TIGIT

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TIGIT is a transmembrane glycoprotein comprising one immunoglobulin variable (IgV) domain, a type I transmembrane domain, and a cytoplasmic tail with an immunoreceptor tyrosine-based inhibitory motif (ITIM) and immunoglobulin tyrosine tail (ITT)-like motif.

cancer immunotherapy | immune checkpoint blockade | TIGIT | PVR

1. TIGIT Structure and Its Ligands

TIGIT is a transmembrane glycoprotein comprising one immunoglobulin variable (IgV) domain, a type I transmembrane domain, and a cytoplasmic tail with an immunoreceptor tyrosine-based inhibitory motif (ITIM) and immunoglobulin tyrosine tail (ITT)-like motif [1][2][3]. The cytoplasmic tail of TIGIT initiates an inhibitory signaling cascade. Previous studies have reported that ITT-like motif (Tyrosine, Y225) mediates a major inhibitory signal in humans, whereas mouse TIGIT inhibitory signal can be triggered by either the ITIM (Y277) or the ITT-like motif residue (Y233) [4]. Upon binding to its ligand, the cytoplasmic tail of TIGIT is phosphorylated and binds to cytosolic adaptor growth factor receptor-bound protein 2 (Grb2), recruiting Src homology 2 (SH2)-containing inositol phosphate-1 (SHIP-1). SHIP-1 inhibits phosphoinositide 3 kinase (PI3K) and mitogen-activated protein kinase (MAPK) signaling cascades [5]. Moreover, phosphorylated TIGIT associates with beta-arrestin 2 and recruits SHIP-1, which further suppresses the auto-ubiquitination of tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF-6) to inhibit nuclear factor kappa B (NF-κB) activation [5][6].

TIGIT has multiple ligands, including PVR (Necl-5 or CD155), nectin-2 (CD112), nectin-3 (CD113), and nectin-4 (PVRL4) [7][8]. Nectin and Necl proteins are cell-surface glycoproteins that belong to the immunoglobulin superfamily. Nectin family comprises four members (nectin-1–4), and the Necl family consists of five members (Necl-1–5). They have three Ig ectodomains, which form homodimeric or heterodimeric complexes in the membrane [9]. The IgV domain of TIGIT exhibits sequence homology with PVR, nectin-1, nectin-2, nectin-3, and nectin-4 [1]. TIGIT binds to PVR with high affinity and nectin-2 and -3 with low affinity. Recently, nectin-4 has been reported to bind to TIGIT with an affinity similar to that of TIGIT and PVR binding [10]. PVR plays immunoregulatory roles by interacting with TIGIT, CD226, and CD96 [11][12][13]. PVR has a greater affinity for TIGIT than either CD226 or CD96, implying a dominant role of TIGIT inhibitory signaling over activation signals. Furthermore, PVR expression is commonly upregulated in several types of cancer and tumor-associated myeloid cells [14][15]. Elevated PVR expression has been associated with an unfavorable prognosis across various solid cancer types [16][17]. Nectin-2 interacts with TIGIT, CD226, and CD112R; however, both TIGIT and CD226 have much weaker binding affinity to nectin-2 than PVR. Similar to PVR, the TIGIT–nectin-2 interaction could transduce an inhibitory

signal, but the CD226–nectin-2 interaction triggers immune cell activation. A recent study has demonstrated that the inhibitory effect of nectin-2 is mediated by CD112R and not TIGIT [18].

2. Role of TIGIT in Immune Cell Regulation

TIGIT is expressed on most NK and multiple T cell subsets, including memory and activated T cells, regulatory T cells (T_{reg}), and follicular T helper cells (T_{FH}) [1][3][4]. Upon activation with its ligands, TIGIT expression is upregulated in both T and NK cells, where TIGIT inhibits cytotoxic activity. TIGIT-deficient mice do not develop spontaneous autoimmunity; however, they exacerbate experimental autoimmune encephalitis when immunized with myelin oligodendrocyte glycoprotein, indicating a suppressive role of TIGIT [12]. In preclinical mouse tumor models, TIGIT deficiency delays the subcutaneous growth of both B16F10 and MC38 cells and lung metastasis of B16 cells [19][20]. Moreover, TIGIT-deficient mice show increased survival when challenged with VK*MYC myeloma cell lines [21]; however, a recent study revealed that TIGIT-deficient mice did not reject the implanted B16F10 and MC38 more efficiently compared with wild-type (WT) mice [22]. Moreover, in B16F10, RM-1, and E0771 cell lung metastasis models, the beneficial effect of TIGIT deficiency on tumor metastasis was not observed [23][24]. These discrepancies might be results of different experimental setups and/or mouse housing conditions [25]. Further studies with immune cell-type-specific TIGIT-deficient mouse models would be helpful to clarify the suppressive role of TIGIT in vivo [20].

