ABSTRACT

Background: TIGIT is a co-inhibitory receptor that is highly expressed on tumor infiltrating lymphocytes (TILs), including effector and regulatory (Treg) CD4+ T cells, effector CD8+ T cells, and NK cells. Engagement of TIGIT with its cognate ligand PVR directly suppresses lymphocyte activation. TIGIT and PVR are broadly expressed in different types of solid tumors, suggesting that TIGIT-PVR signaling may be a dominant immune escape mechanism for cancer. Utilizing COM902, a therapeutic antibody targeting TIGIT, we demonstrate that co-blockade of TIGIT and a new checkpoint inhibitor, PVRIG, augments T cell responses in vitro and in vivo.

Results: COM902 is a mouse/cyano cross-reactive fully human antibody that binds TIGIT with high affinity and specificity and disrupts the binding of TIGIT to PVR. This antibody binds to TIGIT on human CD8+ T cells with higher affinity than tested benchmark antibodies. In dissociated tumor samples, TIGIT expression was highest on TILs in endometrial, head and neck, kidney and lung tumors, and directly correlated with PVRIG expression. Except for breast tumors, PVR was moderately to highly expressed in all tumor types examined, while PVRIL2 expression was highest in prostate, ovarian, liver and endometrial tumors. Combination of COM902 and COM701 resulted in enhanced CD8+ TIL activity in vitro. Furthermore, the combination of chimeric COM902 and anti-PVRIG resulted in significant CT26 tumor growth inhibition and enhanced overall survival, which was comparable to the combination of chimeric COM902 and anti-PD-L1.

Conclusion: COM902 is a high affinity antagonistic TIGIT antibody, that is currently in preclinical development. Co-expression of TIGIT with PVRIG in TILs and their non-redundant inhibitory effects on T cell activation suggest a potential therapeutic advantage in clinical combinations targeting both pathways. Towards this end we are planning a trial that will eventually incorporate combinations of COM902 with the anti-PVRL1 antibody, COM701.

TIGIT AND PVRIG ARE PARALLEL, NON-REDUNDANT IMMUNE CHECKPOINTS IN THE PVR/NECTIN FAMILY

COM902: A HIGH AFFINITY, MOUSE/CYNO CROSS-REACTIVE TIGIT ANTAGONIST

COM902 HAVING SUPERIOR BINDING CAPACITY & SIMILAR OR GREATER FUNCTION COMPARED TO CLINICAL ANTI-TIGIT BM5

TIGIT IS EXPRESSED ON LYMPHOCYTES IN THE TME IN CORRELATION TO PVRIG AND PD1

COMBINATION OF COM902 AND COM701 DEMONSTRATES COMPARABLE OR GREATER POTENCY THAN ANTI-PD1

REDUCED TUMOR GROWTH IN PVRIG-/ AND TIGIT-/ MICE AND SYNERGISTIC TGI IN DOUBLE KO MICE IN B16-F10 MELANOMA CANCER MODEL

COM902 INHIBITS TUMOR GROWTH & INCREASES SURVIVAL IN COMBINATION WITH ANTI-PVRL1 OR ANTI-PD1 IN CT26 COLON CANCER MODEL

PVR AND PVRIL2 ARE EXPRESSED IN MULTIPLE TUMOR TISSUES

Tissue Type Total Samples % PVR Low (score 1) % PVR Moderate (score 2) % PVR High (score 3)

Pancreatic 11 30 50 20
Thyroid 10 60 20 20
Ovarian 10 20 50 30
Kidney 25 32 40 28
Breast 19 84 11 5

% PVRL2 Low (score 1) % PVRL2 Moderate (score 2) % PVRL2 High (score 3)

Pancreatic 11 73 0 0
Thyroid 10 30 0 0
Lung 17 47 0 0
Kidney 25 0 0 0
Brain 10 0 0 0

The expression of PVR (A) and PVRIL2 (B) in 10 different types of tumor tissues with n=10-20 patients per indication is shown. A polyclonal anti-PVRL1 antibody (M9R427/151, IgG2a, κ) and a monoclonal anti-PVRL antibody (Chimeric CHM9, Cell Signaling Technology) were used.

Days post-tumor implantation

Tumor Volume (mm3)

Days post tumour inoculation

Data as mean ± SD. *p<0.05, **p<0.01, ***p<0.001 vs. control; #p<0.05, ##p<0.01, ###p<0.001 vs. other groups.

A. Chimeric COM902 + anti-PD1	B. Chimeric COM902 + anti-PVRL1	C. Anti-PD1 alone

A. Anti-PD1 tumor volume in PVRIG-/ TIGIT-/ PVRIG+/ TIGIT+ double KO mice are represented as the mean volume ± SEM. B. Kaplan-Meier survival curves. C. Individual tumor measurements for each mouse.

The expression of PVR (A) and PVRIL2 (B) in 10 different types of tumor tissues with n=10-20 patients per indication is shown. A polyclonal anti-PVRL1 antibody (M9R427/151, IgG2a, κ) and a monoclonal anti-PVRL antibody (Chimeric CHM9, Cell Signaling Technology) were used.

A. Human CDr3+ T cell binding (from peripheral blood)
B. Inhibition of TIGIT/PVR interaction in cell-based assay
C. Increased IFNg+ secretion in CMV CDR+ T cell assay

A. A. Chimeric COM902 + anti-PD1
B. Chimeric COM902 + anti-PVRL1
C. Anti-PD1 alone