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REVIEW

Anti-TIGIT therapies for solid tumors: a systematic review

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Programmed death-ligand 1[PD-(L)1], cytotoxic T-lymphocyte associated protein 4 (CTLA-4), and lymphocyte-activation gene 3 (LAG-3) inhibitors are recent breakthroughs in cancer treatment, however not all patients benefit from it. Thus new therapies are under investigation, such as anti-TIGIT [anti-T-cell immunoreceptor with immunoglobulin (Ig) and immunoreceptor tyrosine-based inhibitory motif domains] antibodies. TIGIT is an immune checkpoint inhibiting lymphocyte T cells by several mechanisms. *In vitro* models showed its inhibition could restore antitumor response. Furthermore, its association with anti-PD-(L)1 therapies could synergistically improve survival. We carried out a review of the clinical trial about TIGIT referenced in the PubMed database, finding three published clinical trials on anti-TIGIT therapies. Vibostolimab was evaluated in a phase I alone or in combination with pembrolizumab. The combination had an objective response rate of 26% in patients with a non-small-cell lung cancer (NSCLC) naïve of anti-programmed cell death protein 1 (anti-PD-1). Etigilimab was tested in a phase I alone or in combination with nivolumab, but the study was stopped due to business reasons. In the phase II CITYSCAPE trial, tiragolumab demonstrated higher objective response rate and progression-free survival in combination with atezolizumab than atezolizumab alone in advanced PD-L1-high NSCLC. The ClinicalTrials.gov database references 70 trials of anti-TIGIT in patients with cancer, 47 of them with ongoing recruitment. Only seven were phase III, including five about patients with NSCLC, mostly with combination therapy. Data from phase I-II trials highlighted that targeting TIGIT represents a safe therapeutic approach, with an acceptable toxicity profile maintained when adding anti-PD-(L)1 antibodies. Frequent adverse events were pruritus, rash, and fatigue. Grade 3-4 adverse events were reported in nearly one in three patients. Anti-TIGIT antibodies are under development as a novel immunotherapy approach. A promising research area includes the combination with anti-PD-1 therapies in advanced NSCLCs.

Key words: TIGIT, immune therapy, lung cancer, tiragolumab

INTRODUCTION

In the last 10 years, the immunotherapy approach addressing immune checkpoint inhibitor (ICI) receptors such as programmed death-ligand 1 [PD-(L)1], cytotoxic T-lymphocyte associated protein 4 (CTLA-4), and lymphocyte-activation gene 3 (LAG-3) revolutionized anticancer treatment, assuming relevance as a backbone therapy for different solid malignancies.[1] This relevance was also proven across the oncological context where more innovative targeted approaches failed to demonstrate a clear clinical benefit.[2] Immune checkpoint molecules are key modulators of the anti-tumor T-cell response.[3] In physiologic conditions, inhibitory immune checkpoint receptors play a vital role in maintaining immune self-tolerance and preventing T cells from autoimmune reactions. Under pathologic conditions (e.g. malignancy), the same receptors are involved in the immune response against cancer cells. A variety of cell surface receptors, both co-inhibitory [CTLA-4, programmed cell death protein 1 (PD-1), T-cell immunoglobulin and mucin containing protein-3 (TIM-3), LAG-3, V-domain Ig suppressor of T-cell activation (VISTA), T-cell immunoreceptor with immunoglobulin (Ig) and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT)] and costimulatory [CD80, CD86, CD40, OX40, CD137, glucocorticoid-induced TNFR-related protein (GITR), Inducible T-cell COStimulator (ICOS)], contribute to and dictate the strength of the T-cell immune response following T-cell receptor—major histocompatibility complex engagement.[4]

The introduction of ICIs targeting the PD-(L)1 axis improved the prognosis of several advanced cancers, including non-small-cell lung cancer (NSCLC).[5-7] For instance, the 5-year survival rate increased from 5% to 30% by delivering PD-(L1) inhibitors in the therapeutic armamentarium of stage IV NSCLC.[8,9]

To date, the degree of PD-L1 expression is the only established biomarker to predict anti-PD-(L)1 response in

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solid tumors.[10] However, despite promising long-term responses, most patients fail to respond to ICIs treatment. Indeed, ICIs targeting the PD-(L)1 axis are associated with a great variability of efficacy.[11]

Cancer cells adopt different mechanisms to evade the immune system surveillance.[12,13] Both primary and acquired resistance are a result of complex and constantly evolving interactions between cancer cells and the immune system. The overexpression of alternative immune checkpoint receptors with inhibitory function can be responsible for an impaired efficacy of ICIs.[14] As highlighted in preclinical models, targeting multiple receptors with inhibitory functions may represent a promising strategy to generate full antitumor response.[15] The TIGIT is a novel immune checkpoint receptor with inhibitory function, expressed on T cells and natural killer (NK) cells.[16] Similar to the PD-1 receptor, TIGIT limits antitumor immune response in cancer.[17] In this regard, TIGIT inhibition via novel monoclonal antibodies represents an interesting therapeutic strategy to be exploited in early-phase clinical trials in human. Based on positive preclinical studies,[18] several clinical trials are now ongoing that are investigating TIGIT blockade combined with other ICIs, to achieve improvement in patient outcomes (response, progression-free, and overall survival).