Several mechanisms may explain TIGIT-mediated inhibition of T and NK cell activities. First, as aforementioned, TIGIT delivers an inhibitory signal resulting from ITIM and/or ITT motifs within its cytoplasmic domain. Agonistic anti-TIGIT antibodies inhibit human and mouse T cell proliferation and cytokine production without antigen presenting cells (APC) by suppressing T cell receptor/CD28-activating signaling [12][26]; however, TIGIT engagement increases the expression of receptors for T cell maintenance (e.g., interleukin [IL]-2R, IL-7R, and IL-15R) and anti-apoptotic molecules (e.g., Bcl-xL) [12], implying that TIGIT signaling could mediate the survival of T_{ex} cells. Additionally, TIGIT signaling also inhibits cytotoxicity, degranulation, and cytokine secretion of NK cells [3][27]. Moreover, TIGIT disrupts CD226 co-stimulation. TIGIT has higher affinity for the same set of ligands (PVR and CD112) than CD226. Thus, TIGIT outcompetes CD226 for binding to its ligands [1]. Knockdown of TIGIT in human $CD4^+$T cells induces T-bet-mediated interferon (IFN)-γ production, which can be overcome by blocking CD226-CD155 signaling [26]. Additionally, TIGIT hinders CD226 signaling through the physical prevention of CD226 homodimerization [28]. A recent study by Jin et al. has demonstrated that TIGIT directly affects the intracellular regulation of CD226 activation. By using an antibody specifically recognizing the phosphorylated form of CD226 (phospho-Y322), they have shown that CD226 phosphorylation at Y322 is reduced in TIGIT WT-expressing Jurkat cells upon PVR engagement but not in the cells expressing TIGIT mutant (Y225A/Y231A) [29]. In addition, TIGIT has been known to suppress T cell function in a cell-extrinsic manner. Following TIGIT ligation, PVR signaling leads to increased production of IL-10 and diminished production of IL-12p40 in human dendritic cells (DCs), which further downregulates T cell activation [1]. In accordance with this result, TIGIT ligation inhibits macrophage activation and leads to increased M2 macrophage polarization through PVR [30].

The role of TIGIT has been implicated in modulating T_{reg} cell responses. [31][32]. TIGIT expression is observed in a subset of natural T_{reg} cells in both mice and human. $TIGIT^+T_{reg}$ cells express higher levels of T_{reg} signature genes, including *Foxp3*, *CD25*, and *CTLA-4*, compared with $TIGIT^-T_{reg}$ cells. TIGIT expression is strongly correlated with the suppressive capacity and the lineage stability of human T_{reg} cells [31][32][33]. Furthermore, TIGIT engagement leads to the induction of IL-10 and fibrinogen-like protein 2, which selectively suppress T helper type 1 (Th1) and Th17 responses [31].

