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REVIEW ARTICLE

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T cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte-activation gene 3 (LAG-3), and T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT) — an update on emerging negative immune checkpoints in cancer treatment

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ABSTRACT

Immunotherapy is currently one of the most important treatment options for patients with various cancers. It is predominantly based on immune checkpoint inhibitors (ICIs), which are supposed to reverse immune suppression caused by interactions of negative immune checkpoints with their ligands. Cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed death 1 (PD-1), and its ligand, programmed death ligand 1 (PD-L1) are the checkpoints targeted by antibodies registered in various types of cancer to enable effective anti-cancer immune response. Despite numerous possibilities, other molecules belonging to immune checkpoints — T cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte-activation gene 3 (LAG-3), and T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT), are being extensively researched, mainly due to their role in cancer progression and resistance to immunotherapy. Recently, the first antibody against LAG-3 — relatlimab has been registered in melanoma, and many others are tested in the final stages of clinical trials. Thus, understanding their intricate functions and developing strategies to use them can create opportunities to apply immunotherapy in cancer treatment. This article describes their characteristics and potential role in solid-tumor treatment with TIM-3, LAG-3, and TIGIT molecules, which have been connected to tumor progression, poor survival, and poor prognosis in many tumor types.

Keywords: TIM-3, LAG-3, TIGIT, immunotherapy, negative immune checkpoints, solid tumors

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Introduction

Immunotherapy remains one of the most important treatment methods when it comes to solid tumors and leukemias. It is used in advanced stages of disease and is administered as an adjuvant and consolidation treatment after radiation, chemotherapy, and targeted therapies. A key mechanism in tumor escape from immune surveillance is the exhaustion of cells with cytotoxic activity — natural killer (NK) cells and $CD8^+$ T cells, which means that their proliferation, differentiation, and anti-tumor activity are inhibited. This process is caused by interactions of negative checkpoints on T cytotoxic (Tc) lymphocytes and NK cells

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with their ligands expressed on antigen-presenting cells (APCs), tumor cells, and other cells, including those present in the tumor microenvironment (TME). Immune checkpoint inhibitors (ICIs) are designed to prevent the depletion of the anti-cancer immune response by blocking negative checkpoints [1]. Thus far, cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed death 1 (PD-1), and its ligand, programmed death ligand 1 (PD-L1), are targeted by antibodies registered by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in various types of cancer, e.g., melanoma and lung cancer [2]. Recently, relatlimab — the first antibody against LAG-3, has been registered by the FDA in combination with nivolumab (anti-PD-1) in advanced melanoma [3]. However, many patients eventually stop responding to the treatment; their cancers progress and become resistant to immunotherapy. Neoantigen depletion, interferon-gamma (IFN-γ) sensitivity loss, and additional inhibitory checkpoint expression are considered resistance mechanisms in therapy using ICIs [4, 5]. Therefore, other negative immune checkpoints are being investigated in preclinical research and clinical trials. Apart from lymphocyte-activation gene 3 (LAG-3), T cell immunoglobulin and mucin-domain containing-3 (TIM-3), and T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT) are among those new molecules of interest. In this article, their potential role in cancer is highlighted. Moreover, similarities and differences between those three checkpoints are described, as all of them inhibit anti-tumor response but have different mechanisms of action and a variety of distinct ligands. The summary information about the three immune checkpoints is presented in Table 1.

Table 1. The expression of described immune checkpoints with their ligands and function

