a-TIGIT Ab Mediates Antitumor Activity Through Multiple Mechanisms of Action Involving Activation of Intratumor Effector T Cells and Depletion of Regulatory T Cells

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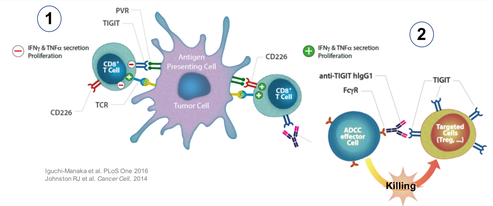
SUMMARY

- T cell Immunoreceptor with Ig and ITIM domains (TIGIT) is a negative costimulatory receptor that inhibits effector T and NK cell function and marks a highly suppressive regulatory T cell (Treg) subset.
- TIGIT ligands belong to the PVR/nectin family, among which PVR (CD155) shows the highest affinity and is commonly expressed on antigen presenting cells (APC) and tumor cells. *See poster #4969.*
- CD226, a co-stimulatory receptor also expressed on NK and T cells, competes with TIGIT for PVR binding but with a lower affinity.
- TIGIT expression is increased on T and NK(T) cells from cancer patients and is correlated to poor outcome and response to aPD1 therapy in some indications.
- EOS884448 properties and functionality make it an attractive Immuno-Oncology therapy candidate:
  - ✓ Strong binding to primary human and cyno T cells (sub nM Kd)
  - ✓ Competition with natural ligands with IC_{50} in sub nM range
  - ✓ Increased primary T cell functions in healthy donors and cancer patients samples
  - ✓ Depletion through ADCC of highly suppressive TIGIT$^+$ Treg
  - ✓ Antitumor efficacy in animal model
  - ✓ Excellent developability profile
  - ✓ Excellent safety profile

EOS884448 PREVENTS TIGIT-DRIVEN IMMUNOSUPPRESSION



1 drug = multiple anti-tumor mechanisms of action

1. Reactivation of immune response by
   - Suppressing TIGIT-mediated inhibitory signaling
   - Increasing ligand availability for CD226 co-stimulatory receptor
2. Depletion of TIGIT$^+$ highly suppressive Treg subpopulation and TIGIT$^+$ tumor cells with ADCC-triggering isotype (FcγR dependent)

iTEOS SURROGATE a-TIGIT Ab SHOWS ISOTYPE DEPENDENT ANTITUMOR EFFICACY in CT26 MODEL

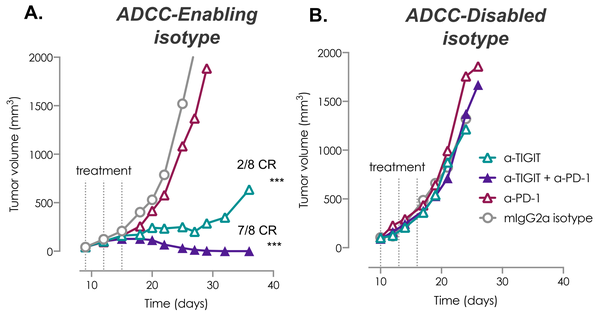


Fig. 1: Surrogate mouse a-TIGIT mAb demonstrates potent isotype-dependent antitumor efficacy. The efficacy of mouse surrogate a-TIGIT mAb antagonist was evaluated in pre-established CT26 syngeneic tumors using a mIgG2a (A) or mIgG1 (B) isotype. Monotherapy and combination of a-TIGIT mAb with a-PD1 resulted in significant tumor growth inhibition only for a-TIGIT mIgG2a. CR indicates Complete Responder mice with no palpable tumor. *** p<0.0001;

EFFICACY OF a-TIGIT Ab THERAPY DEPENDS ON ENGAGEMENT OF ACTIVATING Fcγ RECEPTORS

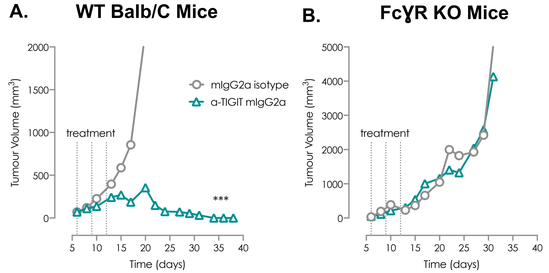


Fig. 2: Efficacy of surrogate mouse a-TIGIT mAb depends on engagement of FcγR receptor. The efficacy of mouse surrogate a-TIGIT mIgG2a antagonist Ab against established CT26 syngeneic tumors was evaluated in WT Balb/c (A) and in FcγR receptor KO (B) mice. Absence of FcγR receptor results in loss of therapeutic activity of a-TIGIT Ab. *** p<0.001;

