TRLS-02. A PILOT STUDY OF EVALUATING EARLY TREATMENT RESPONSE OF BRAIN METASTASES AFTER STEREOTACTIC RADIOSURGERY USING DYNAMIC SUSCEPTIBILITY-WEIGHTED PERFUSION MAGNETIC RESONANCE IMAGING

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PURPOSE: To determine if dynamic susceptibility-weighted perfusion magnetic resonance imaging (DSC-PMR) can be used to predict local recurrence (LR) of brain metastases after stereotactic radiosurgery (SRS). METHODS: This is a prospective observational study of adult brain metastasis patients treated with single-fraction SRS, who were imaged with DSC-PMRs before SRS and after 1 week. DSC-PMRs were performed with tracer method in which injection of gadolinium was followed by repeated T2*-weighted gradient echo-planar image acquisition. Regions of interests (ROIs) were generated based on the T1-enhancing tumors irradiated. Relative cerebral blood volume (rCBV) and relative cerebral blood flow (rCBF) parameter maps were calculated by dividing the top 5% of CBV or CBF values within a ROI by the contralateral normal thalamus. LR was determined according to the RECIST 1.1 criteria. Cox regression was conducted to identify factors associated with time to LR. LR rates were estimated with the Kaplan-Meier method and compared using log-rank test. RESULTS: Twenty-three patients were enrolled from 2013 through 2016, with 24 evaluable lesions from 17 patients. After a median follow-up of 12.8 months (range: 3.0–53.7), 5 lesions (21%) developed LR after a median of 3.4 months (range: 2.3–5.7). On univariable analysis, higher rCBV at week 1 (HR 1.06, 95% CI 1.01–1.11, p=0.02), lower SRS dose (HR 0.43, 95% CI 0.20–0.91, p=0.03), and larger tumor volume (HR 1.52, 95% CI 1.05–2.20, p=0.03) were significantly associated with LR, but not histology, rCBV at baseline, change of rCBV at week 1 from baseline, or any rCBF parameters. Higher rCBV at week 1 (above the median) was associated with significantly higher risk of LR than lower rCBV (44% vs 0% at 1 year, respectively, p=0.02). CONCLUSIONS: DSC-PMR and specifically rCBV at week 1 may be a promising imaging biomarker to predict treatment response of brain metastasis after SRS and warrant further investigation.

TRLS-03. PHASE II TRIAL OF GDC-0084 IN COMBINATION WITH TRASTUZUMAB FOR PATIENTS WITH HER2-POSITIVE BREAST CANCER BRAIN METASTASES (BCBM)

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BACKGROUND: The PI3K/Akt/mTOR is an important pathway in BCBM. Mutations in PIK3CA or PTEN loss are associated with trastuzumab resistance. Inhibition of PI3K and mTOR led to durable responses in 3 of 5 patient-derived xenografts (PDX) models of BCBM. GDC-0084 is a potent, brain-penetrant inhibitor of class I PI3K and mTOR. METHODS: This is a single-center, phase II study to evaluate the efficacy of the combination of GDC-0084 with trastuzumab for the treatment of central nervous system (CNS) metastases in patients with HER2-positive breast cancer. Patients will receive GDC-0084 (45 mg daily) and trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks). Two cohorts will be enrolled: Cohort A: a single-arm, two-stage, phase II cohort; and Cohort B: a pre-surgical window cohort. Inclusion criteria include unequivocal evidence of new and/or progressive HER2-positive CNS metastases, at least one measurable (≥10 mm) CNS metastasis (Cohort A), clinical indication for CNS metastasis resection (Cohort B). Primary endpoint for Cohort A is objective response rate (ORR) in the CNS per Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria. For Cohort B, the primary endpoint is the correlation between p4EBP1 levels in the resected CNS tumor tissue from patients and intracranial response to GDC-0084/trastuzumab in the PDX model generated from the same patient. Secondary endpoints include overall survival, safety and patient-reported outcomes. Mandatory blood and cerebrospinal fluid with optional tumor biopsy will be collected at baseline, on-treatment and at progression. In Cohort A, we will enroll 37 patients in a Simon two-stage design. If ≥4 responses are seen, the regimen will be considered successful. This design has 90% power with alpha < 10%. Cohort B will enroll 10 patients. The trial opened in February, 2019. NCT03765983.