As the future treatment of all solid tumors will widely be covered by association of immunotherapy agents targeting new checkpoints of the immune system, it is essential to summarize all the therapeutic advances achieved so far regarding TIGIT, one of the most promising novel targets of checkpoint inhibitors.

BIOLOGICAL BACKGROUND

TIGIT, also known as WUCAM, Vstm3, and VSIG9, is a member of the Ig superfamily. Its expression is described in several human cancers, including melanoma,[19] NSCLC,[20] and colorectal cancer.[21] The TIGIT receptor consists of an Ig variable domain, a transmembrane domain, and an immunoreceptor tyrosine-based inhibitory motif.[22] Activated T cells, both regulatory CD4+ and effector CD8+, and NK cells, express TIGIT at cell surface and interact with the highest binding capacity to the poliovirus receptor (PVR), also known as CD155, and, at weaker affinity to the nectin-2 receptor or Poliovirus receptor-related 2 (PVRL2) or CD112.[22] Similarly, the costimulatory receptor CD226 is among the ligands of TIGIT, with a lower affinity to TIGIT binding, compared with the CD155.[23] CD155 is an adhesion molecule, preferentially expressed on dendritic cells and macrophages, acting as a recognition molecule for NK cells. The interaction between CD155 and its ligand, TIGIT, was studied in different malignancies, including melanoma and NSCLC. In lung adenocarcinoma, immunohistochemical (IHC) overexpression of TIGIT/CD155 emerged as an unfavorable prognostic factor.[24] The CD155/TIGIT interaction is responsible for the negative regulation of the innate and adaptive immune responses at different levels.[25] In response to CD155/TIGIT pathway activation, T-cell receptor expression is reduced, resulting in impairment of NK cell and CD8 T-cell effector functions. Impaired T-cell activation is also a consequence of immunosuppressive cytokine release such as interleukin-10 by dendritic cells and decrease of interleukin-12 production, which is favored by TIGIT engagement.[22] Inhibition of CD226 signaling by disrupting homodimerization is among the known mechanisms of TIGIT inhibition in T cells. TIGIT expression in humans is a late event in the cancer-immunity cycle, occurring after chronic tumor antigen exposure.[26,27]

TIGIT can compete for ligand binding with CD226, replacing CD226 from CD155 binding, hence impairing antitumor immunity as demonstrated in mice and humans.[28] In addition, TIGIT signaling in regulatory T cells (Tregs) enhances their immunosuppressive functions. In mice and humans TIGIT is highly expressed by a subset of natural Tregs and its upregulation in Tregs is associated with hypomethylation and Foxp3 binding at the TIGIT locus.[29] TIGIT+ Tregs upregulate many Treg gene signature markers in tumors. They include Foxp3, Helios, neuropilin-1, CTLA-4, PD-1, TIM-3, and LAG-3.[30] As with PD-1/PD-L1, binding of TIGIT with its ligands can suppress T-cell function. This pathway is not redundant to the PD-1/PD-L1 axis, but they display more than one similarity. Both PD-1 and TIGIT are increasingly upregulated in activated T lymphocytes, to prevent excessive immune responses.[15] It is now clear that the tumor microenvironment is only one of the many factors able to affect the likelihood of individual response to ICIs. The tumor genome and epigenome, as well as the human microbiome, must be considered when exploring individual variability in clinical outcomes with immune therapy directed at immune checkpoint receptors. A pan-cancer analysis revealed the role of TIGIT in shaping the tumor microenvironment with novel insights on the correlation between TIGIT and epigenetic regulators such as DNA methyltransferases. This evidence suggested that DNA methylation may also participate in the modulation of TIGIT, supporting the possibility to target this receptor by methylation modulators.[31] To date, accumulating data support the inhibition of TIGIT receptor to unleash the immune system against cancer cells, thereby countering the phenomenon of immune escape. Preclinical evidence and early-phase clinical trials prove the feasibility of exploiting novel drugs addressing ICIs' combination, such as TIGIT and PD-(L)1.

