was predominant in the triple negative subgroup. Our data suggests that certain subtypes of breast cancer BrM are more likely to be AR+ or PD-L1+; intracranial efficacy of AR-antagonists and immunotherapy warrants investigation for breast cancer BrM, particularly in biomarker-positive subtypes.

BIOM-08. TARGETSELECTOR™ CEREBROSPINAL FLUID (CSF) CIRCULATING TUMOR CELLS AND BIOMARKER ANALYSIS: IMPROVING SENSITIVITY AND TARGETED TREATMENT OPTIONS IN BREAST AND NSCLC CANCER PATIENTS WITH CNS INVOLVEMENT

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BACKGROUND: Liquid biopsy has emerged as a minimally invasive and cost-effective strategy to assess cancer biomarkers without the risk of complications associated with biopsies. Once a tumor has metastasized to the brain, circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) can be found in the cerebrospinal fluid (CSF). We analyzed CSF samples from patients(pts) with primary lung or breast cancer with either brain (BM) or leptomeningeal disease (LMD). Here we report the analytical and clinical validation of Target Selector™ CSF assays. METHODS: CSF was collected prospectively from pts with a prior solid tumor diagnosis and confirmed or clinical/ radiological suspicion of BM or LMD. CTCs were captured in microfluidic channel and classified as either CK+ or CK-. Cell-free total nucleic acids (cfTNA) was extracted from CSF supernatant and underwent both Target Selector™ single gene and next-generation sequencing (NGS) NSCLC and breast multi-gene testing. For NGS, data analysis was performed using Torrent Suite with annotation and curation by Ion Reporter and Oncomine Knowledgebase Reporter software. RESULTS: The Target Selector™ CTC platform assays performed on clinical samples (n = 89) resulted in clinical sensitivity = 80.0%, clinical specificity = 96.6%, positive predictive value (PPV) = 98%, negative predictive value (NPV) = 70.0% at a limit of detection of 2 CTCs. For molecular analyses, Target Selector™ platform assays resulted in clinical sensitivity = 85.2%, clinical specificity = 88.3%, PPV = 76.7%, and NPV = 93.0%. CONCLUSIONS: Target Selector™ is a viable and sensitive platform for CTC detection and molecular analysis of CSF samples from patients with NSCLC or breast cancer with CNS metastases compared to the current standard of care (CSF cytology) and when imaging findings are equivocal. Identifying CTCs and actionable biomarkers can help to confirm CNS involvement when clinically suspected, guide targeted therapy selection and potentially monitor treatment response.

BIOM-09. MULTIPLEX ANALYSIS OF CSF EXTRACELLULAR VESICLES OF INTRASPINAL TUMORS

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BACKGROUND: Extracellular vesicles (EVs) play an important role in cell-cell communication in different types of tumors, carrying multiple layers of biological functional molecules, including proteins, RNA, DNA and lipids. We previously demonstrated that extracellular vesicles (EV) from central nervous system tumors reflect the molecular subtype of the original tumor and mediate an exchange of pro-oncogenic signals. Their implication as biomarkers in tumor disease is under current investigation. It is unclear, however, to what extent cerebrospinal fluid (CSF) EVs from intraspinal tumors are utilizable for diagnostical purposes and how their marker profiles overlap with EVs derived from non tumorous EVs. We analyzed CSF EVs of intraspinal tumors to define CSF EV profiles that allow tumor subtype classification. METHODS: EVs were isolated from CSF of patients suffering from intraspinal meningioma (n=5), ependymoma (n=7) and neurinoma (n=5). Patients suffering from normal pressure hydrocephalus were used as controls (n=5). EVs were analyzed by multiplex bead based assay, immunoblotting, electron microscopy and NTA. RESULTS: CSF EVs were 97.21 ± 3.37nm (intraspinal tumor patients) and 101.6 ± 3.68nm (controls) in sizes and showed vesicular structures by electron microscopy. Particle number were not significantly different between both groups (p = 0.103). Using our 37 protein mutliplex EV profiling kit we found 29 proteins to be expressed in a sufficient manner on CSF EVs. CSF EVs of intraspinal meningioma showed elevated CD62P, HLA-DR, CD40, CD42a and CD45 expression levels, while ependymoma showed decreased levels of CD9, CD63, CD81, whereas neurinomas had elevated levels of SSEA-3 and CD25. CONCLUSION: This is the first comprehensive analysis of CSF EV of intraspinal tumor patients. CSF EV display distinct subpopulations that may allow tumor classification and long-term surveillance. However as tumor-specific EVs may be rare, there is still the need to identify markers that can enrich tumor-specific EVs for molecular profiling.

