

### 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 ( $\geq 10$  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  $\geq 4$  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, craniectomy, and after conventional white-light surgical resection. **RESULTS:** There were 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 stereotactic 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

radiographic evidence of new or progressive central nervous system (CNS) metastases after radiation therapy with  $\geq 1$  lesion of  $\geq 1$  cm in the longest dimension on gadolinium-enhanced magnetic resonance imaging. Patients received nal-IRI 50 mg/m<sup>2</sup> (free-base equivalent; FBE) every two weeks (q2w) as an intravenous infusion over 90 minutes, escalating to 70 mg/m<sup>2</sup> FBE q2w, if tolerated. RECIST v1.1 and modified RECIST criteria were used to assess 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  $\geq 1$  dose of nal-IRI 50 mg/m<sup>2</sup> FBE. Overall, nal-IRI monotherapy appeared to be well tolerated, and achieved  $\geq 30\%$  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/m<sup>2</sup>, 8.4 mg/m<sup>2</sup>, 16.5 mg/m<sup>2</sup>, 27.5 mg/m<sup>2</sup>). Dose-escalation was managed by the Time-to-Event Continual Reassessment Model (TTE-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 ( $p \leq 0.01$ ). **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 me-

tastases 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. RTG01119: 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