LOCL-03

INTRATUMORAL DELIVERY OF CONDITIONALLY REPLICATIVE HUMAN ADENOVIRUS 657 EXPRESSING THE IMMUNE CO-STIMULATOR CD40L (CRAD657-CD40L) AS A POTENTIALLY PROMISING TREATMENT FOR RECURRENT PEDIATRIC HIGH GRADE GLIOMA

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INTRODUCTION: Malignancies of the central nervous system (CNS) have had largely unchanged survival outcomes despite decades of research. Recently, viral-based therapeutics have shown some benefit for patients with CNS malignancies in early clinical trials. Adenovirus has been demonstrated as safe and is currently being examined in several phase I and II clinical trials. We recently demonstrated that adenovirus expressing CD40L is effective in enhancing survival in murine models of diffuse midline glioma. Therefore, to enhance the tumor specificity of this virotherapy, we hypothesized that by using a novel conditionally replicative adenovirus expressing CD40L, CRAd657-CD40L, we would maintain this survival benefit in multiple murine models for high grade glioma while decreasing off-target toxicity. METHODS: We examined the utility of conditionally replicative adenovirus expressing CD40L in both *in vitro* and *in vivo* studies. Human cell lines from diffuse intrinsic pontine glioma (DIPG) and glioblastoma were used to confirm infectivity and CD40L expression, and syngeneic murine models of glioma were evaluated for toxicity and survival following intratumoral injection of a conditionally replicative adenoviral vector. RESULTS: CRAd657-CD40L generated strong expression of CD40L in human *in vitro* DIPG XIII and U251 cell lines and induced MHCII expression on CD11c+ DC's in U251/DC co-culture. Further, in syngeneic murine models of glioma, conditionally replicative adenoviral treatment significantly reduced toxicity while retaining survival efficacy. CONCLUSIONS: Given these promising results as well as the critical need for novel therapeutics in CNS malignancies, we are now progressing to human trials targeting pediatric HGG, an unmet need in pediatric neuro-oncology. This would be the first-in-human study using CRAd-657-CD40L in pediatric HGG. In this Phase 1 clinical trial, we hypothesize that intratumoral injection of CRAd657-CD40L will cause selective expression of CD40L, increased infiltration of immune cells into the tumor, and safely enhance tumor clearance.

LOCL-04

SAFETY AND FEASIBILITY OF RHENIUM-186 NANOLIPOSOME (186RNL) IN LEPTOMENINGEAL METASTASES [LM] PHASE 1/2A DOSE ESCALATION TRIAL

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BACKGROUND: LM is a devastating subarachnoid (SA) complication most commonly from breast, lung, melanoma, and gastrointestinal malignancies affecting 110,000 in the USA. Common therapies are radiation and SA/IV chemotherapy. Without treatment, survival is short with limited treatment options and better options urgently needed. 186RNL emits beta particles (with gamma-rays) with low dose rate and high radiation density. We report first results of the enrolling ReSPECT-LM phase 1/2a 186RNL-LM dose escalation trial. MATERIAL AND METHODS: Preclinical syngeneic rat model animals were 186RNLtreated at day15 with intraventricular186RNL(0.689 mCi) providing mean CSF-radiation absorbed dose=1,136 ±226Gy. 50% control animals[unloaded liposomes] and 100%186RNL treated animals were alive at 14days. At 4 weeks, 75% control animals and 37.5% treated animals had died. Based on this preclinical data and 186RNL recurrent glioma human experience, a phase I/2a dose escalation ReSPECT-LM Trial was initiated to characterize safety/tolerability of a single intrathecal(IT) 186RNL administration. Following, to identify maximum tolerated/feasible doses, 186RNL anti-tumor activity as a single agent in LM patients (breast and NSCLC), characterize 186RNL pK & dosimetry via Ommaya delivery, determine the overall response rate (ORR) for 186RNL treated patients based on CSF/radiographic findings, and describe survival distribution. RESULTS: ReSPECT-LM is enrolling and 1st patient dosed (6.6 mCi186RNL, 5ml) via Ommaya reservoir. The dose was well-tolerated with no complaints/AEs as of Day 28 following treatment. Imaging and CSF tumor cell assays at pre &post-dose were performed. 186RNL gamma imaging confirmed rapid, complete and durable SA dose distribution through168hours. Pre-dose CSF tumor cell count was 70.77 cells/ml and following treatment, 39.79 cells/ml at 24, and ~6 cells/ml at both 48 &168hours. CONCLUSION: 186RNL's unique formulation and characteristics may have promise for LM patients. An update of the ReSPECT-LM clinical trial will be provided.

