LMD-12. UBIQUITIN CONJUGATING ENZYMES PROMOTE LEPTOMENINGEAL DISSEMINATION AND DECREASE SURVIVAL IN PATIENTS WITH BRAIN METASTATIC DISEASE

Eunice Paisana[1], Rita Cascão[1], Carlos Custódia[1], Nan Qin[2], Daniel Picard[2], David Pauck[2], Tânia Carvalho[1], Pedro Ruivo[1], Pedro Pereira[1], Rafael Roque[3], José Pimentel[3], José Miguéns[4], Marc Remke[2], João T. Barata[1], Claudia C. Faria[1,4]; [1]Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal, [2]Department of Pediatric Neuro-Oncogenomics, German Cancer Research Center (DKFZ), Heidelberg, Germany, and German Cancer Consortium (DKTK), partner site Essen/Düsseldorf, Düsseldorf, Germany, [3]Laboratório de Neuropatologia, Serviço de Neurologia, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte (CHULN), Lisboa, Portugal, [4]Serviço de Neurocirurgia, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte (CHULN), Lisboa, Portugal

The dissemination of cancer cells to the brain parenchyma (brain metastases - BMs) and to the leptomeninges (leptomeningeal dissemination – LD) are a late-stage complication of systemic cancers, with a poor survival. Despite advances in radiation and chemotherapy, including intrathecal administration of anticancer agents, these forms of advanced cancer are incurable. Therefore, there is an unmet clinical need for novel effective therapies that target both parenchymal and leptomeningeal disease. We analysed the transcriptomic profile of BMs from patients with diverse primary tumors, treated at CHULN, to identify genetic drivers of cancer cell dissemination to the brain and potential novel targets for therapy. The most differentially expressed gene codifies a ubiquitin conjugating enzyme (UCE). UCE levels were evaluated in tissue microarrays of BMs from an independent cohort of patients and correlated with clinical data. UCE functional role was assessed *in vitro* and *in vivo* using modulated lung and breast cancer cell lines. A high-throughput drug screening was performed to find UCE-targeting compounds. High protein levels of the UCE were associated with decreased survival in patients with BMs, independently of the primary tumor origin. High levels of UCE led to increased migration and invasion abilities in cancer cell lines *in vitro*, with no effect in proliferation. *In vivo*, high levels of UCE increased leptomeningeal dissemination and decreased survival in orthotopic models of breast cancer BMs. Leptomeningeal disease promoted by UCE was prevented by oral administration of inhibitor A, identified in our high-throughput drug screening. In conclusion, we have identified UCE as a prognostic marker in patients with BMs from different primary tumors. In orthotopic mouse models of the disease, UCE led to a worse survival and promoted leptomeningeal dissemination. Strikingly, this aggressive disease phenotype was prevented by oral therapy with inhibitor A.

LMD-13. RESPECT-LM: MAXIMUM TOLERATED DOSE, SAFETY, AND EFFICACY OF INTRAVENTRICULAR RHENIUM-186 NANOLIPOSOME (^{186}RNL) FOR LEPTOMENINGEAL METASTASES

Andrew Brenner[1], John Floyd[1], Ande Bao[2], William Phillips[1], Gregory Stein[3]; [1]University of Texas Health Science Center, San Antonio, TX, USA, [2]Case Western Reserve University, Cleveland, OH, USA, [3]Plus Therapeutics, Inc., San Antonio, TX, USA

INTRODUCTION: Leptomeningeal metastases (LM) are a rare but typically fatal complication of advanced cancer that affects the fluid-lined structures of the central nervous system and are diagnosed in approximately 5 percent of patients with metastatic cancer. With survival measured in weeks to months, novel approaches are needed that can both improve quality and quantity of life. Rhenium-186 NanoLiposome (186RNL) permits the selective delivery of beta-emitting radiation of high specific activity directly to the tumor. In a Phase 1 trial in adults with recurrent glioblastoma (NCT01906385), the mean absorbed dose to the tumor when coverage was 75% or greater (n=10) was 392 Gy (CI 306 – 478). Thus far, the therapy has been well tolerated with one possible treatment-related serious adverse event, cerebral edema, that resolved after steroid treatment. METHODS: This is a two-part, Phase 1 dose-finding study followed by an expansion cohort to explore efficacy. Part 1 will enroll up to 21 subjects to characterize the safety and tolerability of a single dose of 186RNL administered intraventricularly via an Ommaya reservoir and to identify a maximum tolerated dose (MTD) / maximum feasible dose (MFD) for future studies. The dose limiting toxicity period is 28 days post infusion. Part 2 will independently evaluate 186RNL in 2 different cohorts: Cohort A: up to 20 subjects with a diagnosis of LM from primary breast cancer; Cohort B: up to 20 subjects with a diagnosis of LM from primary non-small cell lung cancer. The primary endpoint is to estimate the anti-tumor activity of 186RNL as a single agent. Secondary endpoints are to characterize the pharmacokinetic and dosimetry profile of a single dose of 186RNL, determine the overall response rate (ORR) based on CSF and radiographic findings, and to describe the survival distribution. Planned enrollment will begin in H2 2021.

