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-