As with anti PD-(L1) agents, identifying biomarkers of response is an active area of clinical research that aims to achieve better selection of patients in early-phase clinical trials and spare unnecessary toxicities in patients. Blessin et al.[32] evaluated TIGIT expression across 86 human tumor entities; results of this study showed highly variable expression levels not only in different cell types but also according to the cellular localization, highlighting the high complexity of immune microenvironments. The variability of TIGIT expression between different cellular compartments emphasizes the importance of going beyond *in situ* analysis of patient tissues. At present, the relevance of TIGIT quantitative expression as a predictive factor of response to anti-TIGIT treatments warrants further investigations. Indeed, few, if any, studies have clarified whether TIGIT expression assessed in a quantitative and spatially resolved manner may help to

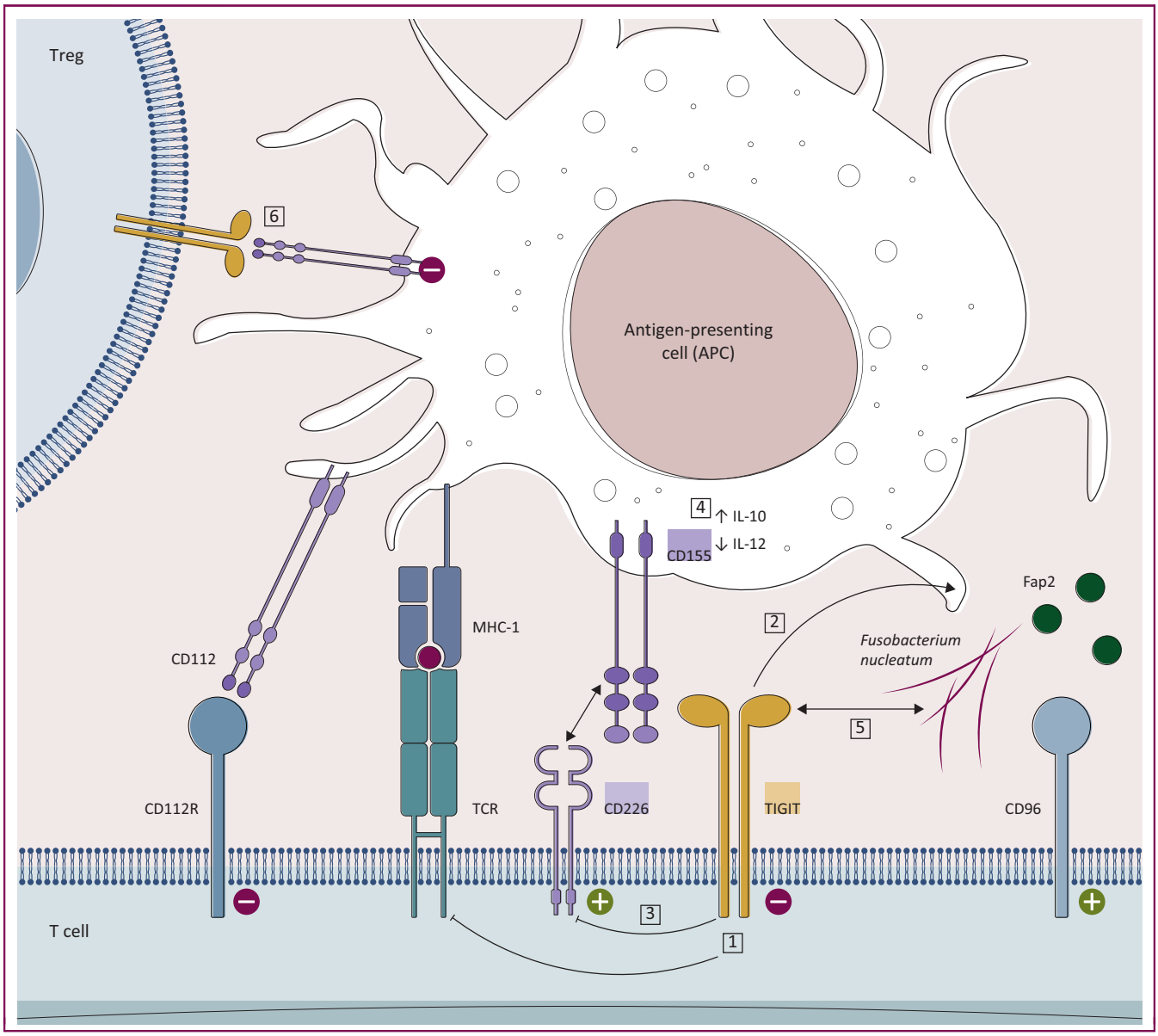

Figure 1. Mechanisms of TIGIT inhibition in T cells. The TIGIT axis comprises the inhibitory receptors TIGIT and CD112R, as well as the excitatory receptors CD226 and CD96, which mediate a series of engagements with ligands of varying specificity, including PVR (CD155) and poliovirus receptor-related immunoglobulin domain-containing (PVRIG) (CD112). TIGIT displays multiple inhibitory mechanisms in T cells. (1) TIGIT binds to CD155 and delivers intracellular inhibitory signals which in turn reduce TCR expression and TCR signaling. (2) TIGIT binds to CD155 with much higher affinity than its costimulatory counterpart CD226 and thereby can replace CD226 from CD155 binding (3) or disrupts CD226 homodimerization to inhibit CD226-mediated T-cell activation. (4) TIGIT binds to CD155 on APCs to trigger IL-10 production and decrease IL-12 production which indirectly inhibits T cells. (5) Fap2 protein from the gut bacteria *Fusobacterium nucleatum*, an anaerobic Gram-negative commensal bacteria associated with colorectal carcinoma, binds directly to TIGIT but not CD226 to inhibit NK-cell- and T-cell-mediated tumor reactivity. (6) TIGIT expression on tumor-associated dendritic cells may inhibit CD8 T-cell function indirectly by stabilizing extremely suppressive Tregs.
APC, antigen-presenting cell; IL, interleukin; MHC, major histocompatibility complex; NK, natural killer; TCR, T-cell receptor; TIGIT, T-cell immunoreceptor with immunoglobulin and ITIM domain; Treg, regulatory T cell.

better identify the ideal candidates to TIGIT inhibition. Most studies have adopted nonobjective and poorly reproducible methods, such as conventional IHC, without further investigating the relevance of TIGIT expression and/or its ligands in shaping the phenotype of tumor microenvironment in immune-cold versus immune-hot. Mechanisms of TIGIT inhibition are summed up in Figure 1.

RESULTS OF AVAILABLE TRIALS

