to SRS, reduces the risk of distant brain failure. Unfortunately, WBRT is also associated with substantial neurocognitive deficits and neither altered fractionation nor the use of available neuroprotectants has adequately addressed this issue. An agent that safely minimizes the adverse effects of WBRT while preserving or enhancing tumor control would provide meaningful clinical benefit. TRIAL DESIGN: BMX-001, a novel Mn-porphyrin superoxide dismutase mimetic, has been shown to protect normal tissues from ionizing radiation in preclinical trials, reducing neurocognitive adverse effects as well as enhancing tumor response. Based on the first-in-human trial of this agent in patients with high-grade gliomas, we have instituted a clinical trial of WBRT +/- BMX-001 in adult patients with more than 10 BM from melanoma, non-small-cell lung, breast and renal cancer. Following a safety lead-in of 5 patients, all of whom will receive WBRT and BMX-001, 69 patients will be randomized to WBRT (3Gy/fraction x 10 fractions) with or without BMX-001 administered subcutaneously before, twice weekly during and once after WBRT (6 injections total.) The primary endpoint is cognition, as measured by the Hopkins Verbal Learning, Trailmaking A/B and Controlled Oral Word Association tests. Secondary endpoints include health-related quality-of-life, overall and progression-free survival, rates of radiation necrosis, DBF and neurologic death. Enrollment began January 2019. (ClinicalTrials.gov Identifier: NCT03608020.)

MEDICAL THERAPY (CHEMOTHERAPY, TARGETED THERAPY/IMMUNOTHERAPY)

THER-01. PRECLINICAL DEVELOPMENT OF EO1001, A NOVEL IRREVERSIBLE BRAIN PENETRATING PAN-ERBB INHIBITOR

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Dysregulation of ErbB-mediated signaling is observed in up to 90% of solid tumors. ErbB family cross-talk is implicated in the development of resistance and metastasis, including CNS metastases. Inhibition of multiple ErbB receptors may result in improved patient outcomes. EO1001 is a novel, patented, oral, brain-penetrating, irreversible pan-ErbB inhibitor targeting EGFR (ErbB1), HER2 (ErbB2) and HER4 (ErbB4). METHODS: (1) *In vitro* testing. EO1001 demonstrates high specificity for the ErbB family of receptors with excellent, balanced equipotent activity against EGFR, HER2 and HER4 (0.4 to 7.4 nM). EO1001 inhibits signaling downstream of wild type EGFR, mutant EGFR (T790M, L858R and d746-750) and HER2. (2) PK and toxicity. In rodent studies *in vivo,* EO1001 exhibited a half-life of 16–20 hours. EO1001 rapidly enters the CNS and penetrates tumor tissue at higher concentrations relative to plasma. Safety of EO1001 was evaluated by repeat-dosing studies in SD rats and beagle dogs. Toxicities typical of the ErbB inhibitor class, including gastro-intestinal effects, weight loss and decreased activity were observed at higher dose groups in both species. Mortality was observed in SD rats at higher dose groups. (3) *In vivo* efficacy studies. EO1001 was studied following oral administration in several erbB-positive mouse xenograft models including N87 (Her2+), H1975 (EGFR/T790M), GBM12 (EGFR+), GBM39 (EGVRvIII+). Following oral administration, treatment with EO1001 resulted in a statistically significant improvement in outcomes compared to positive and negative controls in both CNS and systemic tumor models. EO1001 was well-tolerated with no gastrointestinal side effects observed at efficacious doses in these models. CONCLUSION: Based on research to date, EO1001 has the potential to be a best-in-class CNS-penetrating pan-ErbB inhibitor with a safety and pharmacokinetic profile amenable for use as a single agent and in combination with other agents. EO1001 is poised to enter phase 1-2a clinical testing in the second-half of 2019.

