shown promise but has been limited by toxicity and poor brain penetration. EO1001 is a first-in-class, oral, brain penetrating, irreversible pan-ErbB inhibitor with superior CNS penetration targeting ErbB1, ErbB2 and ErbB4. Preclinical data suggests a favorable pharmacokinetic and safety profile and promising activity against ErbB-driven cancers in patient-derived xenograft models. Male or female adult participants with confirmed ErbB-positive cancer, including patients with CNS involvement, who have progressed after standard of care therapy, with adequate bone marrow, renal and liver function are eligible. An accelerated dose-escalation design is employed. One subject per dose cohort will be recruited until drug related toxicity (≥G2) is observed in the first dosing cycle, after which dose escalation will revert to a 3 + 3 design to determine the maximum tolerated dose (MTD). Dose Escalation: Cycle 1: Patients will receive a single dose EO1001 on day 1 and single dose pharmacokinetics will be performed. Beginning on day 8, EO1001 will be administered once daily for 21 days; multi-dose pharmacokinetics will be performed. Cycles 2–6: Oral EO1001 will be administered once daily in continuous 28-day cycles for up to 20 weeks. MTD Expansion: Oral EO1001 will be administered once daily at the MTD in continuous 28-day cycles for up to 6 cycles (24 weeks). Toxicity is assessed based on NCI CCTCAEv5 and tumor response will be assessed by RECIST 1.1 or RANO for CNS disease. CNS exposure is evaluated in patients via CSF collection with confirmed CNS disease involvement.

71. MGMT PROMOTER METHYLATION IS A PROGNOSTIC BIOMARKER IN EGFR MUTANT LUNG ADENOCARCINOMA WITH BRAIN METASTASES

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EGFR-mutant lung adenocarcinomas (EGFRm-LUAD) have a higher risk of brain metastasis (BM) development than non-mutant lesions regardless of cancer stage. BM development is a marker of tumor aggressiveness and has significant prognostic impact that leads to treatment failure. MGMT promoter methylation is known to determine response to therapy in other cancer types but it has not been investigated in EGFRm-LUAD brain metastases. This work aims to assess whether MGMT promoter methylation predicts patient survival or BM development in EGFRm-LUAD patients. A large cohort of 90 primary EGFRm-LUAD, 33(37%) of which developed BM, were profiled using Illumina Infinium MethylationEPIC Beadchip. We utilized genome-wide methylation signatures to determine MGMT methylation status using the previously reported MGMT-STP27 approach that uses two CpG sites to predict MGMT methylation status. Cox modeling was performed to assess whether MGMT methylation status correlates with overall survival independent of other clinical factors. MGMT methylation significantly predicted poorer survival in EGFRm-LUAD patients developed BM (p=0.0003) and those who did not (p=0.003). A multivariate Cox analysis, adjusting for stage and smoking status as potential confounders, showed that MGMT methylation (HR=6.2, 95%CI:2.2–17.4, p=0.0005) and BM (HR=2.6, 95%CI:1.3–5.3, p=0.007) were both independently predictive of worsened survival. Total Mutation Burden calculated by the number of mutations per megabase of DNA was higher in MGMT methylated tumours with an interquartile range (IQR) of 58(30–71) compared to MGMT unmethylated tumours with IQR of 5.5(4.3–6.1). This work shows that MGMT promoter methylation status is an important prognostic biomarker in EGFRm-LUAD patients. Further work will validate these findings obtained using whole-genome DNA methylation by comparing to results using methylation specific PCR assays. MGMT promoter methylation status in EGFRm–LUAD patients with BM may be used to guide patient treatment with potentially a greater extent of treatment for those higher risk patients.