Using the keywords 'TIGIT' and 'clinical trial', we carried out a review of the literature available in the PubMed database. There were 30 results on 20 January 2023; of these, 27 (90%) did not investigate a therapy against TIGIT, 19 (63.3%) did not concern patients with cancer, and 9 (30%) were not clinical trials. So, three trials remained, each one studying a different molecule. We also inquired the Congress website: ASCO Annual Meetings (meeting.asco.org; keyword 'TIGIT', filter 'abstracts & presentations'), OncologyPRO (oncologypro.esmo.org; keyword 'TIGIT', filters 'webcasts' and 'e-poster'), AACR Journals (aacrjournals.org; keyword 'TIGIT', filter 'research articles'), and Society for Immunotherapy of Cancer (sitcancer.org; keyword 'TIGIT', filter 'clinical trials'). Of the

Table 1. List of drugs with published results

Molecule	Mechanism of action	Phase of clinical trial development	Company
Vibostolimab	Blocking the binding between TIGIT and its ligand	III	Merck
Etigilimab	Blocking the binding between TIGIT and its ligand	I	Mereo BioPharma
Tiragolumab	Blocking the binding between TIGIT and its ligand	III	Roche

TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains.

146 results, 12 (8.2%) concerned communications with results about anti-TIGIT therapy and five of them were duplicates from previous communications or publications.

TIGIT is a receptor present on lymphocyte T cells and is an inhibitory immune checkpoint.[33] It is mainly expressed on memory T cells, T regulatory cells, and NK cells.[34,35] In preclinical studies, its blockade has demonstrated antitumor activity, especially when combined with PD-(L)1 inhibitors.[21] Indeed, TIGIT is expressed with PD-1 on CD8 T cells.[19] This explains why all the clinical trials discussed tested a combination of inhibitors of TIGIT and PD-(L)1. There are 3 therapies with published clinical trial data (Table 1).

Tiragolumab (Genentech)

Also an IgG1 anti-TIGIT, tiragolumab has been tested in the CITYSCAPE randomized phase II study.[36] A total of 135 patients were randomly assigned to tiragolumab 600 mg plus atezolizumab 1200 mg or placebo plus atezolizumab 1200 mg every 3 weeks. To be included, patients had to be chemotherapy naïve, PD-L1 positive, and advanced NSCLC. Most of the patients were locally advanced or metastatic (90% and 84%), had a nonsquamous histology (60% and 59%), and a PD-L1 score $<$50% (both 57%). The only difference between groups was that 58% of patients in the tiragolumab arm were male, whereas it was 71% in the control arm. There were more objective responses in the tiragolumab group (31.3% versus 16.2%; $P = 0.031$), a longer median progression-free survival [PFS; 5.4 versus 3.6 months; hazard ratio = 0.57, CI 95 = (0.37-0.9); $P = 0.015$] and a trend to a longer median OS [23.2 versus 14.5 months; hazard ratio = 0.69, CI 95 = (0.44-1.07); $P = 0.093$]. Subgroup analyses were carried out between high-expression PD-L1 ($\geq$50%) and intermediate expression (1%-49%). In the high expression subgroup ($\geq$50%), there was a difference favoring tiragolumab over placebo for objective response rate (ORR; 69.0% versus 24.1%), PFS (16.6 versus 4.1 months), and OS (not reached versus 12.8 months). However, the number of events needed wasn't calculated to allows this subgroup analysis. Thus, it cannot be considered as a primary conclusion of the study.

