Fc-silent Anti-TIGIT Antibodies Potentiate Anti-tumor Immunity Without Depleting Regulatory T Cells


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Background & Summary

- TIGIT is an inhibitory checkpoint receptor primarily expressed on T and NK cell subsets.
- TIGIT suppresses cell activation through intrinsic mechanisms and by outcompeting a key activating receptor, CD226/DNAM-1, for the shared ligand CD155/PVR
- Analogous to the TCR and CD28, PD-1 can de phosphorylate CD226 to suppress cell activation^3.
- To achieve maximal effector cell activation and functionality, it is hypothesized that simultaneous blockade of TIGIT and PD-1 is necessary, particularly to target cell subsets that co-express TIGIT and PD-1, namely pre-exhausted T cells (T\text{\textsuperscript{reg}}).
- The TIGIT field has largely focused on elucidating mechanisms of action related to blocking antibodies that retain Fc functionality. In mouse models, Fc-enabled anti-TIGIT can deplete regulatory T cells (T\text{\textsuperscript{reg}}), an activity associated with single-agent efficacy^4; however, whether such mechanisms will translate to humans is unclear.
- In contrast, Fc-silent anti-TIGIT can enhance efficacy of anti-PD-1 without T\text{\textsuperscript{reg}} depletion in mice^5.

Here, we report pharmacology and mechanisms of action associated with Fc-silent anti-TIGIT antibodies relative to Fc-enabled counterparts. We found:

- Human and mouse tumor infiltrating lymphocytes express TIGIT and CD226 on T\text{\textsuperscript{reg}} and on CD8\textsuperscript{+} T cells with tumor-reactive or exhausted/dysfunctional phenotypes (Figure 2).
- In mice, in combination with anti-PD-1, Fc-silent anti-TIGIT enhances activation, differentiation, and effector function of tumor-specific CD8\textsuperscript{+} T cells in a manner dependent on T cell egress from the tumor-draining lymph nodes (Figure 3).
- In vitro, Fc-enabled human TIGIT-specific antibodies facilitated antibody-dependent cell-mediated cytoxicity (ADCC) against TIGIT-expressing human T\text{\textsuperscript{reg}} with preferential depletion of a Helios\textsuperscript{-}\text{aTIGIT}\text{ex} subset (Figure 4 & Figure 5).
- In cancer patients, significant and stable decreases in T\text{\textsuperscript{reg}} were measured in the peripheral blood of cancer patients treated with an Fc-enabled (AB308), but not an Fc-silent (domovamab), anti-TIGIT antibody (Figure 6).
- Cancer patients treated with domovamab in combination with anti-PD-1 antibody, zimberelimab, experienced partial responses while maintaining stable peripheral T\text{\textsuperscript{reg}} frequencies on treatment^6.

Silencing the Fc domain of anti-TIGIT antibodies prevents depletion of peripheral T\text{\textsuperscript{reg}} potentially critical for an optimal safety-efficacy profile in cancer patients.

Results

Human and Mouse Tumor Infiltrating Lymphocytes Co-express TIGIT, PD-1, and CD226

Fc-silent Anti-TIGIT Potentiates Tumor-specific T Cell Activation and Differentiation that is Dependent on the Tumor Draining Lymph Node

Peripheral Helios\textsuperscript{-} Effector T\text{\textsuperscript{reg}} (eT\text{\textsuperscript{reg}}) are Preferentially Targeted by TIGIT Directed ADCC

Figure 5. (A) Schematic (key point, example state post, frequency of each state; summary of two different experiments each with different time points and different antibodies) to illustrate how to demonstrate TIGIT\textsuperscript{-}aTIGIT\textsuperscript{-} vs TIGIT\textsuperscript{-}aTIGIT\textsuperscript{-} in different contexts. (B) Distribution of target distributions (TIGIT\textsuperscript{-}aTIGIT\textsuperscript{-} vs TIGIT\textsuperscript{-}aTIGIT\textsuperscript{-}) can tested using chi-square test. (C) Frequency of TIGIT\textsuperscript{-}aTIGIT\textsuperscript{-} in different contexts. (D) Frequency of TIGIT\textsuperscript{-}aTIGIT\textsuperscript{-} in different contexts.

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