72. THE COMBINED USE OF STEROIDS AND IMMUNE CHECKPOINT INHIBITORS IN BRAIN METASTASES PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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INTRODUCTION: Immune checkpoint inhibitors (ICI) are increasingly being administered to cancer patients, including those with brain metastases (BMs). However, little is known about the interaction between ICI and steroids such as dexamethasone. The aim of this study was to perform a systematic literature review and meta-analysis on the association between steroid use and overall survival (OS) in BM patients receiving ICI. METHODS: A systematic literature search was performed in PubMed, Embase, Web of Science, Cochrane, Academic Search Premier, and PsycINFO. Pooled effect estimates were calculated using random-effects models; analysis was performed across all included studies and stratified by tumor type. RESULTS: After screening 978 abstracts, thirteen studies were included for systematic review. Ten studies reported sufficient data for meta-analysis, comprising 838 BM patients of which 335 (40%) had received steroids. In the steroid group, median OS ranged from 2.9 months to 10.2 months across studies. In the non-steroid group, median OS ranged from 4.9 to 25.1 months. Pooling results demonstrated significantly worse survival in the steroid group (HR 1.97; 95% CI 1.65–2.36); no significant heterogeneity (I2 = 0%) or publication bias (Egger's p = 0.29) was identified. Stratified analysis showed a consistent effect across melanoma (HR 1.71, 95% CI 1.34–2.18) and non-small cell lung cancer (HR 2.26, 95% CI 1.49–3.43) subgroups. CONCLUSION: Administration of steroids is associated with a significantly worse OS in BM patients receiving ICI. Further investigation on dose, timing and duration of steroids in this population is needed to elucidate the cause of this association and optimize outcomes in BM patients receiving ICI.

73. PREDICTION OF A SECOND LOCAL RECURRENCE IN SURGICALLY TREATED RECURRENT BRAIN METASTASES PATIENTS

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BACKGROUND: Local recurrence is a common occurrence after resection or radiotherapy for brain metastasis (BM). Very little is known about the benefit of (re-)craniotomy in this scenario: does resecting the initial local recurrence (LR1) invariably lead to a second local recurrence (LR2)? This study aimed to analyze occurrence and predictors of LR2 in BM patients undergoing craniotomy for LR1. METHODS: Patients were identified from a departmental database at the Brigham and Women's Hospital, Boston, MA. Multivariable logistic regression and cox regression analysis was performed to identify predictors of binary occurrence of LR2 (yes/no) and time-to-LR2, respectively. Based on predictors, subgroup-specific prevalence of LR2 was explored. RESULTS: A total of 188 patients were identified. The median age was 59.5 years and 117 patients (62.2%) were female. Treatment-wise, 64 patients (34.0%) underwent subtotal resection (STR) and 66 (35.1%) received adjuvant radiation. Eighty-one (43.1%) patients experienced LR2 at a median of 7 months after craniotomy. Occurrence of LR2 was significantly associated with STR (OR 6.88, p = 0.0008), surgery as treatment for LR1 (OR = 0.26, p = 0.03), larger tumor volume (OR = 1.14 per 1000 mm^3, p = 0.01), and frontal location (OR = 5.23, p = 0.02). Shorter time-to-LR2 was associated with STR (HR = 5.31, p = 0.01) and adjuvant radiation (HR = 2.22, p = 0.03), while temporal (HR = 0.16, p = 0.03) and parietal (0.13, p = 0.03) location were associated with longer time-to-LR2. When stratifying by extent of resection, prevalence of LR2 was 32.8% after gross total resection and 57.1% after STR. CONCLUSION: In this population, LR2 occurred in 43.1% of patients. STR was the strongest risk factor for LR2, while tumor size, location, surgical treatment of LR1, and receipt of adjuvant radiation may also influence subsequent recurrence.

74. EFFICACY OF HER2-TARGETED THERAPY IN HER2-POSITIVE BREAST CANCER BRAIN METASTASES: A NATIONAL ANALYSIS

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BACKGROUND: Breast cancer brain metastases (BCBM) commonly develop in human epidermal growth factor 2-positive (HER2+) breast cancer, but BCBM patients are underrepresented in clinical trials, leading to a lack of knowledge on the efficacy of HER2-targeted therapy in this population. METHODS: We analyzed clinical characteristics and outcomes of HER2+ BCBM patients from the National Cancer Database 2010–2016, comprising 70% of newly-diagnosed cancers in the U.S, to assess overall survival (OS) associated with HER2-targeted monoclonal antibody therapy (HER2-mab; i.e. trastuzumab, pertuzumab, and trastuzumab emtansine; encoded as of 2013). Survival was estimated with Kaplan-Meier techniques and compared with landmark analysis and Cox regression. The landmark timepoint was selected at which 75% of HER2-mab patients received HER2-mab, which was within 58 days of diagnosis. RESULTS: 1,059 HER2+ BCBM patients were identified, 717 (67.7%) patients were estrogen receptor negative (ER-)