3. Targeting TIGIT for Cancer Immunotherapy

3.1. TIGIT as a Potential Prognostic Marker for Cancer

Accumulating data from the immune monitoring of cancer patients have revealed that TIGIT expression is elevated in T and NK cells, and it often appears to be associated with advanced disease status and poor clinical outcomes [20][21][34][35][36][37][38][39][40][41][42][43][44]. In follicular lymphoma (FL) patients, TIGIT is highly expressed on intratumoral T_{reg} and late-stage memory $CD8^+$T cells, and increased numbers of TIGIT-expressing tumor infiltrating T cells reveal a correlation with poor survival rate [34]. Multidimensional flow cytometric analysis of intratumoral T cells obtained from FL patients before and after anti-PD-1 therapy has revealed that $TIGIT^+$ T_{ex} cells majorly respond to this therapy. It has been observed that $TIGIT^+$ exhausted T cell populations are downregulated and $TIGIT^+$ effector cells are upregulated by anti-PD-1 therapy [34]. Increase in the proportion of highly suppressive tumor-infiltrating T_{reg} cells following TIGIT expression is associated with poor clinical outcomes in patients with hepatocellular carcinoma (HCC) and metastatic melanoma [33][43]. Moreover, upregulation of TIGIT indicates unfavorable disease status. High-risk patients with myelodysplastic syndrome (MDS) express higher levels of TIGIT and PD-1 in peripheral blood T and NK cells than low-risk patients [44]. High TIGIT expression renders $CD4^+$T, $CD8^+$T, and NK cells hypo-responsive to stimulation in high-risk MDS patients. Several studies have reported that TIGIT upregulation after treatment is correlated with recurrence. In patients with high-grade serous carcinoma, NanoString analysis of tumor tissues has indicated that recurrent tumors acquire a more inflamed phenotype with increased expression of TIGIT, CTLA4, Lag-3, and Tim-3 compared to primary tumors [45]. The proportion of $TIGIT^+CD8^+$T cells is increased in peripheral blood collected from acute myeloid leukemia (AML) patients, and it becomes more evident in patients with primary refractory disease and leukemia relapse post-allogeneic stem-cell transplantation [35]. Furthermore, TIGIT and/or PD-1 expression in $CD8^+$T cells is increased in patients with gastric cancer relapse after treatment with SOX (S-1 and oxaliplatin) regimen, whereas no notable increase in the proportion of $TIGIT^+$ and/or $PD\text{-}1^+CD8^+$T cells was found in relapse-free patients [46]. The compensatory increase in TIGIT expression post-treatment has also been observed in high-grade neuroendocrine neoplasms upon anti-PD-1 therapy [47].

3.2. TIGIT Blockade in Anti-Tumor Immunity

Based on the mechanism underlying TIGIT-mediated regulation of anti-tumor immune responses, efforts have been made to enhance T or NK cell activity by blocking TIGIT binding to its ligands, PVR and nectin-2, with monoclonal antibodies (mAbs) for therapeutic interventions. Several preclinical mouse models have been used to

assess the anti-tumor efficacy of anti-TIGIT blocking mAbs. In CT26 colon carcinoma, EMT6 breast carcinoma, MC38 colon carcinoma, and GL261 glioblastoma models, treatment with anti-TIGIT-blocking mAbs combined with anti-PD-1 or PD-L1-blocking mAbs leads to nearly complete remission of tumor growth, whereas the treatment of anti-TIGIT mAbs as a single agent presents limited efficacy [28][48][49]. $CD8^+$T cell depletion using anti-CD8α-depleting mAbs in CT26-bearing mice has revealed that the synergistic effect of dual blockade of TIGIT and PD-1 is mainly driven by the promotion of $CD8^+$T cell responses. A triple combination of anti-TIGIT mAbs, anti-PD-L1 mAbs, and radiotherapy elicits almost complete remission of tumor growth in CT26-bearing mice [50].

Sufficient tumor regression by treatment with anti-TIGIT mAbs alone has been reported in different mouse tumor models. In multiple myeloma (MM) mouse tumor model, TIGIT blockade leads to reduced tumor growth and increased survival compared with mice receiving control IgG or anti-PD-1 mAbs [21]. Moreover, TIGIT blockade presents anti-tumor efficacy in *Tgfbr1/Pten2* conditional knock-out (KO) mouse model that spontaneously develops head and neck squamous cell carcinoma (HNSCC) upon tamoxifen injection [41][51]. Both studies suggest that TIGIT is highly expressed on $CD8^+$T and T_{reg} cells in MM or HNSCC TILs and that anti-TIGIT mAbs reverse TIGIT-mediated suppression of $CD8^+$T cell effector functions; however, the potent anti-tumor effect of anti-TIGIT mAbs as a single agent may not be fully guaranteed simply by the increased expression of TIGIT in TILs, since high TIGIT expression is also observed in $CD8^+$ TILs in CT26-bearing mice that are not responsive to TIGIT blockade [28]. A recent study by Chiu et al. provided additional insights into the mechanism through which TIGIT blockade mitigates tumor immune evasion and resistance to PD-1 blockade [52]. They found that anti-PD-1 mAb treatment induced the upregulation of TIGIT in $CD8^+$ TILs in *Trp53* KO/*C-Myc*^{OE} mice, which is a highly aggressive HCC model; however, the compensatory expression of TIGIT upon PD-1 blockade was not observed in Hepa1-6-bearing mice that are known to be an anti-PD-1-sensitive orthotopic HCC model. PVRL1, which does not directly bind to TIGIT, contributed to TIGIT-mediated suppression of $CD8^+$T cells by stabilizing PVR in HCC cells, and PVRL1 deficiency rendered HCC to be more sensitive to anti-PD-1 mAb treatment. In accordance with this finding, a differential level of the ligand expression, such as PVR and PD-L1, or an increase in the binding affinity of TIGIT to PVR under an acidic tumor microenvironment has been recently identified to contribute toward the sensitivity of tumor cells to TIGIT blockade [53][54].