Molecule	Molecule expression	Ligand	Function	Ligand expression
TIM-3	T cells (except for Th2 cells), NK cells, DCs, macrophages, MDSCs, mast cells	Gal-9	Induction of apoptosis by calcium influx into Th1 cells	APCs, MDSCs, CD4+ T cells (naive), plasma
		CEACAM1	Supporting TIM-3 inhibitory function	DCs, macrophages, monocytes, and activated T cells
		HMGB1	Suppression of innate immune responses to nucleic acids	Proliferating tissues or estrogen-stimulated cancer cells
		PtdSer	Clearance of apoptotic bodies and antigen cross-presentation by Tim-3+ DCs	Apoptotic cells
LAG-3	T cells, NK cells, B cells, DCs, myeloid cells, mast cells	MHC-II	Inhibition of T cells antigen-dependent function	APCs (DCs, B cells, macrophages)
		LSECtin	Inhibition of IFN-γ secretion by effector T cells	Liver, tumor-associated macrophages, and other tumor tissues
		Gal-3	Suppression of CD8+ T cell function, apoptosis induction, and inhibition of the expansion of DCs, M1 to M2 polarization	Tumor cells, macrophages, epithelial cells, fibroblasts, T cells (activated)
		FGL-1	Suppression of antitumor immunity	Secreted from hepatocytes
		α-synuclein	Potential role in Parkinson's disease	Neurons, heart, and other tissues
TIGIT	T cells, NK cells	CD155	Induction of IL-10 secretion, Th2 polarization, and NK cell and T cell exhaustion	APCs, fibroblasts, T cells, endothelial cells
		CD112	Inhibition of NK cell and T cell activity	Tissues (hematopoietic and non-hematopoietic), including APCs
		CD113	Inhibition of T cell and NK cell activity	Non-hematopoietic tissues: liver, testes, lungs, placenta, and kidneys
		Nectin-4	Inhibition of NK cell activity	Tumor cells
		Fap2	Inhibition of NK cell cytotoxic functions and T cell activity	*Fusobacterium nucleatum* bacteria

APCs — antigen-presenting cells; CEACAM1 — carcinoembryonic antigen cell adhesion molecule 1; DCs — dendritic cells; Fap2 — fibroblast activation protein 2; FGL-1 — fibrinogen-like protein 1; Gal-3 — Galectin 3; Gal-9 — Galectin 9; HMGB1 — high-mobility group box 1; IFN-γ — interferon-gamma; LAG-3 — lymphocyte-activation gene 3; LSECtin — liver and lymph node sinusoidal endothelial cell C-type lectin; MDSCs — myeloid-derived suppressor cells; MHC — major histocompatibility complex; Nectin4 — nectin cell adhesion molecule 4; NK — natural killer; PtdSer — phosphatidylserine; TIGIT — T-cell immunoreceptor with Ig and ITIM domain; TIM-3 — T-cell immunoglobulin mucin-3

Table 2. Characteristics of molecules described in this paper

	TIM-3	LAG-3	TIGIT
Expression pattern	Constant expression, dependent on immune system stimulation	Expression occurring after stimulation and activation of the cell	Constant expression, dependent on immune system stimulation
Expression on tumor cells	Yes	Yes (leukemia) [24]	Yes
Function in cancer	Suppression of both specific and non-specific immune response, induction of Th1 cells apoptosis	Suppression of antigen presentation, T cell proliferation and functions, and IFN production	Suppression of T cells and NK cells activation and functions
Soluble form	Yes (sTIM-3)	Yes (sLAG-3)	No evidence of a soluble form
Registrations	No registered drugs in solid tumors	Relatlimab in melanoma	No registered drugs in solid tumors

IFN — interferon; LAG-3 — lymphocyte-activation gene 3; sLAG-3 — soluble lymphocyte-activation gene 3; sTIM-3 — soluble T-cell immunoglobulin mucin-3; TIGIT — T-cell immunoreceptor with Ig and ITIM domain; TIM-3 — T-cell immunoglobulin mucin-3

TIM-3 — characteristics, function, and role as a key player in advancing immunotherapy

