COMBINATION TREATMENT WITH ATOR-4066, A NEO-X-PRIME™ BISPECIFIC ANTIBODY TARGETING CD40 AND CEACAM5, AND ANTI-PD-1 REVERSES T CELL EXHAUSTION IN VITRO


Background ATOR-4066 is a preclinical stage bispecific antibody targeting CD40 and CEACAM5, developed from Alligator’s novel Neo-X-Prime™ antibody technology platform, which is able to induce a neoantigen specific T-cell response by activating antigen presenting cells. ATOR-4066 binds to CD40 on dendritic cells (DCs) and CEACAM5, a tumor-associated antigen expressed on tumor cells and on tumor-derived material (i.e. exosomes or tumor debris containing neoantigen), leading to tumor directed activation of the DCs, enhanced uptake of tumor-derived material, cross-presentation of neoantigen and priming of neoantigen-specific T cells.

Methods CECAM5-transfected MC38 tumor-bearing human CD40 transgenic mice (hCD40tg) were used for anti-tumor efficacy studies and analyzing immunological memory in vivo. To investigate the potential of ATOR-4066 in combination with anti-PD-1 for activation of exhausted T cells, a mixed lymphocyte reaction (MLR) assay was used. To further analyze the response to treatment with ATOR-4066 in combination with anti-PD-1, dissociated tumor cells (DTCs, obtained from DLS) from gastric cancer patients were treated with the combination or each monotherapy and cells were stained for different immune cell populations and activation markers and analyzed using flow cytometry.

Results Using in vitro models, we have confirmed that the ATOR-4066 driven activation of CD40-expressing cells is CEACAM5-conditional. In addition, we have shown that ATOR-4066 induces co-localization of CD40-expressing cells and tumor-derived material, which in turn may facilitate uptake of neoantigen and priming of neoantigen-specific T cells. In vivo, this translates to a superior anti-tumor effect of ATOR-4066 treatment compared to a CD40 monospecific antibody. ATOR-4066 treated mice also displayed immunological memory and were able to clear homologous tumors upon re-challenge. In addition to the stand-alone potential for ATOR-4066, we here present evidence of enhanced effect of ATOR-4066 and anti-PD-1 combination treatment. When combining ATOR-4066 and anti-PD-1 in vitro in a MLR assay, a clear synergistic effect was observed on re-activation of exhausted T cells as measured by an increase in interferon gamma production. Furthermore, using DTCs from gastric cancer patients, ATOR-4066 induced activation of multiple immune cell populations.

Conclusions Overall, these data emphasize the potential of ATOR-4066 as monotherapy and as a checkpoint inhibitor combination partner to further enhance the immune response in tumors, demonstrating the promise of this new candidate drug for further clinical development.

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