LOCL-05

CEREBRAL METASTATIC LUNG CARCINOMA: EFFECT OF ALK- AND EGFR-MUTATION STATUS AND SURGICAL MANAGEMENT UPON CLINICAL OUTCOME

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PURPOSE: There have been many advancements in the surgical and medical treatment of metastatic lung carcinoma. In the post-genomic era, new directed-oncological therapies such as monoclonal antibodies (mAbs) and tyrosine-kinase inhibitors (TKIs) may offer increased survival for lung carcinoma patients with EGFR- and ALK- mutations. No surgical series have investigated the role of these mutations upon patient survival in lung brain metastases (BM). METHODS: We performed a multi-site, retrospective study of all patients who had BM with primary lung cancer undergoing surgical resection at Emory University Hospital between January 2012 and March 2021. Driver mutational statuses were categorized as EGFR-amplified, ALK-rearranged, or wild-type from biopsied brain tissue. Descriptive, univariate, and multivariate survival analyses were performed. RESULTS: 95 patients (mean age: 65.8 ± 10.6) met the inclusion criteria. 6 (6.3%) had ALK-rearranged mutations and 19 (20.0%) had EGFR-amplified mutations. 9 (9.5%) received second line therapies in the form of TKIs and mAbs. The majority of patients who underwent craniotomies had gross total resection (GTR) (n=72, 79.1%) with 83.5% (95% CI: 71.2-90.8%) and 89.9% (95% CI: 74.9-96.2%) 1-year overall survival (OS) and progression-free survival (PFS), respectively. On univariate analysis, ALK-rearranged (HR: 2.92; 95% CI: 0.57-9.75; p-value = 0.230) and EGFR-amplified (HR: 0.56; 95% CI: 0.15-1.61; p-value = 0.260) mutations were not significantly associated with OS. CONCLUSION: After assessing ALK- and EGFR- mutations on OS, we found no benefit with mutational status, unlike other cancer types such as Melanoma BRAF mutations. Our low sample size of patients receiving targeted therapies may bias our measures of association to the null hypothesis. However, the OS and PFS in our cohort were better than earlier trials in literature, demonstrating the improvement in systemic lung metastasis therapy. We suspect that as further targeted therapies become available, OS and PFS for lung BM patients will continue to improve.

LOCL-06

SUPERVISED MACHINE LEARNING IDENTIFIES RISK FACTORS ASSOCIATED WITH LEPTOMENINGEAL DISEASE AFTER SURGICAL RESECTION OF BRAIN METASTASES

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BACKGROUND: Resection of brain metastases (BMs) can help with local disease control, yet predictors of leptomeningeal disease (LMD) after surgery are not well defined. This study examined rates and predictors of LMD in patients who underwent resection of a BM. METHODS: A retrospective, single-center study was conducted examining LMD risk for adult patients with a BM that underwent resection with postoperative adjuvant radiation. Logistic regression analyses and a supervised machine learning algorithm (Random forest) were implemented to identify factors within the cohort that were associated with LMD. RESULTS: Of the 182 patients in the cohort, 43 patients (23.6%) developed LMD in the postoperative setting with 18 cases of classical LMD (9.9%) and 25 cases of nodular LMD (13.7%). Median censored time to LMD was not reached, and 6-, 12-, and 24-month LMD-free rates from surgery were 93%, 86.3%, and 71.8%, respectively. Median time from surgery to classical and nodular LMD were 13.1 and 9.5 months, respectively (Log-rank p=0.71). Patients diagnosed with classical LMD had worse survival outcomes from LMD diagnosis compared to nodular LMD (2.6 vs 9.7 mo, Log-rank p=0.02), and LMD-subtype was significantly associated with overall survival from the date of surgery (classical vs nodular vs none: 16.1 vs 20 vs 36.7 mo, p <.0001). Random forest analysis identified primary cancer type, absence of extracranial disease, and tumor volume as the top 3 factors associated with LMD. On multivariate regression analysis, absence of extracranial disease at index surgery was associated with any LMD (OR 2.65, 95% CI 1.15-6.10, p=0.02). Treatment with postoperative checkpoint inhibitors, type of radiation, and performing additional craniotomies were not associated with risk of LMD. CONCLUSIONS: Classical-

type LMD is associated with worse prognosis compared to nodular-type LMD. Absence of extracranial disease at the time of surgery was the most consistent factor associated with LMD on follow-up.