T cell immunoglobulin and mucin-domain containing-3 (also CD366) is a member of the TIM protein family originally found to be expressed on terminally differentiated T helper 1 (Th1) cells and Tc cells [6]. It is a transmembrane molecule, and, as the name suggests, it contains an immunoglobulin variable domain (IgV) in its extracellular tail, followed by a mucin domain. It is also constitutively expressed by T regulatory cells (Tregs) [7], Th17 cells [8], myeloid cells [9], NK cells [10], mast cells [11], and dendritic cells (DCs) [12] (Tab. 1). There are four TIM-3 ligands described in the literature thus far: Galectin-9 (Gal-9), carcinoembryonic antigen cell adhesion molecule 1 (CEACAM1), high-mobility group box 1 (HMGB1), and phosphatidylserine (PtdSer) (Tab. 1). An interaction with the first identified ligand, Gal-9, causes Th1 cells death through calcium influx [13]. Since Th1 cells are one of the crucial populations in anti-tumor response, TIM-3/Gal-9 interaction is certainly unfavorable in terms of cancer disease. This is also true for Treg cells since TIM3-positive Tregs have superior suppressor function compared with TIM3-negative Treg cells [14]. Galectin-9 has been found in many tissues and immune cells, including APCs and T cells [13]. Another ligand, CEACAM1, can interact with TIM-3 in a particular manner — by forming a heterodimer if those molecules are co-expressed [15]. This ligand also endows TIM-3 inhibitory functions and enhances TIM-3 surface expression [15]. Moreover, CEACAM1 has been connected to angiogenic activity in lung cancer [16]. Another ligand, HMGB, binds to DNA released from dying cells (including tumor cells), and then it bonds to TIM-3, suppressing innate immune response through the recognition of nucleic acids by Toll-like receptors and cytosolic sensors in DCs because DNA binding is impaired [17]. Phosphatidylserine is a phospholipid present on the surface of apoptotic cells, and it is relevant in the cross-presentation mechanism in TIM-3$^+$ DCs. However, TIM-3 binds to PtdSer with significantly lower affinity than other TIM family members [18]. The effects of TIM-3/PtdSer interaction in T cells are not clear at the moment. Carcinoembryonic antigen cell adhesion molecule 1, HMGB1, and PtdSer have overlapping binding sites at the FG-CC loop in the TIM-3 IgV domain, and it has been determined that anti-murine and anti-human TIM-3 antibodies with functional efficacy interfere with TIM-3 binding to both PtdSer and CEACAM1 [19]. The binding site of Gal-9 is different. Some studies have shown that TIM-3 has its soluble form (sTIM-3), which, surprisingly, like the membrane form, inhibits anti-tumor immune response by decreasing cytotoxic activity and cytokine production [20, 21]. The cells expressing TIM-3 ligands are shown in Table 1. T cell immunoglobulin and mucin-domain containing-3 has been found on tumor cells and other cells in TME, such as an exhausted subset of CD8$^+$ tumor-infiltrating lymphocytes (TILs), CD4$^+$ Tregs, and DCs (Tab. 2) [17, 22, 23]. Those cell populations may suppress anti-tumor immunity. FoxP3$^+$ Tregs with TIM-3 expression have enhanced suppressor function towards Th1 and Th17 responses [24, 25]. Jiang et al. demonstrated that TIM-3 can promote type 2 macrophage (M2) polarization in colon cancer, and that is another tumor-promoting mechanism, as the M2 phenotype is anti-inflammatory and promotes angiogenesis [26, 27].

Doubtlessly, TIM-3 has inhibitory functions when it comes to anti-tumor immunity. Moreover, it has been shown that its overexpression is connected to resistance to PD-1 agents [28]. This has led researchers to conduct clinical trials with anit-TIM-3 agents, which have been proven to restore anti-tumor immunity in preclinical studies [22]. Additionally, TIM-3 is often co-expressed with PD-1 on both CD4$^+$ T cells and CD8$^+$ T cells, and TIM-3$^+$/PD-1$^+$ T cells are described as the most

dysfunctional [22]. Therefore, combined approach or bispecific antibodies are often considered. In a phase I/Ib clinical trial of sabatolimab (anti-TIM-3 antibody blocking its binding to PtdSer) alone and in combination with spartalizumab (anti-PD-1 antibody), the combination was well tolerated in advanced solid tumors. This method showed preliminary signs of efficacy, in contrast to sabatolimab alone [29]. However, in melanoma and non-small-cell lung cancer (NSCLC) patients pre-treated with anti-PD-1/L1 therapy, a phase II study showed limited success [30].