Overall, 21% patients in the tiragolumab arm had severe treatment-related adverse events (TRAEs) versus 18% in the placebo arm. The most frequent severe TRAE was lipase increase (9% in the tiragolumab arm and 3% in the placebo arm). Immune-mediated AEs were more common in the tiragolumab group (76% versus 47%), and two treatment-related death occurred in the tiragolumab group (pyrexia and infection). AEs leading to interruption were more frequent in the tiragolumab group.

Tiragolumab in combination with atezolizumab has also been tested in metastatic esophageal cancer in a phase Ib trial.[37] A total of 21 patients were included, of whom 33% were Asians; 67% presented with grade 3-4 AEs, of which only one was considered treatment related. The most common AEs were rash (38%), anemia (24%), and hepatitis (24%). The confirmed ORR was 28% and the median duration of response was 15.3 months.

A randomized phase III (SKYSCRAPER-02) including patients with small-cell lung cancer (SCLC) is evaluating the addition of tiragolumab to carboplatin—etoposide—atezolizumab in patients with naïve metastatic SCLC, including those with controlled brain metastasis.[38] The final analysis of PFS and interim analysis of OS data failed to demonstrate a benefit (5.4 versus 5.6 months for PFS, $P < 0.3504$ and 13.6 versus 13.6 months for OS, $P < 0.7963$). Grade 3-4 TRAEs occurred in 52.3% of patients in the tiragolumab arm versus 55.7 in the control arm.

On March 2022, a press release announced interim results of the phase III SKYSCRAPER-01 study of tiragolumab plus atezolizumab in the first-line treatment of PD-L1-high, metastatic NSCLC. The trial did not meet its co-primary endpoint of PFS. However, as OS, the other co-primary endpoint, was immature, the study is still ongoing. The atezolizumab arm in CITYSCAPE underperformed, with 14.5 months of the median OS in all-round population and 12.8 months of the median OS in the high-expression PD-L1 group, whereas in IMpower110 it was 18 months in the all-round population and 20 months in the high-expression PD-L1 group.[39] Thereby, positive result of phase II could be explained by this underperforming control arm, leading to phase III's failure.

Domvanalimab (Gilead)

Domvanalimab is a humanized IgG1 blocking TIGIT that has been evaluated in high PD-L1 NSLC in association with zimberelimab, an anti-PD-1, with or without etrumadenant, a selective dual antagonist of both A2a and A2b receptors. Results of the phase II ARC-7 trial[40] showed that the combination improves ORR and PFS versus zimberelimab alone. Among the 45 patients treated with the three drugs, ORR was 40% and the median PFS was 10.9 months. Among the 44 patients treated with the two drugs, ORR was 41% and the median PFS 12.0 months, whereas the 44 patients treated with zimberelimab only had ORR of 27% and the median PFS of 5.4 months. The population is highly selective because 80%-90% of the included patients did not have brain or liver metastasis at baseline. TRAEs of grade 3-4 was 47% in the doublet arm and 53% in the triplet arm. About 8.7% of patients had a grade 3-4 pneumonitis. Notably, there was one grade 5 myocarditis in the doublet arm and

one grade 5 pneumonitis and one grade 5 heart failure in the triplet arm. The combination of domvanalimab and zimberelimab is investigated in two phase III trials (NCT04736173 and NCT05502237). Domvanalimab is also tested in combination with durvalumab in the phase III PACIFIC-8 trial (NCT05211895).

Vibostolimab (Merck)

Vibostolimab is a humanized IgG1 targeting TIGIT and blocking its binding with its ligands. It has been evaluated in a phase I trial[41] assessing the feasibility and safety of vibostolimab alone or in combination with pembrolizumab 200 mg. Patients were shared between a first cohort (A) of solid tumor with an escalating dose of vibostolimab and a second cohort (B) of NSLSC with a flat dose of 200 mg of vibostolimab.

In cohort A, 34 patients were treated with monotherapy and 42 with combination therapy. In the monotherapy group, 9% had severe TRAEs. The most common TRAEs were fatigue (15%) and pruritus (15%) with monotherapy, and pruritus (17%) and rash (14%) with combination therapy. The confirmed overall response rate (ORR) was 0% and 7% in the monotherapy and combination therapy arms, respectively. The median duration of response was 8 months among patients receiving vibostolimab plus pembrolizumab.