Although TIGIT blockade is known to mainly act on $CD8^+$T and T_{reg} cells, NK cell dependent efficacy of anti-TIGIT mAbs is also suggested. A recent study by Zhang et al. reported that treatment with anti-TIGIT mAbs 3 days after tumor cell implantation prevented tumor-infiltrating NK cell exhaustion in CT26 or methylcholanthrene (MCA)-induced fibrocarcinoma-bearing mice, which resulted in the enhancement of $CD8^+$T cell responses and tumor rejection [20]. However, the mechanism through which TIGIT blockade has an impact primarily on NK cells compared to T cells and the mechanism through which NK cells promote $CD8^+$T cell responses need to be further elucidated, since these results are contradictory to those of previous studies, revealing the $CD8^+$T or the T_{reg} cell-mediated effect of TIGIT blockade using temporary depletion of these populations with specific antibodies [21][28][41]. A more recent study reported that anti-TIGIT mAbs enhanced IL-15-driven NK cell cytotoxicity in both B16F10 and LWT1 metastatic melanoma-bearing mice [55].

The potency of human anti-TIGIT blocking mAbs on $CD8^+$T cells has been demonstrated in cancer patients. Cancer testis antigen NY-ESO-1-specific $CD8^+$T cell responses are increased by the addition of blocking mAbs against TIGIT and/or PD-1 when peripheral blood mononuclear cells (PBMCs) from melanoma patients are stimulated with NY-ESO-$1^{157–165}$ peptide. Furthermore, TIGIT blockade increases the capacity for proliferation and degranulation of $CD8^+$TILs from advanced melanoma patients upon TCR stimulation using autologous non-CD3 cells and anti-CD3 mAbs [36]. Upon TCR stimulation with anti-CD2/anti-CD3/anti-CD28 microbeads, bone marrow (BM) $CD8^+$T cells in MM patients show increased CD107a expression and cytokine production in response to TIGIT blockade [21]. When anti-TIGIT mAbs are added to ex vivo co-culture of $CD3^+$TILs and Mel-624 cells expressing membrane-bound anti-CD3 scFv (Mel-624 OKT3), IFN-γ and IL-2 production by $CD3^+$TILs from patients with endometrial, ovarian, kidney, head and neck, and lung cancers is promoted [18]. A recent study reported that antigen specific responses to CEF (CMV, EBV, flu) peptide are augmented by TIGIT blockade in peripheral blood $CD8^+$T cells derived from pancreatic ductal adenocarcinoma (PDAC) patients after mFOLFIRINOX therapy [29].

3.3. Mode of Action of Anti-TIGIT Therapy

Competitive binding of TIGIT and CD226 to PVR has been known as a key mechanism of TIGIT-driven immune suppression, and anti-TIGIT blocking mAbs are presumed to reverse the suppression by inhibiting TIGIT binding to PVR. This may occur as a mode of action; however, several questions need to be addressed for its clinical success and further translation of other members of TIGIT family receptors into cancer immunotherapy.

- **Intracellular Regulation by Anti-TIGIT mAbs**

Despite the importance of understanding the molecular interplay between TIGIT, CD226, and PVR, the mechanism through which extracellular signals from the receptor-ligand binding/receptor dynamics are integrated into the intracellular regulation, particularly in the context of anti-TIGIT therapy, remains unclear.

A recent study by Jin et al. reported that the effect of TIGIT blockade depends on tyrosine phosphorylation at Y322 of CD226, which was the first study to define the molecular requirements for anti-TIGIT blocking mAbs [29]. They showed that TIGIT-mediated intracellular inhibition of CD226 phosphorylation at Y322 was restored by TIGIT blockade. Moreover, CD226 mutant at Y322 ($CD226^{Y322A}$) expressing $CD8^+$T cells did not respond to TIGIT blockade, whereas $CD226^{WT}$ or $CD226^{Y329A}$ expressing $CD8^+$T cells produced increased IFN-γ upon treatment with anti-TIGIT mAbs, suggesting that TIGIT blockade promotes T cell activation via CD226 phosphorylation at Y322 (Figure 2). CD226 dependent effect of anti-TIGIT mAbs was further shown in effector memory $CD8^+$T cells expressing a low level of CD226 ($CD226^{lo}CD8^+T_{em}$) not responsive to both antigen stimulation and anti-TIGIT mAb treatment. CD226 activation using anti-CD226 agonist mAbs renders $CD226^{lo}CD8^+T_{em}$ responsive to TIGIT blockade.

