sion. Furthermore, intravenous treatment with antisense oligonucleotides targeting *lnc-HLX-2-7* coated with cerium-oxide nanoparticle (CNP-*lnc-HLX-2-7*) reduced tumor growth (40-50%) in intracranial MB xenograft mouse model (n = 10, p < 0.01, t-test). We found that the combinatorial therapy of CNP-*lnc-HLX-2-7* and cisplatin further inhibits tumor growth and significantly prolongs mouse survival compared to CNP-*lnc-HLX-2-7* monotherapy (n = 10, p < 0.01, t-test) only. We report here the importance of the *lnc-HLX-2-7-HLX-MYC* axis in regulating group 3 MB progression and provide a strong rationale for using *lnc-HLX-2-7* as a specific and potent therapeutic target for the group 3 MBs in children.

DDDR-32. A NEW IMMUNOMODULATORY FUNCTION OF PYRIDO-PYRIMIDINE DERIVATIVES TO IMPAIR METASTATIC GROUP 3 MEDULLOBLASTOMA IN VIVO

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Medulloblastoma (MB) is an embryonal tumor of the cerebellum constituting ~ 20% of pediatric brain tumors. To date, four MB molecular groups (further stratified in twelve subtypes) have been described. Among them, Groups 3 and Group 4 MB have the poorest prognosis due to their high metastatic potential. Recently, we have reported a metastatic axis driven by Prune1 overexpression in MB Group3 characterized by canonical TGF-β signaling enhancement and epithelial-mesenchymal transition. Here, we have developed a new not toxic pyrido-pyrimidine derivative with the ability to impair Prune-1-driven-axis, thus ameliorating the survival rate of a murine model of metastatic MB Group3 characterized by overexpression of human Prune1 gene in the cerebellum (under the control of MATH1 promoter). Of importance, this small molecule also is showing immunomodulatory functions thus inhibiting the conversion of tumor-infiltrating T lymphocytes (TILs) to immunosuppressive regulatory T cells (T_{regs}) *in vivo* via impairing the secretion of inflammatory cytokines from MB cells. Furthermore, this molecule can also act synergistically with the currently used modified-intensity chemotherapy (e.g. in PNET5 use of Vincristine) or potential in the combination with epigenetics drugs (e.g., LSD1/KDM1A inhibitors). Altogether these results are of importance for future targeted therapies of high-risk metastatic MB. Acknowledgments: We thank for funding support: the Italian Association for Cancer Research (AIRC) Grant IG no. 22129 (M.Z.) and Lazio Innova Grant n. 85-2017-14785 (FT; MZ)

DDDR-33. TARGETING TGFB PATHWAY DEPENDENCIES IN GROUP 3 MEDULLOBLASTOMA

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Medulloblastoma (MB) is one of the most prevalent malignant brain tumors in children, with tremendous cognitive and neuroendocrine disability among survivors. Group 3 (G3) MBs have poor overall survival at < 50%, few recurrent mutations, higher frequency of metastasis, and no targeted therapies. Amplification of *MYC (c-myc)* and activation of TGFβ signaling are frequent in G3 MB. We hypothesize that the TGFβ pathway and *MYC* contribute to the intrinsic resistance of G3 MB through deregulation of key genes and pathways. We previously established humanized models for SHH MB by introducing *MYCN* or *PTCH1* deletions into neuroepithelial stem (NES) cells derived from normal human induced pluripotent stem cells (hIPSCs). In this study, we transduced NES cells with TGFb effectors activated in G3 MB (ACVR2A, TGFbR1, TGFb1, TGFb3, and SMAD5) alone and/or in combination with MYC, prioritizing combinations observed in patients. Excitingly, both *MYC* and TGFβ effectors drove tumor formation *in vivo* with the combination of TGFβ effectors with *MYC* leading to more aggressive tumors. We thus describe six new humanized isogenic models for both non-*MYC* and *MYC* driven G3 MB. We next found that NES cells expressing MYC with either TGFβR1 or TGFβ1 showed resistance to clinical TGFβR1 inhibitors, compared to cells driven by either TGFβR1 or TGFβ1 alone. To decipher mechanisms of resistance, we integrated CUT & RUN to probe for *MYC* genomic localization and relevant histone PTMs with RNA-seq analysis of *MYC* and TGFβ pathway driven NES cells. We discovered a subset of genes upregulated in *MYC* and TGFb-driven lines that are targets of the histone demethylase KDM2B. We postulate that epigenetic remodeling via *MYC* and recruitment of other *MYC*-interacting cofactors culminates in transcriptional changes that lead to aggressive disease. Overall, our studies provide insights on identifying new therapeutic avenues for patients with *MYC* and TGFβ driven G3 MB.