In cohort B, 39 PD-(L)1 naïve patients received the combination, 34 PD-(L)1 refractory patients received the monotherapy, and 33 PD-(L)1 refractory patients received the combination. Nearly 69% of patients with PD-(L)1 naïve advanced NSCLC were men and 74% had already received a previous line of systemic treatment. The most common TRAEs were pruritus (38%) and hypoalbuminemia (31%). The confirmed ORR was 26% and the median duration of response was not reached. The median overall survival (OS) was 11 months. In a subgroup analysis, OS was higher in PD-L1-positive patients (not reached versus 14 months). Nearly 55% of the patients with NSCLC refractory to anti-PD-(L)1 were men and 97% had previously received a line of systemic treatment; 34 of them were treated by monotherapy, with the most common TRAE being rash and fatigue (21% for both). Among 33 patients receiving combination, the most common TRAEs were pruritus (36%) and fatigue (24%). The confirmed ORR was 3% in both monotherapy and combination therapy arms and the median OS was 11 months and 13 months, respectively.

A phase III, multicenter, randomized trial (NCT04738487) is ongoing, comparing the association of pembrolizumab and vibostolimab versus pembrolizumab monotherapy as upfront treatment in patients with PD-L1-positive metastatic NSCLC. OS and PFS will be the primary endpoints.

Etigilimab (Mereo BioPharma)

Etigilimab is another humanized IgG1 monoclonal antibody against TIGIT, blocking its interaction with its ligand and activating antibody-dependent cellular cytotoxicity. It has been tested in a phase I dose-escalation study in patients with advanced solid tumors.[42] A total of 33 patients with solid tumors refractory to standard therapies were enrolled. Nearly half were <65 years old (51.5%), 48.5% were male, and 78.8% had already received at least three prior therapies. In phase Ia, etigilimab was tested alone. Nine patients (39.1%) already received anti-PD-(L)1 therapy. The most common AEs were rash (43.5%), nausea (34.8%), and fatigue (30.4%). Three patients discontinued the drug due to AEs: alanine aminotransferase increase, chest pain, and general status alteration with dyspnea (not considered as related to treatment). The ORR was 0%. In phase Ib, which was stopped for business reasons, nine patients were included and treated in combination with nivolumab. Most common AEs were decreased appetite (50%), nausea (50%), and rash (40%). There was no discontinuation due to AEs. Only one patient with ovarian cancer had a partial response. Secondary analysis showed that pharmacokinetics of etigilimab was typical of a monoclonal antibody and that immune modulation was dose dependent.

Biomarker effects of the combination strategy are being studied in the phase Ib/II basket study (ACTIVATE) as an exploratory endpoint, highlighting the enrichment of TIGIT high tumor expression for patients with clinical benefit (Sarikonda et al).[43]

M6223 (Merck)

M6223 is an anti-TIGIT antibody, studied alone or in combination with bintrafusp alfa (anti PD-L1 and transforming growth factor-beta) in a phase I trial.[44] 24 patients received M6223 and 17 the combination. 33% patients experienced grade 3-4 AE in M6223 group and 71% in the combination group.

Ociperlimab (BeiGene)

Ociperlimab is an anti-TIGIT antibody evaluated in a phase I trial in patients with NSCLC in combination with tislelizumab and chemotherapy.[45] Among the 76 evaluable patients, ORR was 45.9% in squamous tumors and 25.6% in nonsquamous tumors. Serious TEAEs occurred in 26 patients (31.0%). The most common TRAEs were anemia (41.7%), decrease in neutrophil count (33.3%), and decrease in white blood cell count (33.3%).

EOS884448 (iTeos Therapeutics)

Ongoing trials. We carried out a search on the ClinicalTrial.gov database using the keywords 'TIGIT' and 'Cancer'. Among the 70 results, 46 trials were recruiting (65.7%), 37 were phase I (52.8%), 37 were phase II (52.8%), and 7 (10%) were phase III.

Concerning lung cancer trials, 2 (15.4%) were phase I, 1 (7.7%) was phase I/II, 5 (38.5%) were phase II, and 5 (38.5%) were phase III; 7 (58.3%) were recruiting. Among the recruiting trials, we can highlight two innovative strategies: the NCT04995523 trial, which is a phase I/II trial studying AZD2936, a bispecific antibody targeting both PD-1 and TIGIT, and the NCT04791839 and NCT04262856 trials, which