The phase I AMBER study evaluated cobolimab in monotherapy and combination with PD-1 inhibitors (nivolumab or dostarlimab) in advanced solid tumors, such as NSCLC and melanoma. Approximately 30% of the study participants underwent at least 2 lines of prior therapy. Cobolimab plus dostarlimab was well tolerated and showed preliminary anti-tumor activity [31]. Among 28 patients with advanced melanoma who received cobolimab with dostarlimab, 12 patients (42.9 %) achieved partial response (PR), and stable disease (SD) was observed in 3 (10.7 %) [32]. In another phase Ia/Ib study, TIM-3 monoclonal antibody (mAb) — LY3321367, alone or in combination with the anti-PD-L1 antibody — LY300054, was tested in patients with advanced solid tumors. Again, the therapy was safe but with modest efficacy, and, interestingly, in the NSCLC cohort, the outcome was better in anti-PD-1/L1 responders than in anti-PD-1/L1 refractory patients [33]. As for the bispecific approach, after investigating TIM-3 and PD-L1 bispecific antibody LY3415244 in a phase I study, Hellmann et al. described high immunogenicity of this agent and the occurrence of treatment-emergent antidrug antibodies (TE-ADA), which has led to the termination of the study [34]. Despite many attempts, very few antibodies are tested in phase III clinical trials currently, and those concern leukemias and not solid tumors [35]. Nevertheless, more research is required to evaluate the efficacy of TIM-3 inhibitors.

LAG-3 — leading the way with new monoclonal antibody therapies

Lymphocyte-activation gene 3, also referred to as CD223, is a transmembrane protein first identified in the NK cell line [36]. It is a homolog to CD4, and therefore, it binds to major histocompatibility complex (MHC) class II molecules with high affinity, leading to the suppression of antigen presentation and negative T cell regulation [37]. Other ligands are liver and lymph node sinusoidal endothelial cell C-type lectin (LSECtin), fibrinogen-like protein (FGL-1), α-synuclein, and the Galectin-3 (Gal-3) molecule [38]. The cells expressing LAG-3 ligands are shown in Table 1. Investigation of melanoma cells with LSECtin expression revealed that LSECtin/LAG-3 interaction inhibits the proliferation and IFN-γ secretion of tumor-specific effector T cells [38]. Galectin-3 may suppress CD8+ T cell function at the tumor site and hinder the expansion of DCs [39]. When secreted by tumor cells, Gal-3 has been demonstrated to alter the polarization of macrophages from M1 (anti-tumor) to M2 (pro-tumor), induce $CD8^+$ T cell apoptosis, and hinder T cell receptor (TCR) clustering [40]. It is overexpressed in many cancers and associated with metastasis formation as it promotes protease secretion [41]. A study on mice demonstrated that FGL-1 is a LAG-3 ligand that also suppresses antitumor immunity, but underlying mechanisms are yet to be unraveled. It may be secreted from hepatocytes, but it was also found in human cancer cells, and high FGL-1 plasma levels were associated with poor outcomes in patients receiving anti-PD-1 therapy [42]. Another ligand, α-synuclein, has a central role in the pathogenesis of Parkinson's disease. As α-synuclein fibrils are binding to LAG-3, this checkpoint is thoroughly investigated in this context [43, 44]. However, α-synuclein's role in the immune system is not clear.

Lymphocyte-activation gene 3 is expressed on activated CD4-positive and activated CD8-positive T cells [45], NK cells [36], B cells [46], and plasmacytoid dendritic cells [47]. A soluble form of LAG-3 (sLAG-3), when present in TME, can inhibit the antigen-presenting function of DCs or impair the differentiation of monocytes into DCs [48]. Furthermore, high baseline sLAG-3 level was associated with shorter progression-free survival (PFS) and overall survival (OS) in patients with head and neck squamous cell carcinoma (HNSCC) treated with chemotherapy or ani-PD-1 antibody [49]. As for the LAG-3 mechanism of action, a unique 'KIEELE' motif in the cytoplasmic tail is essential for signal transduction of the molecule [37]. Once the signal has been triggered, the consequence is the depletion of T cell function by inhibiting cytokine and granzyme production and proliferation (apart from the above-described mechanisms) [50]. In Tregs, LAG-3 induces the release of IL-10 and TGF-β1 (immunosuppressive cytokines), and $LAG\text{-}3^+$ Tregs are more suppressive than $LAG\text{-}3^-$ cells and are involved in indirect inhibition of DCs [51, 52]. The presence of LAG-3 on TILs or T cells ($CD4^+$ and $CD8^+$) has been described in several types of tumors, e.g., breast cancer [53], NSCLC [54], colon cancer [55], gastric cancer [56], ovarian cancer [57], and HNSCC [58]. In HNSCC, high LAG-3 expression has been associated with unfavorable prognosis [58]. Similarly, in NSCLC, the same factor correlated positively with PD-1 expression and was related to poor prognosis [54]. In another study, patients treated with anti-PD-1/PD-L1 antibodies with high

