radiographic evidence of new or progressive central nervous system (CNS) metastases after radiation therapy with ≥1 lesion of ≥1 cm in the longest dimension on gadolinium-enhanced magnetic resonance imaging. Patients received nal-IRI 50 mg/m^2 (free-base equivalent; FBE) every two weeks (q2w) as an intravenous infusion over 90 minutes, escalating to 70 mg/m^2 FBE q2w, if tolerated. RECIST v1.1 and modified RECIST criteria were used to assses non-CNS and CNS disease, respectively. RESULTS: In total, 30 patients were enrolled (10 with active BM). Median age was 53 years (range 29–70 years) and median number of prior cytotoxic anti-cancer regimens was 3 (range 0–6); 29 patients received ≥1 dose of nal-IRI 50 mg/m^2 FBE. Overall, nal-IRI monotherapy appeared to be well tolerated, and achieved ≥30% objective response rates for both CNS and non-CNS disease. Among the 10 patients with active BM, 6 achieved CNS disease control (3 partial responses [PRs] and 3 stable disease [SD]), including one patient with durable CNS SD and non-CNS PR for 2 years. Among 7 patients with serial evaluation of CNS metastases posttreatment, 6 patients achieved a reduction in target CNS lesions compared with baseline. CONCLUSION: Treatment with nal-IRI resulted in CNS disease control among 6 of 10 heavily pretreated patients with mBC and active BM. Further exploration of nal-IRI in patients with mBC and active BM is warranted.

TRLS-07. BRAINSTORM: OUTCOMES FROM A MULTI-INSTITUTIONAL PHASE I/II STUDY OF RRX-001 IN COMBINATION WITH WHOLE BRAIN RADIATION THERAPY FOR PATIENTS WITH BRAIN METASTASES

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INTRODUCTION: To determine the recommended Phase II dose of RRx-001, a radiosensitizer with vascular normalizing properties, when used with whole-brain radiation therapy (WBRT) for brain metastases, and to assess whether quantitative changes in perfusion MRI after RRx-001 correlate with response. METHODS AND MATERIALS: Five centers participated in this phase I/II trial of RRx-001 given once pre-WBRT then twice weekly during WBRT (30 Gy/10 fractions). Four dose levels were planned (5 mg/m2, 8.4 mg/m2, 16.5 mg/m2, 27.5 mg/m2). Dose-escalation was managed by the Time-to-Event Continual Reassessment Model (TITE-CRM). Correlative DCE-MRI was performed in a subset of patients and linear mixed models used to correlate change in 24-hour T1, Ktrans (capillary permeability) and Vp (plasma volume) with change in tumor volume. RESULTS: Between 2015–2017, 31 patients were enrolled. Two patients dropped out prior to any therapy and 7 were treated with concurrent temozolomide following a study amendment. Median age was 60 years (range, 30–76) and 17 were male. The most common tumor types were melanoma (58%) and non-small cell lung cancer (20%). No dose-limiting toxicities were observed. The most common severe adverse event was grade 3 asthenia in 6.9% (2/29). The median intracranial response rate was 46% (95%CI 24–68) and median overall survival was 5.2 months (95%CI 4.5–9.4). No neurologic deaths occurred. Among 10 evaluable patients undergoing DCE-MRI, a reduction in Vp 24 hours after RRx-001 was associated with reduced tumor volume at 1 month and 4 months (p≤0.01). CONCLUSION: The addition of RRx-001 to WBRT is safe and well-tolerated with favorable intracranial response rates. Because activity was observed across all dose levels, and in the absence of a dose response, the recommended Phase 2 dose is 10 mg administered twice weekly. A reduction in Vp by DCE-MRI 24 hours after RRx-001 suggests anti-angiogenic activity that is associated with longer-term tumor response.

