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ENHANCERS AND REPRESSORS OF IMMUNOTHERAPY: TRANSLATIONAL PERSPECTIVES ON GENE-MEDIATED CYTOTOXIC IMMUNOTHERAPY IN GLIOBLASTOMA

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Background Gene-mediated cytotoxic immunotherapy (GMCI) is a local tumor immunotherapy that uses aglatimagene besadenovec (a non-replicating serotype 5 adenovirus, expressing HSV1 thymidine kinase) with the prodrug ganciclovir to induce DNA double strand breaks (DSB), leading to immunogenic tumor cell death and intratumoral immune cell invasion. Here we investigate potential repressors and enhancers of GMCI's effectiveness. GMCI is currently in clinical trials in combination with immune checkpoint blockade in glioblastoma. Thus we set out to identify potential areas to improve this approach for future application. Dexamethasone is used in symptomatic treatment of glioma patients, although it is known to cause immune suppression. However, the influence of dexamethasone on the efficacy of GMCI has not been explored. In contrast, DNA damage response inhibitors like the ATR inhibitor (ATRi) AZD6738 might not only amend the cytotoxic but also the immunogenic profile of GMCI, rendering it an attractive combination partner.

Methods We investigated the effects of ATR-inhibition and dexamethasone on GMCI in vitro using cytotoxicity, flow cytometry and T-cell-killing assays in glioblastoma cell lines. The impact of dexamethasone and ATRi in vivo was assessed in an orthotopic syngeneic murine glioblastoma model. Tumor immune infiltrates were analyzed with flow cytometry.

Results Cytotoxicity assays showed that dexamethasone has a slight impact on GMCI in vitro. In T-cell-functional assays, we observed a significantly impaired tumor cell killing. Immune cell response assays revealed a reduced immune cell proliferation after co-culture with supernatant from dexamethasone or combination treated glioblastoma cells. In vivo, while treatment with GMCI alone resulted in longer median symptom-free survival (39.5d) versus no treatment (23d), the

combination of GMCI and dexamethasone resulted in the significant reduction of this effect (29d vs 39.5d ; p = 0.0184).

The combination of ATRi with GMCI proved to be synergistic in cytotoxicity assays. Flow cytometry revealed a significant increase in DSB-associated H2AX foci as well as an improved immune profile by downregulation of GMCI-induced PD-L1 expression. In vivo, the combination with ATRi led to an increase in long-term surviving animals (66.7%) compared to GMCI (50%) and proved to be highly significant compared to the untreated control (p=0.0022).

Conclusions Our data suggest that dexamethasone may decrease the efficacy of immunotherapy for glioma through impaired T cell function: this emphasizes the need in identifying alternatives to dexamethasone to prevent attenuated responses in immunotherapies. The combination of GMCI with ATRi however points to additional therapeutic benefit through enhanced cytotoxic efficacy, improved immunogenicity in vitro and increased long-term survival in vivo, making it a promising future approach for the treatment of glioblastoma.

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COOPERATION BETWEEN CHECKPOINT INHIBITORS TARGETING THE PD-1/PD-L1 AXIS AND ATRC-101, A NOVEL CLINICAL-STAGE CANDIDATE FOR THE TREATMENT OF SOLID TISSUE MALIGNANCIES

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Background We have previously described ATRC-101, a fully human, engineered IgG1 antibody binding a tumor-restricted ribonucleoprotein (RNP) complex as its target. ATRC-101 is currently under evaluation in the clinic as a monotherapy for solid tumors. Following target engagement, ATRC-101 functions in an Fc-mediated fashion to deliver the target to the innate immune system, which modifies the tumor microenvironment and generates an adaptive immune response involving CD8+ T cells leading to anti-tumor activity in syngeneic mouse models. Binding of ATRC-101 appears restricted to malignant tissues in both mouse models and human, across a range of cancer histologic phenotypes, including carcinomas that are known candidates for anti-PD-1 treatment. In the EMT6 mouse model, representing a T cell-excluded phenotype in which anti-PD-1 agents display limited activity, ATRC-101 monotherapy was uniformly vigorous with persistent anti-tumor memory. When co-administered at a lower dose with anti-PD-1, the combination of therapy demonstrated a robust and heightened anti-tumor response relative to either agent dosed as monotherapy at similar concentrations.

Methods To gain insight into the mechanisms that contribute to the anti-tumor effect with combination therapy, in vivo experiments in the EMT6 syngeneic mouse model were performed to determine temporal and spatial patterns of infiltrates and assessed tumors by using whole exome sequencing following administration of ATRC-101 vs. vehicle control. Within naive human tumor samples, coincident immunoreactivities of ATRC-101 and PD-L1 were also characterized.