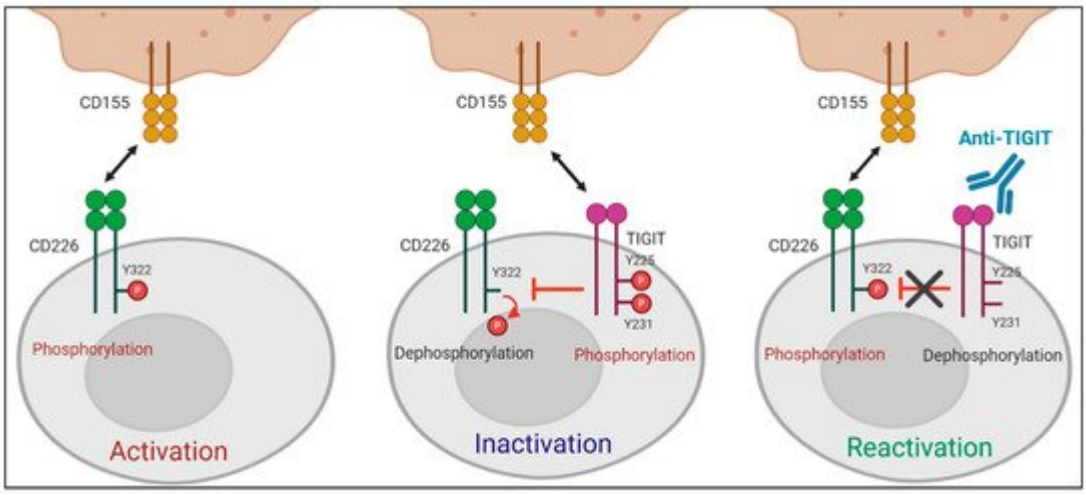

Figure 2. Role of CD226 in anti-TIGIT immunotherapy. TIGIT has a direct effect on intracellular regulation of CD226 activation in response to PVR binding. (**Left**) When TIGIT expression is absent or low, engagement of CD226 with PVR induces the phosphorylation of tyrosine 322 (Y322) on CD226, which leads to the activation of intracellular signaling cascades. (**Middle**) PVR preferentially binds to upregulated TIGIT over CD226. Upon interaction with PVR, the cytoplasmic tail of TIGIT is phosphorylated. This PVR-induced TIGIT phosphorylation inhibits T cell responses by promoting CD226 dephosphorylation. (**Right**) TIGIT blockade suppresses PVR-induced TIGIT phosphorylation and restores the impaired Y322 phosphorylation of CD226, thereby leading to T cell activation.

- **Isotype Selection of Anti-TIGIT mAbs**

Recently, several studies have highlighted the importance of selecting appropriate fragment crystallizable (Fc) region for therapeutic antibodies. To date, the approved human therapeutic IgG antibodies belong to IgG1, IgG2, or IgG4 subclasses [56]. It is increasingly clear that binding of the Fc region of antibody to Fc gamma receptors (FcγRs) can elicit various immunomodulatory functions, including antibody dependent-cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP) [57]. In addition, FcγR binding was reported to enhance agonistic activity of mAbs targeting tumor necrosis factor receptor superfamily members, such as CD28, CD137, CD40, and OX40 (CD134) [58].

The importance of the Fc domain of anti-TIGIT mAb is emphasized by the findings that anti-TIGIT mAb with Fc devoid of effector functions, which was intended to solely block TIGIT binding to its ligands, fails to exert any of anti-tumor efficacies in preclinical models [22][59][60]. It may be due to the loss of its depleting activity against TIGIT-expressing intratumoral T_{reg} cells, which has been considered as a potential mechanism of anti-TIGIT mAb-mediated anti-tumor effect [60]; however, it is still not clear whether the anti-tumor efficacy of anti-TIGIT mAbs depends on T_{reg} depletion, since there are recent reports that anti-TIGIT mAbs on mIgG2a isotype induce anti-tumor responses without evidence of T_{reg} depletion in mouse tumor models [22][59]. It may possible that FcγR on APC could act as a scaffold to crosslink anti-TIGIT mAb bound to TIGIT on immune cells, which may enhance the effect of TIGIT antagonism independent of T_{reg} cells. In addition, Han et al. recently have shown that the antibody-FcγR engagement induced activation of myeloid cells, leading to pro-inflammatory chemokine and cytokine

secretion (Figure 3) [22]. Comparison of clinical activities of anti-human TIGIT mAbs with different Fc scaffolds could provide insight into whether FcγR binding is required for optimal anti-tumor responses of TIGIT blockades.

