23ME-01473, a novel anti-ULBP6/2/5 monoclonal antibody, reinvigorates anti-tumor NK cell function through NKGD2 and FcγRIIa activation

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GENETIC SIGNATURE

- Using the 23andMe database, novel immune-oncology (I/O) drug targets were identified as genetic variants associated with clinical effects on the risk for cancer and immune diseases, referred to as an I/O signature. NKGD2 (gene encoded sULBP6) activate NK cell IU (signature figure 1).

ULBP6
- ULBP6 binding protein (ULBP6) is a member of the stress-induced NKGD ligand (NKGD2) family that is upregulated on the surface of cancer cells and binds to the immune-activating receptor NKp44 on NK and T cells.
- Cancer cells shed NKGD2, including ULBP6, from their surface via proteolytic cleavage or maximal release to evade immune recognition and killing, and soluble NKGD2s are elevated in cancer patient plasma (figure 2). 23ME-01473 (‘1473) is a high-affinity Fc-enhanced humanized monoclonal antibody that binds with high specificity to ULBP6, ULBP2, and ULBP5 and these antibodies are selected for their ability to induce ADCC (figure 3).
- To leverage the binding of 23ME-01473 to ULBP6/2/5 on the surface of cancer cells, the Fc domain of 23ME-01473 has enhanced affinity for FcγRIIIa to induce antibody-dependent cellular cytotoxicity (ADCC) (Figure 2B).

The combined synergistic mechanisms of NKGD2 and FcγRIIa activation mediated by 23ME-01473 restore NK and T cell-mediated tumor immunity, which may provide benefit to patients with cancers resistant to immune-checkpoint inhibitors due to the loss of neoantigen presentation.

23ME-01473 is currently being evaluated in a Phase 1 clinical trial as a monotherapy for patients with advanced solid tumors.

RESULTS

ULBP6/2/5 are upregulated in squamous cell carcinomas and a subset of adenocarcinomas
- Figure 3. 23ME-01473 binds with high affinity to ULBP6, ULBP2, and ULBP5 and these antibodies are selected for their ability to induce ADCC (figure 3).

Soluble ULBP6 is immunosuppressive even in the presence of membrane-bound NKGD2s
- Figure 4. The two most prevalent ULBP6 isoforms have the highest binding affinity for NKGD2.

Fc-attenuated anti-ULBP6/2/5 blocks sULBP6 to restore immune activation and tumor growth control
- Figure 5. Fc-attenuated anti-ULBP6/2/5 antibody promotes activation of NK and CD8+ T cells.

23ME-01473 (Fc-enhanced anti-ULBP6/2/5) induces superior anti-tumor immunity
- Figure 8. Fc-enhanced anti-ULBP6/2/5 antibody, 23ME-01473, augments NK and T cell activation and tumor killing.

CONCLUSION

- Table 1. 23ME-01473 (‘1473) binds ULBP6, 2, and 5 to block their interaction with NKGD2.

- 23ME-01473 elicits enhanced tumor cell killing with anti-CD8 T cells. 23ME-01473 elicits enhanced tumor cell killing with anti-CD8 T cells.

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REFERENCES