514 DEVELOPMENT OF AIM-104, A POTENTIAL BEST-IN-CLASS PAN-ALLELE ANTI-SIRPα ANTIBODY FOR ANTI-TUMOR THERAPY

[1]Michihisa Umetani*, [1]Jessica Yu, [1]Ariel Chen, [1]Courtney Le, [2]Li-Fen Lee, [1]Kan Lu. *[1]Apeximmune Therapeutics, Mountain View, CA, USA; [2]Apeximmune Therapeutics Inc, Palo Alto, CA, USA*

Background SIRPα is an innate immune checkpoint receptor that suppresses macrophage phagocytosis through interaction with its ligand CD47. Unlike CD47 which is ubiquitously expressed, SIRPα is expressed primarily on myeloid cells, and therefore targeting SIRPα is a promising approach for enhancing anti-cancer immunity without the safety and therapeutic index liabilities associated with targeting CD47.

Methods We have generated and characterized AIM-104, a highly selective and potent pan-allele anti-SIRPα monoclonal antibody that blocks the SIRPα-CD47 interaction and has minimal SIRPγ binding. Phagocytic activity was evaluated in vitro by co-cultured human macrophages with various human tumor cell lines. Effects on human T-cell function through SIRPγ binding were tested using an allogeneic mixed lymphocyte reaction. Additional safety criteria were addressed in vitro using a hemagglutination assay and a platelet binding assay. SIRPα/CD47-double-humanized mice and MC38-human CD47 knock-in cells were used for a syngeneic tumor model to evaluate the in vivo anti-tumor efficacy of AIM-104.

Results AIM-104 binds to the V1 and V2 alleles of SIRPα with picomolar range affinity and blocks CD47 binding to SIRPα AIM-104 potently induces macrophage phagocytosis of tumor cells in the absence or presence of tumor-targeted opsonizing antibodies. AIM-104 induced the highest in vitro phagocytic activity amongst several anti-SIRPα antibodies currently in clinical development, particularly when macrophages were derived from donors heterozygous or homozygous for the V2 allelic variant of SIRPα AIM-104 inhibited in vivo tumor growth in a mouse tumor model, and its phagocytotic activity appeared unaffected regardless of effector function in the Fc backbone. AIM-104 exhibits only very weak affinity to SIRPγ and did not compromise T cell IFNγ secretion in an allogeneic MLR, unlike anti-CD47 or anti-SIRPγ antibodies. In contrast to CD47-targeting antibodies which have experienced adverse events including acute anemia and thrombocytopenia, AIM-104 did not trigger hemagglutination or platelet binding in vitro.

Conclusions We have identified AIM-104 as a potentially best-in-class antagonistic anti-SIRPα antibody that is distinguished by its superior phagocytic activity on macrophages harboring the SIRPα V2 allelic variant. AIM-104 binds strongly to all major human SIRPα polymorphic alleles, potently induces macrophage phagocytosis of multiple tumor cell lines, and significantly inhibits *in vivo* tumor growth in mice without negatively affecting red blood cells, platelets, or T cell function. AIM-104 is currently undergoing IND-enabling studies.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0514