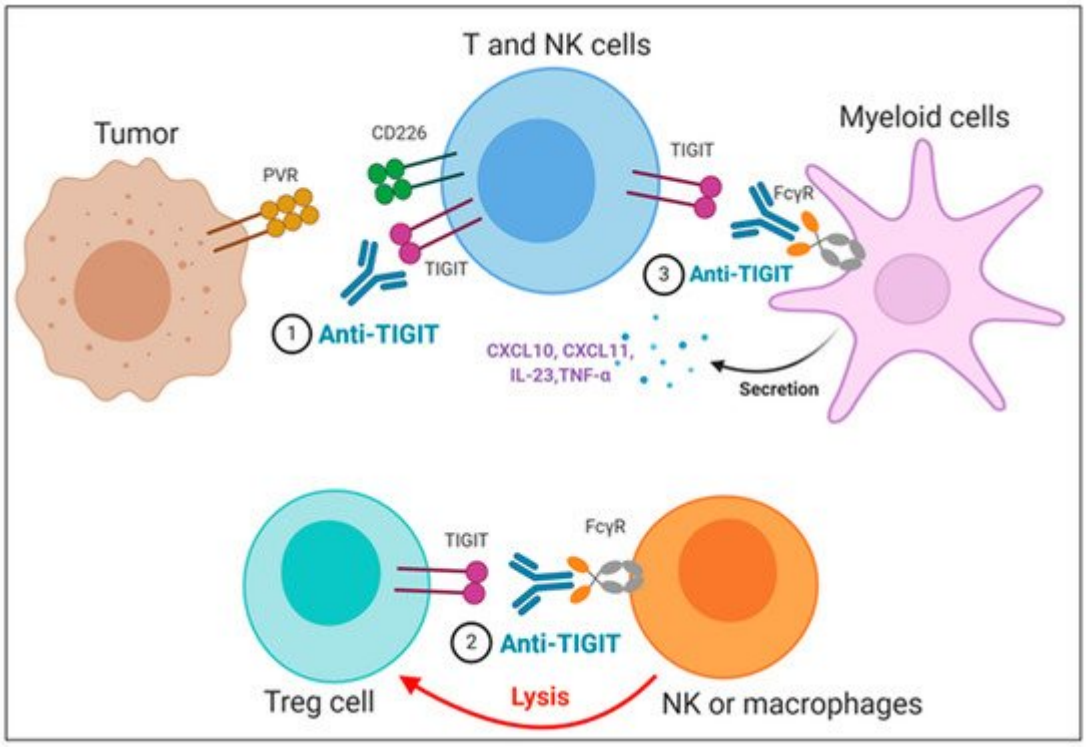

Figure 3. Proposed mechanisms of anti-TIGIT monoclonal antibodies (mAbs) in cancer immunotherapy. (**1**) Blockade of TIGIT could reverse the exhaustion of T and NK cell-mediated anti-tumor immunity. (**2**) Intratumoral regulatory T cells (T_{reg}) cells expressing high levels of TIGIT could be preferentially depleted by anti-TIGIT mAbs, presumably through antibody-dependent cellular phagocytosis (ADCP) by macrophages and/or antibody-dependent cellular cytotoxicity (ADCC) by NK cells. (**3**) The TIGIT mAb- fragment crystallizable (Fc) gamma receptors (FcγR) engagement could activate myeloid cells, leading to enhanced antigen presentation function and proinflammatory chemokine and cytokine secretion.

4. Anti-TIGIT Antibodies in Clinical Trials

Approximately 10 human anti-TIGIT mAbs, which have different IgG isotypes or mutant forms, have entered clinical trials. Table 1 summarizes publicly available data regarding antibody isotype, combination with different drugs, current development phase, and cancer types. Numerous clinical trials are evaluating the safety and the efficacy of anti-TIGIT mAb either as a monotherapy or in combination with PD-1/PD-L1 blockade or chemotherapies for the treatment of various cancers. Recently, the phase II CITYSCAPE trial presented significant response rates of tiragolumab plus atezolizumab in PD-L1-positive non-small cell lung cancer (NSCLC). The study revealed a significant objective response rate (ORR) improvement for the combination group (37% vs. 21%) as well as progression-free survival (PFS) improvement (5.6 vs. 3.9 months; hazard ratio [HR] 0.58). Importantly, patients in the combination group with high PD-L1 expression had an ORR of 66% compared with 24% in the atezolizumab group [61].