TRLS-08. CNS PENETRATION AND PRELIMINARY EFFICACY OF SACUTIZUMAB GOVITECAN IN BREAST BRAIN METASTASIS AND GLIOBLASTOMA: A SURGICAL STUDY

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Sacituzumab govitecan (SG) is an antibody drug conjugate (ADC) that targets Trop-2 for the selective delivery of SN-38 to tumors. SG carries SN-38, a topoisomerase inhibitor active in the nanomolar range for most cells (including TNBC and GBM) and freely cross the blood brain barrier. SN-38 is conjugated to SG by a linker designated CL2A which is sensitive to acidic conditions. SG has since been granted priority review designation by the FDA, with approval anticipated for triple negative breast cancer. Brain metastases is a significant concern in this patient population, but whether this agent is able to target the CNS through the blood brain barrier is unknown. Based upon the characteristics of this specific ADC, including the use of a pH labile linker and a payload with good CNS penetration, it is our specific hypothesis that the SG can achieve intratumoral concentrations of SN-38 sufficient to achieve therapeutic benefit in patients with neoplastic involvement of the brain. We further hypothesize that while total concentration of SN-38 will correlate with expression of trop2, free SN-38 will correlate more strongly with intratumoral hypoxia. To address this, we are performing a non-randomized, prospective study of SG in subjects with CNS involvement and planned surgical resection. SG is given as single dose at 10mg/kg pre-operatively on Day-1. Surgery will be followed by post-operative treatment with sacituzumab govitecan given intravenously with standard dose of 10 mg/kg on day1 and day 8 of 21-day cycle, until disease progression. Approximately 20 patients, 2 cohorts of 10 patients each with GBM and breast brain tumors, will be enrolled. Tumors will be analyzed for total antibody, free SN-38, and total SN-38 (free SN-38 + Antibody-SN38) concentrations in tumor tissue. Correlations will be made to Trop2 expression and hypoxia. Interim results will be presented.

TRLS-09. RTOG1119: PHASE II RANDOMIZED STUDY OF WHOLE BRAIN RADIOTHERAPY / STEREOTACTIC RADIOSURGERY IN COMBINATION WITH CONCURRENT LAPATINIB IN PATIENTS WITH BRAIN METASTASIS FROM HER2-POSITIVE BREAST CANCER

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The addition of trastuzumab to cytotoxic chemotherapy has improved outcomes for patients with HER2 positive breast cancer. Increased survival coupled with limited blood-brain barrier (BBB) penetration of trastuzumab may contribute to the increased incidence of brain metastasis in these patients. Half of these patients die of intracranial disease progression rather than extracranial disease. Therefore, strategies to improve survival must include increased CNS disease control in these patients. Lapatinib crosses the BBB and demonstrates modest activity against intracranial metastases. Based upon preclinical data and results of a phase I study, we hypothesized that lapatinib plus WBRT /SRS can improve the intracranial disease control compared to WBRT / SRS alone. A randomized phase II trial of WBRT (37.5 Gy/3 weeks) or SRS plus or minus concurrent lapatinib (daily 1000 mg for 6 weeks) was initiated. CNS penetrating HER2 targeted therapy is permitted throughout the study, but patients not on trastuzumab, pertuzumab or any other breast cancer therapy at study entry are not permitted to begin this therapy while on protocol treatment, but may begin it 24 hours after completion of protocol treatment. Eligibility includes HER2+ breast cancer with at least one measurable, unirradiated parenchymal brain metastasis. The two populations targeted for accrual include patients with 1) newly diagnosed, multiple brain metastases or 2) progressive brain metastases after stereotactic radiosurgery (SRS) or surgical resection of 1–3 metastases. Prior lapatinib is allowed. Patients are stratified by breast-specific graded prognostic assessment; use of non-CNS penetrating HER2 targeted therapy; and prior SRS or surgical resection. The primary endpoint is complete response rate in the brain 12 weeks after WBRT. Secondary endpoints include objective response rate, lesion-specific response rate, CNS progression-free survival, and overall survival. 140 of 143 target accrual have enrolled (4/22/2019).

TRLS-10. MITIGATING NEUROCOGNITIVE DEFICITS FROM WHOLE-BRAIN RADIOTHERAPY IN PATIENTS WITH NUMEROUS BRAIN METASTASES VIA A NOVEL SUPEROXIDE DISMUTASE MIMETIC: RATIONALE & DESIGN OF A CLINICAL TRIAL

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BACKGROUND: Patients with a large number of brain metastases (BM) and/or micrometastatic disease in the brain present a clinical challenge. While technical innovations in stereotactic radiosurgery (SRS) have extended the number of BM that can be effectively treated, SRS does not treat occult disease and distant brain failure (DBF) post-SRS remains high. Immuno- and targeted therapies show promise in treating metastatic disease to the brain, though response rates are variable. In contrast, whole-brain radiotherapy (WBRT) provides high rates of local control and, compared

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.