PRECLINICAL EFFICACY OF CLEC-1 ANTAGONIST AS NOVEL MYELOID IMMUNE CHECKPOINT THERAPY FOR ONCOLOGY

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Background C-type lectin receptors (CLRs) are powerful pattern recognition receptors shaping immune cell-mediated tissue damage by positively or negatively regulating myeloid cell functions and hence tumor elimination or evasion. We previously reported that the orphan CLR CLEC-1 expressed by dendritic cells (DCs) tempers T cell's responses in vivo by limiting antigen cross-presentation by cDC1. Furthermore, we observed that CLEC-1 is highly expressed by myeloid cells purified from human tumor microenvironment, in particular tumor-associated macrophages.

Methods Macrophages were generated from monocytes of healthy volunteers for phagocytosis assays. MC38 and Hepa 1.6 murine tumor cells were implanted in Clec1a KO or KI mice for immunotherapeutic treatment evaluation.

Results Using newly developed anti-human CLEC-1 monoclonal antibodies (mAbs), we found that antagonist anti-CLEC-1 mAbs with the capacity to block CLEC-1/CLEC-1Ligand interaction, as opposed to non-antagonist CLEC-1 mAbs, increase the phagocytosis of CLEC-1Ligand-positive human tumor cells by human macrophages, in particular when opsonized by tumor-associated antigen mAbs (Rituximab, Cetuximab, Trastuzumab) or with anti-CD47 mAb (Magrolimab). In-vivo, CLEC-1 knock-out (KO) mice (n=19) display significant prolonged survival in monotherapy as compared to wild-type littermates (n=12) in an orthotopic hepatocellular carcinoma (HCC) model and anti-tumor memory responses was demonstrated by tumor rechallenge in cured mice. CLEC1 KO mice also illustrate significant eradication of MC38 colorectal tumors in combination with chemotherapy promoting CLEC-1Ligand expression by tumor cells (n=16 with Gemcitabine or n=11 with Cyclophosphamide). HCC tumor microenvironment analysis after 2 weeks of tumor implantation shows significantly higher number of CD8+ and memory CD8+ T cells with reduced PD1 expression in CLEC1 KO animals (n=16 versus n=12 for KO vs WT mice respectively). Finally, we recently generated human CLEC-1 knock-in mice expressing the extracellular human CLEC1 domain fused to the intracellular mouse CLEC1 tail and confirmed preclinical efficacy in vivo with anti-human CLEC1 antagonist mAb in monotherapy in the orthotopic HCC model.

Conclusions These data illustrate that CLEC-1 inhibition represents a novel therapeutic target for immuno-oncology modifying T cell immune responses and tumor cell phagocytosis by macrophages.

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