Table 1. Clinical trials of TIGIT inhibitors.

TIGIT Inhibitor	Sponsor	Isotype	Identifiers	Cancer Type	Combination	Phase	Recruitment Status	Start Date
ASP-8374	Astellas Pharma Inc.	IgG4	NCT03260322	Advanced solid tumor	ASP-8374 alone; Pembrolizumab (anti-PD-1)	Phase 1b	No longer recruiting	8 September 2017
			NCT03945253	Advanced solid tumor	ASP-8374 alone	Phase 1	No longer recruiting	5 August 2019
BGB-A1217	BeiGene Co Ltd.	IgG1	NCT04047862	Advanced solid tumor	Tislelizumab (anti-PD-1)	Phase 1	Recruiting	26 August 2019
BMS-986207	Bristol-Myers Squibb Co.	IgG1 (Fc receptor disabled)	NCT02913313	Advanced solid tumor	BMS-986207 alone; Nivolumab (anti-PD-1)	Phase 1/2	No longer recruiting	29 November 2016
			NCT04150965	Multiple myeloma	BMS-986207 alone; Dexamethasone+Pomalidomide	Phase 1/2	Recruiting	16 April 2018
			NCT04570839	Advanced solid tumor	COM-701 (PVRIG inhibitor) + Nivolumab (anti-PD-1)	Phase 1/2	Recruiting	31 August 2020
			NCT04065425	Multiple myeloma	Dexamethasone + Pomalidomide	Phase 1/2	Not yet recruiting	1 October 2019
COM-902	Compugen Ltd.	IgG4	NCT04354246	Advanced solid tumor	COM-902 alone	Phase 1	Recruiting	31 March 2020
AB154 (Domvanalimab)	Arcus Biosciences Inc.	IgG1 (Fc receptor disabled)	NCT03628677	Advanced malignancy	AB154 alone; Zimberelimab (anti-PD-1)	Phase 1	Recruiting	12 September 2018
			NCT04656535	Recurrent Glioblastoma	Zimberelimab (anti-PD-1)	Phase 1	Not yet recruiting	31 January 2021
			NCT04262856	PD-L1 positive lung cancer	Zimberelimab (anti-PD-1); Zimberelimab + etrumadenant (A2aR and A2bR antagonist)	Phase 2	Recruiting	28 May 2020
EOS-884448	iTeos Therapeutics	IgG1	NCT04335253	Advanced tumor	EOS-884448 alone	Phase 1/2	Recruiting	18 February 2020
Etigilimab (OMP-313M32)	OncoMed	IgG1	NCT03119428	Advanced solid tumor	Etigilimab alone; Nivolumab (anti-PD-1)	Phase 1	Terminated	2 May 2017
IBI-939	Innovent Biologics Inc.	Not disclosed	NCT04353830	Advanced tumor	IBI-939 alone; Sintilimab (anti-PD-1)	Phase 1a	Recruiting	22 May 2020