Table 2. List of anti-TIGIT trials registered in lung cancer

ClinicalTrials.gov identifier	Status	Tumor type	Setting	Phase	Treatment cohorts	Target	Biomarker selection
NCT04952597	Active, not recruiting	SCLC	Early stage	II	Ociperlimab + tislelizumab + chemoradiotherapy Tislelizumab + chemoradiotherapy Concurrent chemoradiotherapy	TIGIT PD-1	
NCT04995523	Recruiting	NSCLC	Metastatic	I/II	AZD2936	TIGIT/PD-1 bispecific	PD-L1 positive
NCT04746924	Recruiting	NSCLC	Metastatic	III	Tislelizumab + ociperlimab Pembrolizumab Tislelizumab	TIGIT PD-1	PD-L1 ≥50%
NCT03563716	Active, not recruiting	NSCLC	Metastatic	II	Tiragolumab + atezolizumab Atezolizumab	TIGIT PD-1	PD-L1 positive
NCT04256421	Active, not recruiting	SCLC	Metastatic	III	Tiragolumab + atezolizumab + chemotherapy Atezolizumab + chemotherapy	TIGIT PD-1	
NCT04294810	Recruiting	NSCLC	Metastatic	III	Tiragolumab + atezolizumab Atezolizumab	TIGIT PD-1	PD-L1 high
NCT04672356	Active, not recruiting	NSCLC and SCLC	Metastatic	I	IBI939 + sintilimab	TIGIT PD-1	
NCT04791839	Recruiting	NSCLC	Metastatic	II	Zimberelimab + domvanalimab + etrumadenant	PD-1 TIGIT A2aR/A2bR	PD-L1 positive
NCT04672369	Active, not recruiting	NSCLC	Metastatic	I	IBI939 + sintilimab Sintilimab	TIGIT PD-1	
NCT04262856	Recruiting	NSCLC	Metastatic	II	Zimberelimab Zimberelimab + domvanalimab Zimberelimab + domvanalimab + etrumadenant	PD-1 TIGIT A2aR/A2bR	PD-L1 high
NCT04736173	Recruiting	NSCLC	Metastatic	III	Chemotherapy Zimberelimab Zimberelimab + AB154	PD-1 TIGIT	PD-L1 positive
NCT05014815	Recruiting	NSCLC	Metastatic	II	Ociperlimab + tislelizumab + chemotherapy Tislelizumab + chemotherapy	TIGIT PD-1	
NCT04513925	Recruiting	NSCLC	Locally advanced	III	Tiragolumab + atezolizumab Durvalumab	TIGIT PD-1	

NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SCLC, small-cell lung cancer; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains.

are both phase II trials studying a combination of anti-PD-1, an anti-TGIT, and anti-A2aR/A2bR antibodies in patients with documented PD-L1 expression by IHC. The details are summarized in Table 2. Concerning other tumors, 13 (40.6%) were phase I, 7 (21.9%) were phase I/II, 11 (34.4%) were phase II, and 1 (3.1%) was phase III. A total of 24 (75%) were recruiting, of which 3 (NCT03708224, NCT05009069, and NCT05394337) are testing the use of anti-TIGIT before surgery. Details of these trials are summarized in Table 3.

FUTURE STRATEGIES

First large studies showed disappointing results with basic anti-TIGIT antibodies. Thus several innovative approaches are being developed. Instead of combining two antibodies, some teams are developing bispecific PD-1/TIGIT antibodies,[46] which have shown improvement in OS in mouse model.[47] Another strategy can be to modify the backbone: SEA-TGT is a nonfucosylated antibody designed to have its effector function enhanced, which elicits better immune response than classical anti-TIGIT antibodies.[48] It will be evaluated in a phase I in patients with advanced solid tumors.[49] Ociperlimab is another antibody with enhanced FCγR engagement activity[50] that will be evaluated in several clinical trials (Table 2).

CONCLUSIONS

After the era of anti-PD-(L)1 immunotherapy, anti-TIGIT drugs could be novel actors in cancer therapeutics development. Nevertheless, the promising preclinical data do not fully translate yet in clinical trials. Anti-TIGIT antibodies showed little activity in monotherapy in advanced solid tumors. However, their association with anti-PD-1 drugs enhanced the efficacy of outcomes. In CITYSCAPE phase II, the association of tiragolumab with atezolizumab improved ORR and PFS in the first line of advanced NSCLCs in comparison to atezolizumab alone. Selection of potential interesting subgroups beyond NSCLCs and prediction of efficacies with biomarkers could help the development of such therapies. Interrogating about the timing of administration is also open with the development of adjuvant and neoadjuvant immune therapies.

