DUAL CHECKPOINT BLOCKADE OF CD47 AND PD-L1 USING AN AFFINITY-TUNED BISPECIFIC ANTIBODY MAXIMIZES ANTI-TUMOR IMMUNITY AND IMPROVES THERAPEUTIC WINDOW

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Background T cell checkpoint immunotherapies have shown promising results in the clinic, but most patients remain non-responsive. CD47-SIRP α myeloid checkpoint blockade has shown early clinical activity in hematologic malignancies. However, CD47 expression on peripheral blood limits α CD47 antibody selectivity and thus efficacy in solid tumors.

Methods To improve the antibody selectivity and therapeutic window, we developed a novel affinity-tuned bispecific antibody targeting CD47 and PD-L1 to antagonize both innate and adaptive immune checkpoint pathways. This PD-L1-targeted CD47 bispecific antibody was designed with potent affinity for PD-L1 and moderate affinity for CD47 to achieve preferential binding on tumor and myeloid cells expressing PD-L1 in the tumor microenvironment (TME).

Results The antibody design reduced binding on red blood cells and enhanced selectivity to the TME, improving the therapeutic window compared to α CD47 and its combination with α PD-L1 in syngeneic tumor models. Mechanistically, both myeloid and T cells were activated and contributed to anti-tumor activity of α CD47/PD-L1 bispecific antibody. Distinct from α CD47 and α PD-L1 mono- or combination therapies, single-cell RNA sequencing (scRNA-seq) and gene expression analysis revealed that the bispecific treatment resulted in unique innate activation, including Pattern Recognition Receptor (PRR)-mediated induction of type I IFN pathways and antigen presentation in DCs and macrophage populations. Furthermore, treatment increased the Tcf7+ stem-like CD8 T cell population in the TME and promoted its differentiation to an effector-like state. Consistent with mouse data, the compounds were well tolerated and demonstrated robust myeloid and T cell activation in non-human primates (NHPs). Notably, RNA-seq analysis in NHPs provided evidence that the innate immune activation was mainly contributed by CD47-SIRP α but not PD-L1-PD-1 blockade from the bispecific antibody.

Conclusions These findings provide novel mechanistic insights into how myeloid and T cells can be uniquely modulated by the dual innate and adaptive checkpoint antibody and demonstrate its potential in clinical development (NCT04881045) to improve patient outcomes over current PD-(L)1 and CD47-targeted therapies.

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