TIGIT Inhibitor	Sponsor	Isotype	Identifiers	Cancer Type	Combination	Phase	Recruitment Status	Start Date
			NCT04672356	Advanced lung cancer	Sintilimab (anti-PD-1)	Phase 1a	Not yet recruiting	28 January 2021
			NCT04672369	Advanced NSCLC	Sintilimab (anti-PD-1)	Phase 1b	Not yet recruiting	6 June 2021
M-6223	Serono Research Institute Inc, Merck KGaA	Not disclosed	NCT04457778	Advanced solid tumor	M-6223 alone; Bintrafusp alfa (TGF beta ligand inhibitor)	Phase 1	Recruiting	10 July 2020
Vibostolimab (MK-7684)	Merck Sharp & Dohme Corp.	IgG1	NCT02964013	Advanced solid tumor	Vibostolimab alone; Pembrolizumab (anti-PD-1); Pembrolizumab + Pemetrexed + Carboplatin; Pembrolizumab + Carboplatin or Cisplatin + Etoposide	Phase 1	Recruiting	13 December 2016
			NCT04305054	Advanced melanoma	Pembrolizumab (anti-PD-1);	Phase 1/2	Recruiting	1 July 2020
			NCT04303169	Melanoma	Pembrolizumab (anti-PD-1)	Phase 1/2	Recruiting	26 June 2020
			NCT04305041	Refractory melanoma	Pembrolizumab + Quavonlimab (anti-CTLA4)	Phase 1/2	Recruiting	26 June 2020
			NCT04165070	Advanced NSCLC	Pembrolizumab + Carboplatin + Paclitaxel; Pembrolizumab + Pemetrexed	Phase 2	Recruiting	19 December 2019
			NCT02861573	Prostate cancer	Pembrolizumab (anti-PD-1)	Phase 1/2	Recruiting	17 November 2016
Tiragolumab (MTIG7192A)	Genentech Inc., Chugai Pharmaceutical Co. Ltd., Roche Holding AG	IgG1	NCT04045028	Relapse/Refractory Multiple myeloma and B-cell Non-Hodgkin lymphoma	Tiragolumab alone; Daratumumab (anti-CD38); Rituximab (anti-CD20)	Phase 1	Recruiting	22 July 2019
			NCT02794571	Metastatic solid tumor	Tiragolumab alone; Atezolizumab (anti-PD-L1); Chemotherapy (Carboplatin, Cisplatin, Etoposide, Paclitaxel, Pemetrexed)	Phase 1	Recruiting	23 May 2016
			NCT03281369	Metastatic esophageal cancer	Atezolizumab (anti-PD-L1); Atezolizumab + Cisplatin+5FU	Phase 1/2	Recruiting	13 October

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TIGIT Inhibitor	Sponsor	Isotype	Identifiers	Cancer Type	Combination	Phase	Recruitment Status	Start Date
								2017
			NCT04513925	NSCLC	Atezolizumab (anti-PD-L1)	Phase 3	Recruiting	24 August 2020
			NCT04294810	Metastatic NSCLC, PD-L1 selected	Atezolizumab (anti-PD-L1)	Phase 3	Recruiting	04 March 2020
			NCT04665843	Metastatic head and neck cancer, PD-L1 positive	Atezolizumab (anti-PD-L1)	Phase 2	Not yet recruiting	21 January 2021
			NCT04543617	Esophagus squamous cell carcinoma	Atezolizumab (anti-PD-L1)	Phase 3	Recruiting	28 September 2020
			NCT04300647	Metastasis/Recurrent uterine cervix tumor, PD-L1 positive	Atezolizumab (anti-PD-L1)	Phase 2	Recruiting	30 June2020
			NCT03563716	NSCLC, chemotherapy-naïve	Atezolizumab (anti-PD-L1)	Phase 2	No longer recruiting	10 August 2018
			NCT04665856	Small-cell lung cancer	Atezolizumab + Carboplatin + Etoposide	Phase 3	Recruiting	4 January 2021
			NCT04619797	Metastatic NSCLC	Atezolizumab + Pemetrexed + Carboplatin or Cisplatin	Phase 2	Recruiting	11 December 2020
			NCT04584112	Triple-negative breast cancer	Atezolizumab + Nab-paclitaxel; Atezolizumab + Nab-pac-carbo-AC; Atezolizumab+Nab-pac-AC;	Phase 1b	Recruiting	28 September 2020
			NCT04256421	Metastatic small-cell lung cancer	Atezolizumab + Carboplatin + Etoposide	Phase 3	Recruiting	4 February 2020
			NCT04540211	Metastatic esophageal cancer	Atezolizumab + Paclitaxel + Cisplatin	Phase 3	Recruiting	4 November 2020
			NCT04524871	Metastatic hepatocellular carcinoma	Atezolizumab + Bevacizumab (anti-VEGF)	Phase 1/2	Recruiting	2 November 2020
			NCT03869190	Advanced urothelial carcinoma	Atezolizumab (anti-PD-L1)	Phase 1/2	Recruiting	1 June 2019

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TIGIT Inhibitor	Sponsor	Isotype	Identifiers	Cancer Type	Combination	Phase	Recruitment Status	Start Date
			NCT03193190	Metastatic pancreatic ductal adenocarcinoma	Atezolizumab + Nab-Paclitaxel + Gemcitabine	Phase 1/2	Recruiting	5 July 2017

PD-L1: programmed death-ligand 1; NSCLC: non-small cell lung cancer; TGF: transforming growth factor; VEGF: vascular endothelial growth factor.

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