LOCL-07

LOCO-REGIONAL INFUSION OF GB-13 (IL13.E13K-PE4E) AS A POTENTIALLY PROMISING TREATMENT FOR RECURRENT HIGH-GRADE GLIOMA

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INTRODUCTION: High grade gliomas (HGG) are devastating diseases with largely unchanged survival outcomes despite decades of research. Recent studies suggest the interleukin 13 receptor subunit alpha 2 (IL-13Rα2) is selectively upregulated in up to 80% of HGG, including glioblastoma (GBM) and diffuse midline gliomas (DMG) harboring H3K27 alterations. Immunotoxins targeting IL-13Rα2 have been demonstrated as safe and have shown some benefit for patients with HGG in previous phase I/II and III clinical trials. We hypothesized that by using GB-13 (IL13.E13K-PE4E), a novel peptide-toxin that binds IL-13Rα2 with high specificity and possesses a Pseudomonas exotoxin moiety, we would enhance the anti-tumor effects of this immunotherapy for HGG *in vitro* and *in vivo* while decreasing off-target toxicity. METHODS: We examined the pharmacological effects of GB-13 in multiple patient-derived cell lines and rodent models of HGG. GBM and DMG lines were used to confirm IL-13Rα2 expression and sensitivity towards GB-13. Tumor naïve rats were evaluated for toxicity, and orthotopic PDX mice were used to monitor tumor size and survival following loco-regional infusion of GB-13. RESULTS: GB-13 induced a potent cytotoxic response strongly predicated on IL-13Rα2 expression in vitro. No treatment-related adverse effects were noted after 7-day continuous intracranial infusion of GB-13 in tumor naïve rats. Further, in IL-13Rα2-upregulated orthotopic PDX mice, direct intratumoral administration of GB-13 via convection-enhanced delivery abrogated tumor growth and prolonged survival. CONCLUSIONS: Given these promising results as well as the critical need for novel therapies in CNS malignancies, we are progressing to human trials using GB-13 targeting recurrent HGG. Ongoing safety studies in tumor-bearing animals will be able to define dose levels for the initial adult study-arm and the following pediatric study-arm. In this Phase 1 clinical trial, we hypothesize that loco-regional infusion of GB-13 will safely enhance tumor clearance by causing selective killing of IL-13Rα2-upregulated HGG cells.

LOCL-08

SAFETY AND FEASIBILITY OF RHENIUM-186 NANOLIPOSOME (186RNL) IN RECURRENT GLIOMA: THE RESPECT™ PHASE 1 TRIAL

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BACKGROUND: Liposomal rhenium-186 (186RNL) is a potent source of electrons with short path length, low dose rate, high radiation density and gamma emission. Preclinically, 186RNL via convection enhanced delivery (CED) achieves very high doses of targeted radiation and a wide therapeutic index. We report the updated results of ReSPECT, the first in man, dose escalation phase 1 trial of 186RNL in recurrent glioma. METHODS: Following computer assisted treatment planning and placement of intracranial catheter(s), we performed a single administration of 186RNL by CED. Whole body planar and SPECT/CT imaging was obtained on days 1-8 following treatment for dosimetry and distribution. Patients were followed for safety, progression and survival. RESULTS: Twenty-one patients across 7 cohorts received 1.0-22.3mCi in a tumor volume of 0.6-8.80mL. Mean tumor volume was 8.3mL (0.9-22.8mL). Patients had a mean of 1.7 recurrences, 5 with prior bevacizumab. 19 (91%) were grade 4 gliomas, and 100% were after cohort 4. We used a CED rate of 5-20µl/min per catheter, with 1-4 catheters per patient. Tumor mean absorbed radiation dose was 255Gy (8.9-740Gy) while exposure outside the brain was negligible. The mean percentage tumor in the treated volume (Tu/Tv) was 60.3% (19.8%-100%). Thus far, we have observed no dose limiting toxicities, one grade 3 treatment related adverse event (AEs), and the majority of AEs were mild in intensity. The incidence and severity of AEs did not correlate with increasing dose. Mean Tu/Tv in patients not receiving prior bevacizumab was 75% vs. 48% in those that had. Thus far, overall survival (OS) in 16 bevacizumab naïve patient is 49 weeks with 7 patients still alive and a positive correlation of OS to Tu/Tv. CONCLUSIONS: 186RNL achieves high absorbed doses without significant toxicity with favorable overall survival. Updated delivery feasibility, safety and overall survival will be presented.