DDDR-34. RECURRENT RELA FUSION-POSITIVE EPENDYMOMA TREATED WITH VAL-083 UNDER EXPANDED ACCESS: A CASE REPORT

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Ependymoma is a relatively rare central nervous system tumor accounting for 2-9 % of all neuroepithelial tumors. RELA fusion-positive ependymoma is a subgroup associated with supratentorial location, higher WHO grade and worse prognosis. In addition, there is no standard systemic chemotherapy treatment for adults with recurrent disease. VAL-083 is a bi-functional DNA-targeting agent which rapidly induces inter-strand DNA cross-links at N7-guanine inducing double-strand breaks causing cell death and acts independent of MGMT DNA-repair in high-grade gliomas. We report a 40-year-old male who was initially diagnosed with a right parieto-occipital high-grade glioma, with no somatic mutations including IDH1/2 genes, and with unmethylated MGMT promoter status. He initially underwent gross total resection, followed by chemoradiation with concurrent and adjuvant temozolomide for 12 cycles. Sixteen months later, he developed recurrent disease and had a second resection. Inter- and intragenic fusion analysis of tumor tissue revealed C11orf95-RELA fusion and the diagnosis of RELA fusion-positive ependymoma was established. The patient was not eligible to participate in any clinical trial and received VAL-083 under an expanded access program. He was then treated with VAL-083 (30 mg/m2 for 3 consecutive days every 21 days) and completed 12 cycles during a period of 9 months. No grade 3/4 adverse events such as thrombocytopenia, anemia, neutropenia, or lymphopenia were observed. His liver and renal functions were normal. No dose reduction was required. He also received levetiracetam, alprazolam and prochlorperazine, with no drug interactions. Steroid were not required. He has been under surveillance since completion of systemic treatment with VAL-083 and has remained radiologically stable, with no CSF dissemination, after 12 months. This case highlights that VAL-083 may be a treatment option for recurrent RELA fusion-positive ependymoma refractory to temozolomide-based regimens. Clinicaltrials.gov Identifier: NCT03138629. The treatment plans for this EAP patient were approved by MD Anderson Cancer Center IRB.

DDDR-35. TARGETING GBM INVASION BY INHIBITING KCNA1 WITH 4-AMINOPYRIDINE: AN FDA APPROVED DRUG THAT EASILY PASS THROUGH THE BBB

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Diffuse invasion is a hall mark of glioblastoma (GB) and one of the primary causes of poor clinical outcomes in GBM patients. Tumor cells migrate deep into the normal brain tissues are frequently protected by the BBB, making them particularly difficult to treat. New therapeutic targets are needed. Our previous studies using spatially dissected and functionally validated matching pairs of invasive and tumor core GBM cells identified KCNA1 as a shared gene that is selectively over-expressed in the invasive GBM cells in 6 patient derived orthotopic xenograft (PDOX) mouse models of pediatric GBM (Huang YL et al, Adv Science 2021). A subsequent analysis of adult GBM RNAseq data from IVY Atlas revealed a significantly elevated expression of KCNA1 (4.9 fold) in the invasive edges of patient GBM tumors. It is also one of the 11 core molecules identified in GEO and TCGA databases through an integrated bioinformatic analysis (Yang J, Front Onc 2021). To determine the anti-invasive activities