EFFICACY OF a-TIGIT Ab CORRELATES WITH INCREASED FREQUENCY OF IFNg$^+$ T CELLS AND DEPLETION OF Treg in TME

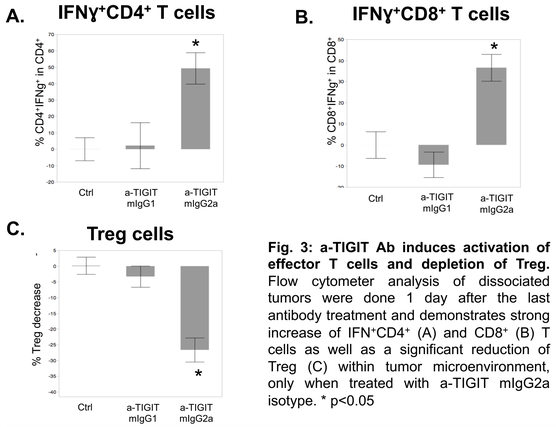


Fig. 3: a-TIGIT Ab induces activation of effector T cells and depletion of Treg. Flow cytometer analysis of dissociated tumors were done 1 day after the last antibody treatment and demonstrates strong increase of IFN$^+$CD4$^+$ (A) and CD8$^+$ (B) T cells as well as a significant reduction of Treg (C) within tumor microenvironment, only when treated with a-TIGIT mIgG2a isotype. * p<0.05

a-TIGIT Ab DEMONSTRATES DIRECT CYTOTOXIC ACTIVITY ON TIGIT EXPRESSING TUMOR CELLS

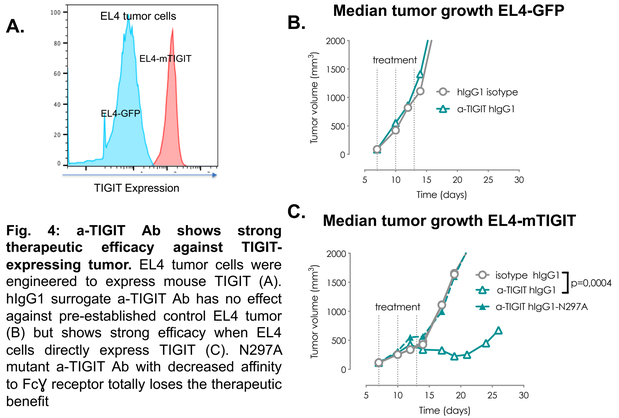


Fig. 4: a-TIGIT Ab shows strong therapeutic efficacy against TIGIT-expressing tumor. EL4 tumor cells were engineered to express mouse TIGIT (A). hIgG1 surrogate a-TIGIT Ab has no effect against pre-established control EL4 tumor (B) but shows strong efficacy when EL4 cells directly express TIGIT (C). N297A mutant a-TIGIT Ab with decreased affinity to FcγR receptor totally loses the therapeutic benefit

a-TIGIT Ab DEMONSTRATES STRONG THERAPEUTIC EFFICACY IN COMBINATION WITH 2ND GENERATION IC

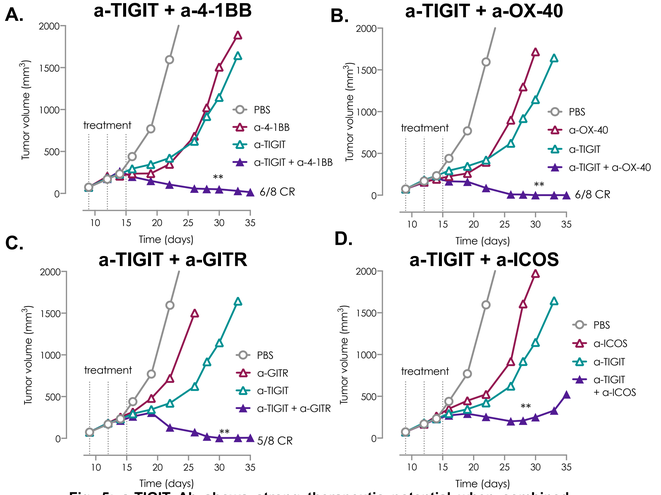


Fig. 5: a-TIGIT Ab shows strong therapeutic potential when combined with 2nd generation Immune Checkpoint. In addition to combination with a-PD1 (Fig. 1), the efficacy of mouse surrogate a-TIGIT mAb mIgG2a was evaluated in pre-established CT26 syngeneic tumors in combination with other immune checkpoint Abs. Strong synergistic or additive therapeutic efficacy was observed when a-TIGIT Ab was combined with a-4-1BB (A), a-OX-40 (B), a-GITR (C) or a-ICOS (D). CR indicates Complete Responder mice with no palpable tumor. ** p<0.001;

CONCLUSIONS

a-TIGIT Ab therapy demonstrates strong preclinical efficacy and high potential for cancer patients

- Strong single agent activity against established tumors
- Remarkable combination potential with several IC beyond a-PD1
- Therapeutic activity depends on engagment of FcγR receptor
- Increased frequency of activated T cells and depletion of regulatory T cells within tumor microenvironment
- Therapeutic efficacy mediated by direct cytotoxicity of TIGIT-expressing tumor cells

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Wallonie SPW Avec le soutien de la DGO6 Département du Développement Technologique