LOCL-09

SHORT-TERM SEIZURE OUTCOMES IN PATIENTS WITH TREATED WITH LASER INTERSTITIAL THERMAL THERAPY

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Laser interstitial thermal therapy (LITT) is a minimally invasive treatment modality for intracranial tumor and radiation necrosis (RN). A transient increase in edema following LITT typically resolves within three months post-procedure. We sought to characterize the short-term seizure outcomes during this period for patients undergoing LITT for tumor or RN. A retrospective analysis of 86 consecutive patients treated with LITT from 2015-2019 at a single institution was conducted. Data on baseline demographics, treatment details, and clinical course were collected. Thirty-one (36%) had a seizure within one year following LITT, 19 (22%) of which occurred within the first 90 days post-LITT (71% of all seizures). Forty-three (50%) patients had documented pre-LITT seizures, with 27 (63% of all seizures) of those occurring within 90 days pre-LITT. Between patients with and without post-LITT seizures within the first 90 days, there were no significant differences in gender, age, pre-LITT KPS, pre-LITT volume, pre-LITT resection, pre-LITT stereotactic radiotherapy, pre-LITT chemo- or immuno-therapy, use of AEDs or steroids before or after LITT, location, or pathology at the time of treatment. Patients with seizures in the first 90 days post-treatment were significantly more likely to have received pre-LITT whole brain radiotherapy (WBRT) (32% vs. 9%, p=0.02). Of the 18 patients with pre-LITT seizures within 90 days, 9 (50%) were entirely seizure free in the 90-day post-LITT period. In summary, seizure is a known complication of LITT for intracranial lesions, with the majority occurring in the first 90 days post-procedure. WBRT was significantly associated with 90-day post-LITT seizure, which may represent a diminished neurologic reserve in these patients. These findings may help guide clinicians in determining patients appropriate for LITT and those who may require closer monitoring and longer AED tapers in the short-term period following ablation.

LOCL-10

EVOLUTION OF FUNCTIONAL OUTCOMES AFTER LASER INTERSTITIAL THERMAL THERAPY (LITT) VERSUS RESECTION IN THE TREATMENT OF LESIONS IN OR NEAR THE PRIMARY MOTOR CORTEX

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Laser interstitial thermal therapy (LITT) has become increasingly common, particularly in the treatment of progressive lesions after stereotactic radiosurgery for brain metastases. Previous work has illustrated the sensitivity to its use near critical structures, including the corticospinal white matter tracts. A single-surgeon retrospective study was performed of patients who underwent LITT or open resection for lesions located in or near the primary motor cortex, with functional outcomes graded relative to pre-treatment symptoms at 30, 90, and 180 days. Forty patients met inclusion criteria, with median age 64 years (57-72), and estimated baseline KPS 80 (80-90). Nineteen (47.5%) received LITT and 21 (42.5%) resections with intra-operative motor mapping. LITT patients trended towards smaller maximum diameters (2.1 cm vs 2.8 cm, p<0.01), with shorter ICU (0 vs 1 day, p<0.01) and hospital stays (1 vs. 2 days, p<0.01). At 30 days after treatment, 88.9% of resected patients had stable or improved symptoms compared to 35.3% of the LITT cohort (p<0.01). At 90 days, the difference was 87.5% to 50% (p=0.04), and at 180 days 100% to 85.7% (p=0.3684). When separated by new vs. progressive lesions, steroid responsiveness, and lesion histology, similar though not statistically significant trends were identified. In summary, LITT and resection provided similar functional outcomes in the treatment of lesions in or near the primary motor cortex for patients who survived at least 180 days post-treatment. Patients who received resection tended to have better functional outcomes in the nearer term. These differences are likely due to transient, expected post-LITT edema that subsides with time.

LOCL-11

EGFR-MUTATED NON-SMALL CELL LUNG CANCER (NSCLC) LEPTOMENINGEAL DISEASE (LMD) IN A LARGE STEREOTACTIC RADIOSURGERY PATIENT COHORT: INCIDENCE AND OUTCOME

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AIM: Patients with EGFR-mutated NSCLC brain metastases (BM) treated with targeted agents +/- radiosurgery (SRS) have increasing life expectancies. Systemic treatment may become less effective in preventing CNS progression