LAG-3 expression had shorter PFS [59]. Interestingly, LAG-3 expression on TILs was associated with better 5-year disease-free survival in patients with colon cancer undergoing adjuvant chemotherapy [55]. The synergistic effect of LAG-3 and PD-1 in immune tolerance in tumor models was described by Woo et al. [60]. The authors have proposed that a synergistic blockade of those two checkpoints may be effective in clinics as the genetic knockout of LAG-3 and PD-1 inhibited tumor growth in mice [60].

The interest in using anti-LAG-3 agents as an anti-tumor therapy resulted in the first registration of such medication. Relatlimab (anti-LAG-3) combined with nivolumab (anti-PD-1) has proven beneficial compared to nivolumab alone in melanoma patients. In the RELATIVITY-047 (phase II/III) study, median PFS was 10.1 months [95% confidence interval (CI) 6.4–15.7] in the relatlimab/nivolumab group *versus* 4.6 months (95% CI 3.4–5.6) in the nivolumab group [hazard ratio (HR) for progression or death = 0.75; 95% CI 0.62–0.92; p = 0.006 by the log-rank test] [3]. Based on this study, relatlimab has received FDA registration in unresectable or metastatic melanoma. This combination appears superior to ipilimumab and nivolumab, partially due to significantly decreased ratios of adverse event occurrence. Nevertheless, a triple blockade (targeting LAG-3, PD-1, and CTLA-4) is also considered in advanced melanoma, and the first report from the RELATIVITY-048 phase I/II study shows promising efficacy with no safety signals. The overall response rate (ORR) was 58.7%, and the 48-month OS rate was 71.7%; however, the sample size was small (n = 46) [61]. Nivolumab and relatlimab are currently also investigated in phase I or II clinical trials in other solid tumors, e.g., in metastatic colorectal cancer. In the RELATIVITY-123 phase III study, this combination is tested *versus* regorafenib or trifluridine plus tipiracil (TAS-102) [35, 62]. A combinatorial approach may also emerge as bispecific antibodies, and tebotelimab is one of them [anti-LAG-3 and anti-PD-1 dual-affinity re-targeting (DART) antibody]. Its safety and tolerability were tested in a phase I study in advanced solid tumors. With fatigue as the most common adverse event, the safety profile was similar to the relatlimab plus nivolumab combination [63]. Eftilagimod Alpha (efti, IMP321) was researched in a phase I study as an alternative to checkpoint blockade. It is a recombinant soluble human LAG-3Ig fusion protein that binds to MHC class II molecules and activates APCs. $CD8^+$ T cell activation is a consequence of this process. When administered with pembrolizumab, it was well tolerated in melanoma patients [64]. Efti has also shown antitumor activity in patients with 1st-line anti-PD-1/PD-L1-refractory NSCLC [65]. Overall, there seem to be many opportunities for the use of anti-LAG-3 agents in the treatment of solid tumors.