LMD-14. PRECLINICAL SAFETY AND ACTIVITY OF INTRAVENTRICULAR RHENIUM-186 NANOLIPOSOME (^{186}RNL) FOR LEPTOMENINGEAL METASTASES

Maria Guerra-Garcia[1], Henriette Balinda[1], Ande Bao[2], Michael Garcia[1], Andrea Gilbert[1], William Phillips[1], John Floyd[1], Andrew Brenner[1]; [1]Mays Cancer Center at UT Health San Antonio, San Antonio, TX, USA, [2]Case Western Reserve University School of Medicine, Chicago, IL, USA

INTRODUCTION: Leptomeningeal metastases (LM) is a clinical complication that occurs when cancer cells invade the leptomeninges and cerebrospinal fluid of patients with malignant tumors. Once diagnosed, limited treatment options exist, and survival is poor. Rhenium-186 Nanoliposome (^{186}RNL) is a liposomal encapsulated beta emitter with a short path length of 1.8 mm, thereby allowing high specific activity brachytherapy with limited exposure to surrounding tissues. METHODS: To establish the maximum tolerated dose (MTD) of ^{186}RNL by intraventricular (IT) injection, eight cohorts of Wistar rats (n=3 each) were injected IT with increasing activity of ^{186}RNL at doses of 0 (control), 0.480, 0.800, 1.000, 1.150, and 1.340 mCi. Toxicity was assessed by daily food and water intake, daily weights, and observing for neurological deficits. To assess efficacy, C6-Luc glioma cells were injected IT and 15 days post inoculation the animals were treated with 0.69 mCi of ^{186}RNL. Absorbed doses were assessed with gamma camera imaging at 0h, 24h, and 48h post-treatment. Tumor growth was assessed by luciferase bioluminescence. RESULTS: No evidence of adverse ^{186}RNL-related effects was observed in rats through 3 months following administration of up to 1.34 mCi with an absorbed dose of up to 1075 Gy. Hence, the MTD exceeded the doses evaluated in this study. A significant difference in survival between the control and treatment groups (n=8 each) was observed at 2 weeks post treatment, with 50% survival in the control group and 100% survival in the treatment group (p=0.0087). The only significant treatment-related histologic finding among treated rats was slight focal thickening of the leptomeninges, suggesting a mild reactive hypertrophy. CONCLUSION: Intraventricular delivery of ^{186}RNL is well tolerated and improves animal survival at 2 weeks in a rat model of LM.

LMD-15. BEYOND CYTOLOGY - A SINGLE INSTITUTION EXPERIENCE USING CNSIDE™ FOR DIAGNOSING AND MONITORING TREATMENT RESPONSE IN NON-SMALL CELL LUNG CANCER PATIENTS WITH LEPTOMENINGEAL CARCINOMATOSIS (LMC)

Wallace Akerley[1,2], Sonam Puri[1,2], Anna Chalmers[1,2], Barbara Blouw[3], Smitha Boorgula[3], Robbie Schultz[3], Deanna Fisher[3], Michael Dugan[3], Julie Mayer[3]; [1]University of Utah, Salt Lake City, UT, USA, [2]Huntsman Cancer Institute, Salt Lake City, UT, USA, [3]Biocept, Inc., San Diego, CA, USA

INTRODUCTION: Leptomeningeal Carcinomatosis (LMC) occurs in 3–9% of Non-Small Cell Lung Cancer (NSCLC) patients. Diagnosis of LMC includes clinical evaluation, imaging, and cytology. These have modest sensitivity and are inadequate for monitoring treatment response. Biocept's CNSide™ is a proprietary assay utilizing a 10-antibody capture cocktail with microfluidic chamber that quantitatively detects tumor cells in the cerebrospinal fluid (CSF). Switch Blocker™ is a proprietary single gene assay that detects actionable mutations in the CSF. We describe a retrospective single institution experience using these assays in NSCLC patients with confirmed LMC or suspected LMC, treated between 2017 and 2021. METHODS: For fresh samples, CNSide and cytology were used to detect tumor cells, NGS and Switch Blocker was used to detect actionable mutations. Frozen samples were analyzed by NGS and/or Switch Blocker assays. RESULTS: CSF was collected from 30 samples (16 unique patients), of which frozen (8 unique patients) and fresh samples (8 unique patients; 5 with and 3 without LMC). CNSide detected tumor cells in 100% samples (10/10) vs cytology in 40% samples (4/10). Of those without LMC, neither CNSide nor cytology identified tumor cells. In patients with serial samples, CNSide tracked the clinical course. Analysis of frozen CSF by NGS identified mutations including EGFR in six (6), ALK in three (3) and BRAF in one (1) patient, which correlated with the primary tumor. The median survival from diagnosis of LMC for those with frozen samples was 71.6 weeks. CONCLUSION: We demonstrate that 1) survival of patients with LMC can be prolonged, especially when an actionable target is identified, 2) CNSide has greater sensitivity in detecting LMC than cytology, and 3) quantitative monitoring of CSF tumor cells can be used to guide initial and subsequent therapies. Larger clinical trials are needed to better establish the utility of CNSide in managing LMC.

LMD-16. CHOROID PLEXUS ORCHESTRATES ANTI-CANCER IMMUNITY IN LEPTOMENINGES

Jan Remsik, Xinran Tong, Min Jun Li, Ugur Sener, Jessica Wilcox, Kiana Chabot, Russell Kunes, Danielle Isakov, Ahmed Osman,