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Abstracts

2nd ANNUAL CONFERENCE ON CNS CLINICAL TRIALS AND BRAIN METASTASES, CO-SPONSORED BY SNO AND ASCO

Submission Categories and Abbreviations:

BSCI - Basic Science
CLRM - Clinical Research Methods
SPIN - Innovations in Spinal Tumors
LOCL - Local Therapies
MMAP - Multimodality Approaches
NEIM - Neuroimaging
SPCR - Supportive Care
SYST - Systemic Therapeutics

FINAL CATEGORY: BASIC SCIENCE

BSCI-01

INTRATHECAL DELIVERY OF DENDRITIC CELL VACCINE ERADICATES TUMOR GROWTH AND PROTECTS AGAINST LEPTOMENINGEAL DISEASE (LMD) RE-INOCULATION IN IMMUNOCOMPETENT HER2+ AND TRIPLE NEGATIVE BREAST CANCER (TNBC) LMD XENOGRAFT MODELS

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BACKGROUND: LMD occurs in ~5% of patients with breast cancer (BC) and has a median survival of 2-4 months. We found a loss of the anti-HER2 and anti-HER3 CD4 Th1 immune responses in BC patients. In pre-clinical and clinical trials the administration of class II HER2 peptide-pulsed dendritic cell vaccine (HER2-DCV) partially restores anti-HER2 Th1 immune responses with pathologic complete responses in HER2+ BC patients. Here, we examined the intrathecal (IT) delivery of HER2/HER3-DCV in BC-LMD immunocompetent animal models. MATERIALS AND METHODS: Luciferase-labeled HER2+ TUBO BCs were injected into the cisterna magna of BALB/c mice to produce LMD. We used our Murine Ommaya (mimics an Ommaya reservoir clinically in patients) for the IT administration of DCVs into the cerebral spinal fluid (CSF). RESULTS AND DISCUSSION: BC-LMD mice were randomized into following groups: 1) HER2-DCV IT 2) HER3-DCV IT 3) HER2/HER3-DCV IT. The median survival of untreated (control) group was 15 days. All groups given DCV IT prolonged survival ($p<0.001$). Interestingly, HER2-/HER3-DCV IT was able to rescue disease mice (71% in HER2+ BC-LMD and 28% in TNBC-LMD) and showed complete tumor regression. Some surviving mice were immune to subsequent tumor rechallenge. In mice CSF, we found the presence of CD4+ and CD8+ T-cells, and robust IFN-gamma and IL18 response upon DCV treatment. Collectively, this suggests IT delivery of DCV elicits immune response in CSF targeting LMD. CONCLUSION: Our preclinical data supported a clinical trial (submitted) of the IT delivery of DCV in BC patients with LMD.

BSCI-02

CSF PROTEOMICS AS A MINIMALLY-INVASIVE STRATEGY FOR DISTINGUISHING BRAIN METASTASES FROM OTHER PRIMARY BRAIN MALIGNANCIES

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BACKGROUND: Accurate diagnosis and prognostication of intra-axial brain tumors hinges on invasive brain sampling, which carries risk of morbidity. Minimally invasive sampling of proximal fluids, also known as liquid biopsy, can mitigate this risk. Although the cerebrospinal fluid (CSF) is the ideal liquid biopsy source, the traditionally high volumes required for impactful analyses have deterred progress. The objective of this study was to identify diagnostic and prognostic CSF proteomic signatures in glioblastoma (GBM), brain metastases (BM), and central nervous system lymphoma (CNSL). METHODS: CSF samples were retrospectively retrieved from the Penn State Neuroscience Biorepository and profiled using shotgun proteomics with low sample volumes. Proteomic signatures were identified using machine learning classifiers and survival analyses. RESULTS: Using 30µL CSF volumes, we recovered 800 unique peptides across 73 samples [20 normal pressure hydrocephalus (NPH, non-tumor control), 22 GBM, 17 BM, and 14 CNSL]. Externally-validated proteomic-based classifiers identified malignancy with AUROC of 0.94 and distinguished individual tumor entities from others with AUROC ≥0.96. More clinically relevant triplex classifiers, comprised of just 3 peptides, distinguished individual tumor entities with AUROC ≥0.90. Novel biomarkers were identified among the top classifiers, including TFF3 and CACNA2D2, and characterized using single-cell RNA sequencing data. Survival analyses validated previously implicated prognostic signatures, including blood brain barrier disruption. DISCUSSION: Reliable classification of intra-axial malignancies using low CSF volumes is feasible, which has ramifications for longitudinal tumor surveillance. Novel biomarkers identified here necessitate future validation. Based on emerging evidence, upfront implantation of CSF reservoirs in brain tumor patients warrants consideration.

BSCI-03

THE ROLE OF LONP1 IN DRIVING ENHANCED PMT IN THE 'LEADING EDGE' NICHE IN GLIOBLASTOMA

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Glioblastoma (GBM), a high grade brain tumor, possesses poor overall survival with less than 5% surviving past five years. Previously, the TCGA classifications for GBM have included the mesenchymal, proneural, classical and neural subtypes with their own respective expression profiles and survival. Recent omics analysis has revealed other key aspects of GBM pathology, including intratumoral heterogeneity spanning all subtypes and enhanced stemness and treatment resistance and other hallmarks of proneural mesenchymal transition (PMT) following treatment with first-line standard of care treatment with radiation therapy and temozolomide (TMZ). Invading glioma stem cells (GSC) with high Nestin and hypoxia-inducible factor 1 alpha (HIF-1α) expression have been theorized to contribute to recurrence. HIF-1α acts as a master regulator driving increased stemness, invasiveness and angiogenesis. Interestingly, HIF-1α and nuclear respiratory factor-2 both upregulate Lon peptidase 1 (LonP1) in response to increased hypoxia or reactive oxygen species (ROS) production. LonP1 has been shown to drive increased metastasis, tumor growth and epithelial-mesenchymal transition (EMT), an analog of PMT, in colon cancer, melanoma and other cancer types. In a recently elucidated GBM organoid model, we present new findings demonstrating the importance of LonP1 in driving enhanced, transient PMT near the 'invading edge'. This includes the enhanced expression of several key drivers of PMT and phenotypic hallmarks, such as increased invasiveness, proliferation and poorer survival.

BSCI-04

TARGETING THE PI3K-MTOR PATHWAY TO TREAT UBE2C-DRIVEN BRAIN METASTASES

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Brain metastases (BMs) are a devastating complication of advanced cancers associated with poor prognosis. Contrarily to the current improvement in systemic therapies, BMs are still incurable and one of the main causes of death in cancer patients. We analyzed BMs from thirty patients with various primary tumor origins by RNA sequencing and identified the upregulation of UBE2C, a gene involved in the correct transition from metaphase to