Simultaneous De-repression of Innate and Adaptive Immune Responses Through Dual Targeting of ILT4 and PD-(L)1 with Bispecific Antibodies

BACKGROUND

- ILT4 (CD87/2CD95) is an ILT family member that suppresses immune responses to myeloid cells.
- Binding and activation of the receptor by its cognate ligands HLA-G and HLA-C Class I in myeloid cells has immunosuppressive effects through multiple mechanisms.
- Expression of ILT4 on myeloid cells is associated with poor outcomes, and ILT4 is several tumor types is associated with poor outcomes.
- Antagonist Abs to ILT4 have immune enhancing and antitumor effects in preclinical models and recently demonstrated early clinical activity and safety.

PD-(L)1-ILT4 Bispecific Antibody Development

- bsAbs that revert myeloid cell suppression by mechanisms preclinical models and recently demonstrated early clinical activity and safety.
- ILT4 mAbs were generated by immunizing mice with purified human ILT4.
- Each mAb was humanized and expressed as IgG1 with Fc null mutations.
- No effector function but retains FcRn binding for PK enhancement.
- ILT4 mAbs do not cross-react with other LT family members.

Simultaneous Binding of Both PD-(L)1 and ILT4

- PD-L1-ILT4 bsAbs retain parental antibody functional activity.
- Co-targeting ILT4 and PD-(L)1 synergizes effector function.
- PD-L1-ILT4 bsAbs retain parental antibody functional activity.
- Co-targeting ILT4 and PD-(L)1 synergizes effector function.

Cytokine Release

- Tensor cell response measured by cytokine secretion in vitro.
- BS Abs blocked cytokine secretion in a dose dependent manner.
- BS Abs blocked cytokine secretion in a dose dependent manner.

Activated Immune Response in Human Mφs

- BS Abs promoted M1 Mφ polarization.
- BS Abs promoted M1 Mφ polarization.

Activation of Immune Responses in Human Mφs

- BS Abs synergistically induced cytokine/chemokine secretion.
- BS Abs synergistically induced cytokine/chemokine secretion.

PD-(L)1-ILT4 Bispecific Antibody Development

- BS Abs co-targeting ILT4 and PD-(L)1 synergizes effector function.
- BS Abs co-targeting ILT4 and PD-(L)1 synergizes effector function.

Conclusions

- ILT4 receptor inhibition with monoclonal antibodies lead to myeloid cell de-repression.
- Newed humanized mAbs 7A3 and 7B1 bind to ILT4 with high specificity and efficiency block HLA-G.
- Treatment of human monocytes with 7A3 or 7B1 mAbs leads to enhanced cytokines/chemokines secretion in vitro and M1 polarization.
- Simultaneous de-repression of myeloid and T cell checkpoints with ILT4 and PD-L1 bsAbs may be of clinical utility, particularly in the CPI refractory setting.