BIOM-10. PREVALENCE OF NF1 MISSENSE MUTATIONS AND CANDIDATE MODIFIER GENES IN SPINAL NEUROFIBROMATOSIS PATIENTS

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INTRODUCTION: Spinal Neurofibromatosis (SNF), a distinct clinical entity of NF1, characterized by bilateral neurofibromas involving all spinal roots and a few, if any, cutaneous manifestations, entails greater morbidity than the classical form of disease. Nevertheless, there are no reliable patterns to sort out patients at risk for developing SNF. MATERIALS AND METHODS: We investigated 19 NF1 families with at least one SNF member, 37 sporadic SNF patient and 100 NF1 patients with classical form of disease. We applied Targeted NGS using a panel consisting of 139 genes encoding RAS pathway effectors, neurofibromin interactors and genes mapping at 17q11.2 region. RESULTS: In SNF patients we found a higher percentage of missense (21% versus 8%, p=0 0.016, OR 3.13 (95% CI 01.1 -8.2) and a lower percentage of nonsense NF1 mutations (12.5% versus 28%,, p= 0.026, OR 0.36 (95% CI 0.14–0.9) than in classical NF1 cases. Furthermore, we evaluated rare variants with damaging potential predictors in genes of the RAS pathway and in neurofibromin interactors. In more than one sporadic case possible pathogenic variants were found in LIMK2 (neurofibromin interactor), RASAL1, RASAL3, SOS1, A2ML1, MAP3K1 (RAS pathway effectors), while in more than one SNF family were detected RASAL1, RASAL3, MAP3K1 genes variations. CONCLUSIONS: Our results confirm the correlation between NF1 genotype and SNF phenotype as previously reported (Ruggieri, 2015), suggesting that neurofibromin gain-of-functions mutations are associated to SNF. In some patients, the co-occurrence of potential pathogenic variants in NF1 related genes with severe phenotypes was detected supporting their role as modifier genes and promising therapeutic targets.

BIOM-11. ENZYMATIC ASSAY USED TO MONITOR CHANGES IN ONCO-METABOLITE, D2HG, IN RESPONSE TO THERAPY

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INTRODUCTION: Gliomas are the most common and deadly adult brain cancers with a median survival time of less than 18 months. Many therapeutics have failed translating into effective therapies due to incomplete understanding of the disease and heterogeneity of tumors between patients. There is a need for methods that allow for continual access and analysis of glioma biomarkers. We sought to establish a reliable method for quantifying the onco-metabolite, D2HG. After optimizing this method, we used microdialysate and microperfusate to test our hypothesis that analysis of D2HG in response to therapy can indicate therapeutic efficacy sooner than current methods permit. METHODS: Microdialysate and microperfusate were collected from the tumor centers and lateral ventricles of athymic nude mice implanted with IDH1 mutant PDX line GBM196. We performed microdialysis and microperfusion on consecutive days to determine baseline D2HG concentration. Following a five day period of TMZ treatment, we collected another round of microdialysis and microperfusion one week after treatment and again two weeks after treatment. We then used our optimized D2HG enzymatic assay to quantify the changes in D2HG in response to therapy. RESULTS: Using our enzymatic D2HG assay, we were able to quantify D2HG as low as 30nM (30fmol/uL). We found a ~20% decrease in D2HG concentration in the tumor center and right lateral ventricle after 1 week of TMZ treatment (n=2), and ~36% decrease after 2 weeks of TMZ treatment (n=2). CONCLUSION: Using a D2HG quantification assay to monitor changes in concentration of D2HG in microdialysate/ microperfusate can predict sensitivity to therapy.