THER-02. IMPACT OF SYSTEMIC THERAPY IN MELANOMA BRAIN METASTASIS

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BACKGROUND: Melanoma brain metastasis is associated with a median overall survival (OS) of approximately 9 months. In recent years, management of melanoma brain metastases (MBM) by surgery and radiation [stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBRT)] has been bolstered by targeted therapy and immune checkpoint inhibitors (ICI). METHODS: 351 patients, who underwent treatment for MBM at our tertiary care center from 2000 to 2018, were grouped into those that received chemotherapy, ICI, or targeted therapy. Thirty-four percent of patients treated with ICI had received other systemic therapies as well as part of their management. OS was calculated from the date of diagnosis of the brain metastases. The Kaplan Meier analysis was utilized to determine median OS and difference in OS was determined by utilizing the Cox proportional hazard model. RESULTS: The median survival after the diagnosis of brain metastasis was 10.4, 11.96, and 7.06 months in patients who received ICI, chemotherapy and targeted therapy respectively. A multivariate model was developed including the type of systemic therapy, presence of extracranial metastases, age, KPS and number of intracranial lesions. 114 patients underwent SRS alone, 56 underwent SRS and WBRT, 43 underwent SRS and surgical removal, 28 had surgical removal, SRS and WBRT, and 78 had no intracranial therapy. Compared to patients who received chemotherapy, patients who received immunotherapy had a hazard ratio, HR = 0.628 (confidence interval = 0.396 – 0.994, p-value = 0.047). Presence of EC metastases (HR= 1.25, p-value < .001), lower KPS (HR = .97, p-value < .0001) and multiple brain lesions (HR = 1.117, p-value < .0001) were associated with significantly worse OS. CONCLUSIONS: Addition of ICI significantly improves the OS in MBM compared to chemotherapy. Lower performance status, multiple brain metastases, and EC metastases are associated with poor OS.

THER-03. USING SUCCESSIVE EGF RECEPTOR ANTAGONISTS TO TREAT A PATIENT WITH EXTENSIVE METASTATIC DISEASE: CASE REPORT AND REVIEW OF THE LITERATURE

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INTRODUCTION: EGFR-targeted agents can be useful in the treatment of systemic metastatic cancer including that which has spread to the brain. We present the case of a patient with two different EGFR mutations that responded to receptor blockade. CASE REPORT: A 38 year old right-handed female presented with a one week history of progressive left-sided weakness and focal seizures. Neuroimaging revealed multiple enhancing brain lesions and a lesion in the left maxillary antrum. Body imaging revealed a right lung mass, hilar and mediastinal nodes and multiple bony lesions. Biopsy of the maxillary antrum lesion showed metastatic poorly differentiated adenocarcinoma, TTF-1 positive, suggesting a lung primary. ALK was not mutated but there was an EGFR mutation (exon 19 deletion). The patient underwent treatment with dexamethasone, levetiracetam, whole brain radiation and afatinib, an oral EGFR-targeted agent. Most of the brain lesions responded completely with only two small residual lesions. Seizures were controlled. There was major partial response from the systemic lesions. Two years later the patient was clinically well but the lung lesion, mediastinal nodes and bony lesions were all enlarging. A new pituitary lesion was identified on brain MRI. A liquid biopsy (blood) revealed a T790M mutation and the patient underwent stereotactic body radiation and EGFR-targeted therapy with osimertinib. All lesions responded to treatment and four years after initial diagnosis the patient is clinically well with stable disease. DISCUSSION: Successful treatment of widespread metastatic disease is possible with the use of multiple EGFR-targeted agents in certain patients.

THER-04. THE USE OF AN ADENOSINE A2 AGONIST TO IMPROVE THE PREVENTION AND TREATMENT OF BRAIN METASTASES

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As systemic therapies for cancer become increasingly effective, there is generally a rise in the incidence of brain metastases as a site of first recurrence. This occurs because most antineoplastic agents do not reach the brain in therapeutic concentrations. Many approaches have been studied to improve drug distribution to the central nervous system (CNS) such as intra-arterial administration, osmotic blood-brain barrier (BBB) disruption, focused ultrasound, convection-enhanced delivery, development of CNS penetrant pro-drugs, and the use of vasoactive peptides to transiently disrupt the BBB. However, none of these has improved the prevention or treatment of CNS metastases. Regadenoson is an adenosine A2 agonist that is FDA approved for use in cardiac stress tests. In animals, it has been shown to transiently increase BBB permeability allowing high molecular weight dextran and chemotherapy to enter brain in higher concentrations. A clinical study designed to determine if regadenoson will perform similarly in humans has been CTEP approved and will soon be accruing patients through the Adult Brain Tumor Consortium. If the results are encouraging, future studies will focus on administering regadenoson concurrently with systemically administered chemotherapy in an effort to reduce the incidence of CNS metastases and to improve CNS drug delivery in patients with known brain metastases. This presentation will focus on the available pre-clinical and clinical data supporting this approach and the potential advantages and risks associated with transient BBB disruption in this setting.