TIGIT — an old molecule is back in the research spotlight

Another negative immune checkpoint, TIGIT, is also known as Washington University cell adhesion molecule (WUCAM), V-set and transmembrane domain-containing protein 3 (Vstm3), and V-set and immunoglobulin domain-containing protein 9 (VSIG9) [66]. It is expressed by NK cells and T lymphocytes (not-naive), including CD4-positive (follicular helper cells), CD8-positive lymphocytes, Tregs, and memory T cells (Tab. 1) [66]. T cell immunoreceptor with immunoglobulin and ITIM domain belongs to the poliovirus receptor-like (PVR-like) family, containing a PVR signature motif in the IgV domain. PVR-like co-signaling network co-stimulates or co-inhibits NK and T cell activation against cancer cells [67]. Most TIGIT ligands are nectin and nectin-like adhesion molecules: CD155 (PVR, or Necl-5), CD112 (PVRL2, Nectin-2), CD113 (PVRL3, Nectin-3), and nectin-4 (PRR4, PVRL4) [67]. CD155, CD112, and CD113 are expressed throughout numerous tissues of endothelial origin and, importantly, on APCs and tumor cells (Tab. 1) [68–70]. DNAX accessory molecule-1 (DNAM-1, CD226) molecule, which is also part of this protein family, interacts with CD155 and CD112 to deliver a positive signal to T cells or NK cells, and TIGIT may outcompete DNAM-1 to trigger negative signaling [71]. Reches et al. [72] reported nectin-4 as a novel TIGIT ligand and a member of the PVR-like protein family, expressed mainly during fetal development and then in cancer. Binding to CD155 in TME results in direct inhibition of T cell functions and indirect inhibition by increased IL-10 (anti-inflammatory) production and decreased IL-12 (proinflammatory) production when CD155 is expressed on APCs [66]. Additionally, TIGIT-CD155 binding disrupts DNAM-1-mediated activating mechanisms by outcompeting DNAM-1 from its interaction with the ligand or preventing cis-homodimerization on the cell surface [73]. T cell immunoreceptor with immunoglobulin and ITIM domain signaling in Tregs enhances their immunosuppressive functions, and melanoma patients undergoing immune checkpoint blockade therapy with a high TIGIT/DNAM-1 expression ratio (as assessed on tumor-infiltrating Tregs) have shorter PFS than patients with low values of this rate [74]. Chen et al. [75] showed in mice that another inhibition mechanism of TIGIT may be the polarization of $CD155^+$ macrophages to M2, an anti-inflammatory (tumor-promoting) type. Fap2 has also been described as a TIGIT ligand. It is a protein of *Fusobacterium nucleatum* bacteria, and its binding to TIGIT results in the inhibition of NK cells' cytotoxic functions and T cell activity [76]. Because *F. nucleatum* may be present at the tumor site, especially in colorectal adenocarcinoma (*F. nucleatum* bacteremia was described in other cancer types as well), it may affect anti-tumor immunity [77].

T cell immunoreceptor with immunoglobulin and ITIM domain is described as one of the factors relevant to tumor escape from immunological surveillance. Its expression on TILs or/and peripheral blood mononuclear cells (PBMCs) has been reported in various tumor types, such as gastric cancer [78], esophageal squamous cell carcinoma [79], NSCLC [80], and colorectal cancer [81]. In gastric cancer patients, the researchers have found that in circulating TIGIT-positive CD8-positive T cells, IFN-γ and TNF-α production and cell migration were impaired, while apoptosis was higher. Functional exhaustion (similar to $CD8^+$ T cells) was observed also in TIGIT-positive CD4-positive T cells [78]. As it has been mentioned earlier, immune checkpoints are often co-expressed, e.g., functionally altered $TIGIT^+$ NK cells infiltrating endometrial cancers co-express LAG-3 and TIM-3 [82]. Importantly, some research has indicated that the co-blockade of PD-L1 and TIGIT elicits $CD8^+$ T cell effector function more effectively than a single anti-PD-L1 or anti-TIGIT antibody in preclinical cancer models [83]. Hence, the frequent testing of a combinatorial approach when it comes to immune checkpoint blockade in clinical trials. Wang et al. [79] connected PD-L1 co-expression with TIM-3/TIGIT on $CD8^+$ TILs with poor OS in patients with esophageal squamous cell carcinoma.

