with orthotopic BRAF-mutant glioma. CONCLUSIONS: Clinically relevant molecular targeted therapy by dabrafenib and trametinib and immune checkpoint blockade synergize in pre-clinical models.

EXTH-43. IL-13RA2 IMMUNOCONJUGATE TARGETED THERAPY FOR H3K27M MUTANT MIDLINE GLIOMAS

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High grade gliomas are devastating diseases. In the pediatric population, diffuse midline gliomas with the H3K27M mutation (H3K27M DMG) are the most aggressive primary malignant brain tumors. With no effective therapies available, children typically succumb to disease within one year of diagnosis. In adults, glioblastoma (GBM) remains a death sentence despite standard clinical care. Therefore, effective therapies for these tumors remain one of the most urgent and unmet needs in modern medicine. Interleukin 13 receptor subunit alpha 2 (IL-13Rα2) is a cell-surface transmembrane protein upregulated in H3K27M DMG and GBM versus normal brain tissue, posing a potentially promising therapeutic target for both tumors. In this study, we investigated the pharmacological effects of a novel peptide-toxin conjugate, IL13.E13K-PE4E (also known as GB-13), that contains a targeting moiety designed to bind IL-13Rα2 with high specificity and a point-mutant cytoxic domain derived from Pseudomonas exotoxin A. We demonstrated that IL13.E13K-PE4E was a potent killer of cultured H3K27M DMG and GBM cells in vitro. Intratumoral administration of IL.13.E13K-PE4E via convection-enhanced delivery (CED) decreased tumor burden and prolonged survival in both H3K27M DMG and GBM murine xenograft models. Furthermore, we observed enhanced drug tissue retention and volume of distribution after CED, suggesting IL13.E13K-PE4E is capable of covering the target area and remaining at the site of infusion long enough to impart therapeutic effects. In summary, the immunomodulatory effect of IL13.E13K-PE4E demonstrated a powerful pharmacological response in H3K27M DMG and GBM models both in vitro and in vivo in a manner strongly associated with IL13Rα2 expression, underscoring the potential of IL-13Rα2 targeted therapy in a subset of these tumors.

EXTH-44. SYSTEMIC CCL3 TREATMENT ENHANCES IMMUNOTHERAPY EFFICACY THROUGH IMPROVED DENDRITIC CELL MIGRATION

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INTRODUCTION: Dendritic cell (DC) vaccines have shown marginal success in treating glioblastoma (GBM), with inefficient vaccine migration a major limitation. Prior evidence from our clinical trials demonstrated that tetanus diphtheria (Td) preconditioning produced greater DC migration to vaccine domain from peripheral blood (PB) DCs compared to Td alone. We demonstrated that DCs numbers reaching VDLNs was also associated with long-term survival. We found from preclinical studies and our patients that increased DC migration was dependent upon the chemokine (C-C motif) ligand 3 (CCL3). METHODOLOGY: The effect of systemic CCL3 treatment on DC vaccine migration was dependent upon the chemokine (C-C motif) ligand 3 (CCL3).

7 days compared to DC vaccine alone (p=0.0045). CCL3+OVA-DC treat

EXTH-45. MICROGLIA-SPECIFIC DISRUPTION OF SIALIC ACID SIGLEC-9/E-INTERACTIONS: A NOVEL IMMUNOTHERAPY AGAINST Glioblastoma

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Recently, ‘don’t eat me’-signals like CD47 have emerged as novel innate immune checkpoints, enabling cancer cells to evade clearance by phagocytes such as monocyte-derived macrophages (MDM) or microglia (MG). Here, we aim at defining the role of inhibitory Siglec-9 in human and its mouse orthologue Siglec-E in an MCT3-centered immune response against glioblastoma (GBM). TCGA RNA-sequencing data revealed a significant correlation between high expression of immunoinhibitory SIGLEC9 and poor survival in GBM patients (log-rank p = 0.02). Siglec-E blockade increased murine MG mediated GBM cell in vitro phagocytosis (normalized phagocytosis of 1.00 in isotype vs. 1.76 in anti-Siglec-E antibody, p < 0.001). By employing a CT-2A orthotopic GBM mouse model with MG-specific spatio-temporal deletion of SiglecE (Sall1CreERT2 x SiglecEfox), we observed high MG-proliferation upon SiglecE knockdown (Ki-67+ MG 14% in Cre vs. 34.5% in Cre-, p < 0.0001) accompanied by an enhanced microglial GBM-cell uptake (5.6% in Cre vs. 12.3% in Cre-, p < 0.001). This beneficial response was counteracted by an accentuated influx of pro-tumorigenic MDM in the Cre’ group (CD163+CD68+ MDM of total MDM 47.1% in Cre vs. 65.3% in Cre’, p = 0.02), which prevented an efficient adaptive anti-tumor immune response and survival benefit. Currently, we are investigating the cross-talk between GBM-associated MG and MDM upon SiglecE knockdown by scRNAseq of the tumor-infiltrating immune compartment, including TCR clonotypes, target gene expression and cytokine profile in GBM MDM and MBM cells, aiming to translate our preclinical results to a clinical GBM therapy and may be translatable to increase heterogeneous tumor antigen presentation following vaccine-targeted tumor killing.

EXTH-46. MRS BASED BIOMARKERS OF IDH1 MUTANT GLIOMA RESPONSE TO THE IDH INHIBITOR BAY-1436032

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Glomas are the most prevalent type of brain tumor in the central nervous system. Mutations in the cytosolic enzyme isocitrate dehydrogenase 1 (IDH1) are a common feature of primary low-grade gliomas, catalyzing the conversion of α-ketoglutarate (αKG) to the oncometabolite 2-hydroxyglutarate (2HG), and mutant IDH1 is a therapeutic target for these tumors. Several mutant IDH inhibitors are currently in clinical trials, nonetheless, complementary non-invasive early biomarkers to assess drug delivery and potential therapeutic response are still needed. The goal of this study was therefore to determine the potential of 1H MRS as a predictive tool for the efficacy of mutant IDH1 inhibitor BAY-1436032 in established GBM xenograft models. We hypothesized that hyperpolarized 13C-labeled αKG or 13C-labeled 2HG production from hyperpolarized 13C-leucine (13C-LEU) was produced by GBM cells in vivo. To achieve this, we used hyperpolarized 13C-MRS and probed the fate of hyperpolarized 1-[13C]αKG. 1H MRS showed a significant decrease in 2HG as well as a significant increase in glutamate (Glu) and phosphocholine (PC) following BAY-1436032 treatment in both cell and animal models compared to controls. Furthermore, hyperpolarized 13C-MRS showed that hyperpolarized 2HG production from hyperpolarized 1-[13C]αKG was decreased and hyperpolarized glutamate production from hyperpolarized 1-[13C]αKG was increased in the BAY-1436032 treated groups compared to controls. These findings are consistent with our previous study, which investigated the MRS-detectable consequences of two other mutant IDH inhibitors: AG120 and AG881. Collectively, our work identifies translatable MRS-based metabolic biomarkers of mutant IDH1 inhibition.

EXTH-47. SAFETY AND EFFECTS OF TRANSCRANIAL MAGNETIC STIMULATION ON GLIOBLASTOMA MEASURED IN VITRO

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BACKGROUND: Although gross total resection (GTR) with chemoradiation is the standard of care for treating glioblastoma (GBM), tumor infiltration and treatment sequelae can impair activity of eloquent regions. Transcranial magnetic stimulation (TMS) has been explored as an...