TRLS-04. NEAR INFRARED FLUORESCENT DYE LOCALIZES BRAIN METASTASIS PRIOR TO DURAL OPENING AND IS MORE SENSITIVE THAN WHITE LIGHT IN BRAIN METASTASIS SURGERY

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INTRODUCTION: To improve surgical resection of brain tumors, our lab has pioneered a novel fluorescent dye technique, Second-Window Indocyanine-Green (SWIG), that relies on passive delivery and accumulation of indocyanine-green (ICG) in neoplastic tissue via the enhanced permeability and retention effect. We hypothesize that SWIG can provide early localization of brain metastasis prior to dural opening and can improve identification of surgical margins. METHODS: Subjects were prospectively enrolled in clinical trial after informed consent. Approximately 24 hours prior surgery, subjects were infused intravenously with 2.5mg/kg or 5mg/kg of ICG. Intraoperatively, a dedicated near-infrared (NIR) camera was used to detect ICG signal. After bone flap removal, the NIR imaging system was positioned above the presumed location of tumor. Additional NIR images were obtained after dural opening, corticectomy, and after conventional white-light surgical resection. RESULTS: We enrolled 50 patients with 51 total intraparenchymal brain metastases (23 lung, 7 breast, 8 GU/GI, 4 melanoma, and 7 others). Prior to dural opening, NIR signal was identified in 35 patients at an average depth of 4.3mm with SBR = 5.3 + 3.7. In the seven patients where NIR signal could not be identified prior to dural opening, tumor depth was an average of 8.4mm from cortical surface. Upon dural opening and tumor identification, all 51 tumors demonstrated strong NIR signal with SBR = 6.2 + 2.8. With white light alone, sensitivity/specificity/PPV/NPV for tumor detection was 83%, 94%, 98%, 57%. With NIR, sensitivity/specificity/PPV/NPV for tumor detection was 100%, 29%, 85%, 100%. DISCUSSION: NIR fluorophores are superior to visible light fluorophores in their depth of penetration. All contrast-enhancing brain metastasis accumulate ICG using our SWIG technique, and NIR fluorescence could be used to localize brain metastasis prior to dural opening. NIR fluorophores are likely to represent the next phase in tumor visualization given the rapid growth of fluorophores targeted to systemic cancers.

TRLS-05. EARLY RESULTS FROM A PROSPECTIVE PHASE I/II DOSE ESCALATION STUDY OF NEOADJUVANT RADIOSURGERY FOR BRAIN METASTASES

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OBJECTIVES: Single-session stereotacic radiosurgery (SRS) alone for brain metastases larger than 2cm in maximal dimension results in local control of only 50%. Surgical resection followed by SRS to the resection cavity can result in leptomeningeal failure (LMD). This Phase I/II study aims to determine the safety and local control of neoadjuvant SRS at escalating doses followed by surgical resection of brain metastases greater than 2 cm. METHODS: Radiosurgery dose was escalated at 3 Gy increments from currently accepted RTOG standard. If no dose-limiting toxicities (DLT) were observed, the dose was escalated. Patients underwent surgical resection of brain metastases within 2 weeks and were followed with brain MRIs and neurologic evaluations every 3 months. RESULTS: 27 patients were enrolled. For tumor size >2.0–3.0 cm, 2 patients completed treatment at 18 Gy and 3 patients at 21Gy. For tumor size >3.0–4.0 cm, 4 patients were treated at 15 Gy and 9 patients were treated at 18 Gy and 1 patient at 21 Gy. For tumor size >4.0–5.0 cm, 1 patient was treated at 12 Gy and 7 patients at 15 Gy. No DLT have occurred. With a mean follow-up of 13.1 months, the 6 and 12 month local control was 93.8% and 72.3%, respectively. Six and 12 month distant brain control was 38.6% and 25.8%. Overall survival at 12 months was 53.5%. One patient developed LMD 5 months following SRS. 4 patients (15%) had acute grade 1/2 toxicity, and no grade 3/4 toxicity was observed. CONCLUSIONS: Neoadjuvant SRS with dose escalation followed by surgical resection for brain metastases greater than 2 cm results in local control comparable to postoperative SRS or WBRT, and demonstrates acceptable acute toxicity. A low rate of LMD failure was found. The Phase II portion of the trial will be conducted at the maximum tolerated SRS doses.

TRLS-06. PHASE 1 EXPANSION STUDY OF IRINOTECAN LIPOSOME INJECTION (NAL-IRI) IN PATIENTS WITH METASTATIC BREAST CANCER (MBC): FINDINGS FROM THE COHORT WITH ACTIVE BRAIN METASTASIS (BM)

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BACKGROUND: nal-IRI is a liposomal formulation of irinotecan (topoisomerase-1 inhibitor). Preclinical data show that nal-IRI accumulates in BMs and prolongs survival in animal models of BM. Findings from a phase 1 expansion study (NCT01770353), evaluating patients with mBC and active BM, are reported. METHODS: This phase 1 expansion study enrolled patients with mBC who received multiple prior lines of cytotoxic therapy in the metastatic setting, including one cohort with mBC and active BM, defined as