After confirmation of immunosuppressive functions in cancer and encouraging results of phase I trials, anti-TIGIT agents could move forward. The CITYSCAPE phase II trial was the first randomized study to show the preliminary efficacy of an anti-TIGIT (tiragolumab) and anti-PD-L1 (atezolizumab) combination for advanced cancer. Patients with advanced NSCLC and tumor PD-L1 expression ≥ 1% were enrolled in this study. Among 135 participants, 67 (31.3%) patients in the tiragolumab plus atezolizumab group had an OR *versus* 68 (16.2%) in the placebo plus atezolizumab group (p = 0.031). Median PFS was 5.4 months (95% CI 4.2–not estimable) in the tiragolumab plus atezolizumab group *versus* 3.6 months (2.7–4.4) in the placebo plus atezolizumab group (stratified HR = 0.57; 95% CI 0.37–0.90; p = 0.015). The treatment was well tolerated, and the safety profile was similar to that of atezolizumab in monotherapy [84]. This combination received a 'breakthrough therapy' designation from the FDA for PD-L1-high NSCLC. The ARC-7 trial (phase II study) is evaluating the safety and efficacy of zimberelimab (anti-PD-1 mAb) monotherapy, domvanalimab in combination with zimberelimab, and domvanalimab in combination with zimberelimab and etrumadenant in front-line, PD-L1 positive [tumor proportion score (TPS) ≥ 50%], metastatic NSCLC. Domvanalimab is an anti-TIGIT, Fc-silent antibody, and etrumadenant is a selective dual antagonist of both A2a and A2b adenosine receptors expressed on immune cells. The study evaluates whether inhibition of TIGIT and adenosine pathways augments the activity of zimberelimab. Preliminary results confirm that domvanalimab-containing arms demonstrated improved ORR and PFS compared to zimberelimab in monotherapy, and the safety profiles were similar among the groups [85]. Another study with tiragolumab, SKYSCRAPER-01, is a global, randomized, double-blind, phase III study evaluating tiragolumab plus atezolizumab *versus* atezolizumab alone as first-line treatment in patients with PD-L1–high, locally advanced, unresectable or metastatic NSCLC. The study is still ongoing, the second interim analysis (with OS data still not mature) showed numerically better median OS: 22.9 months (95% CI: 17.5–NE) in the tiragolumab plus atezolizumab arm and 16.7 months (95% CI: 14.6–20.2) in the atezolizumab monotherapy arm (HR = 0.81; 95% CI 0.63–1.03). The combination was well tolerated [86]. The SKYSCRAPER-02 trial in untreated advanced-stage small-cell lung cancer (SCLC) showed that tiragolumab did not provide additional benefit over atezolizumab plus carboplatin and etoposide [87]. Another anti-TIGIT mAb, vibostolimab, was tested in combination with pembrolizumab (anti-PD-1) in patients with high-risk stage II-IV melanoma as adjuvant therapy. The phase III KEYVIBE-010 study has been suspended due to immune-mediated adverse effects, and thus, adjuvant therapy was discontinued in all patients in the investigational arm compared with the pembrolizumab-only arm [88, 89]. Despite the lack of positive results for tiragolumab in phase III studies, experts are willing to continue the research in NSCLC and other tumors [90].

Summary

As mentioned in the introduction, TIM-3, LAG-3, and TIGIT have their differences and similarities. All three checkpoints regulate T cell-mediated anti-cancer immunity, as their expression on TILs is often associated with poor prognosis. Inhibition of anti-cancer response by blockade of cytotoxic function is a feature they have in common. However, given the multitude of their ligands and types of cells with expression of those molecules, the interaction network is highly complex. By blocking one checkpoint, many interactions by several ligands on multiple types of cells are inhibited, which has wide implications. This should be considered when therapy with checkpoint inhibitors is researched. Not only does it influence the T cells but also the other cells present in TME. Moreover, more studies are required for a better understanding of checkpoint-ligand binding and designing the best drugs possible. Nevertheless, there are already several options of treatment that

have been proven effective, and this also should be investigated deeply to exploit their potential fully. Additionally, ligand-blocking strategies are also being investigated. Given the impressive number of approaches possible, further evaluation of various combinations and indications is needed to determine the relevance of anti-TIM-3, anti-LAG-3, and anti-TIGIT antibodies.

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