Table 3. List of anti-TIGIT trials registered in other solid tumors

ClinicalTrials.gov identifier	Status	Tumor type	Setting	Phase	Treatment cohorts	Target	Biomarker selection
NCT04693234	Active, not recruiting	Cervical	Metastatic	II	Tislelizumab + ociperlimab Tislelizumab	PD-1 TIGIT	
NCT03119428	Terminated	Multicancer	Metastatic	I	OMP-313M32 + nivolumab Nivolumab	TIGIT PD-1	
NCT04353830	Recruiting	Multicancer	Metastatic	I	IBI939 IBI939 + sintilimab	TIGIT PD-1	
NCT05102214	Recruiting	Multicancer	Metastatic	I/II	HLX301	TIGIT/PD-L1 bispecific	PD-L1 positive in some localizations
NCT05061628	Recruiting	Multicancer	Metastatic	I	JS006 JS006 + toripalimab	TIGIT PD-1	
NCT04570839	Recruiting	Multicancer	Metastatic	I/II	COM701 + BMS-986207 + nivolumab	PVRIG TIGIT PD-1	PVRL2 high
NCT04047862	Recruiting	Multicancer	Metastatic	I	Ociperlimab + tislelizumab Ociperlimab + tislelizumab + chemotherapy	TIGIT PD-1	PD-L1 positive in some localizations
NCT04354246	Recruiting	Multicancer	Metastatic	I	COM902 COM902 + COM701	TIGIT PVRIG	
NCT05120375	Recruiting	Multicancer	Metastatic	I	BAT6021	TIGIT	
NCT05417321	Recruiting	Multicancer	Metastatic	I/II	HB0036	TIGIT/PD-L1 bispecific	PD-L1 positive
NCT05073484	Recruiting	Multicancer	Metastatic	I	BAT6021 BAT6021 + BAT1308	TIGIT PD-1	
NCT04457778	Recruiting	Multicancer	Metastatic	I	M6223 M6223 + bintrafusp alfa	TIGIT Anti-PD-L1/TGF-β Trap	
NCT05394168	Recruiting	Multicancer	Metastatic	I	HLX53	TIGIT	
NCT05253105	Withdrawn	Multicancer	Metastatic	I	TAB006 + toripalimab	TIGIT PD-1	
NCT03628677	Active, not recruiting	Multicancer	Metastatic	I	Domvanalimab Domvanalimab + zimberelimab	TIGIT PD-1	
NCT05060432	Recruiting	Multicancer	Metastatic	I/II	EOS-448 EOS-448 + pembrolizumab EOS-448 + inupadenant EOS-448 + dostarlimab Inupadenant + dostarlimab EOS-448 + inupadenant + dostarlimab EOS-448 + dostarlimab + chemotherapy EOS-448 + dostarlimab	TIGIT PD-1 A2aR	PD-L1 positive in some localizations
NCT04150965	Recruiting	Myeloma	Refractory	I/II	BMS-986016 BMS-986016 + chemotherapy BMS-986207 BMS-986207 + chemotherapy	LAG-3 TIGIT	
NCT05289492	Recruiting	Myeloma	Refractory	I/II	EOS884448 EOS884448 + chemotherapy	TIGIT	
NCT05329766	Recruiting	Gastric	Metastatic	II	Zimberelimab + domvanalimab + chemotherapy Zimberelimab + domvanalimab	TIGIT PD-1	
NCT04933227	Active, not recruiting	Gastric	Metastatic	II	Atezolizumab + tiragolumab + chemotherapy	PD-L1 TIGIT	
NCT05251948	Active, not recruiting	Gastric	Metastatic	I/II	Atezolizumab + tiragolumab + chemotherapy Atezolizumab + chemotherapy	PD-L1 TIGIT	
NCT04543617	Recruiting	Esophageal	Metastatic	III	Atezolizumab + tiragolumab	PD-L1 TIGIT	
NCT04732494	Recruiting	Esophageal	Metastatic	II	Tislelizumab + ociperlimab Tislelizumab	PD-1 TIGIT	PD-L1 $\geq$10%
NCT03708224	Recruiting	Head and neck	Neoadjuvant	II	Atezolizumab Atezolizumab + tiragolumab Atezolizumab + tocilizumab	PD-L1 TIGIT IL-6	
NCT05026606	Recruiting	Ovarian	Refractory	II	Etiglimab Nivolumab	TIGIT PD-1	
NCT05009069	Recruiting	Rectal	Neoadjuvant	II	Atezolizumab + tiragolumab + chemoradiotherapy Atezolizumab + chemoradiotherapy	PD-L1 TIGIT	
NCT05023109	Recruiting	Biliary tract	Metastatic	II	Tislelizumab + ociperlimab + chemotherapy	PD-1 TIGIT	

Continued

Table 3. Continued

ClinicalTrials.gov identifier	Status	Tumor type	Setting	Phase	Treatment cohorts	Target	Biomarker selection
NCT05019677	Withdrawn	Biliary tract	Metastatic	II	Tislelizumab + ociperlimab + chemotherapy	PD-1 TIGIT	
NCT05130177	Recruiting	Melanoma	Metastatic	II	Zimberelimab + domvanalimab	PD-1 TIGIT	
NCT05394337	Not yet recruiting	Bladder	Neoadjuvant	I	Atezolizumab + tiragolumab	PD-L1 TIGIT	
NCT05327530	Recruiting	Bladder	Metastatic	II	Avelumab Avelumab + sacituzumab govitecan Avelumab + M6223 Avelumab + NKTR-255	PD-L1 TROP2 TIGIT IL-15	
NCT04656535	Recruiting	Glioblastoma	Refractory	I	AB122 AB154 AB122 + AB154	PD-1 TIGIT	

IL, interleukin; LAG-3, lymphocyte-activation gene 3; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PVRIG, poliovirus receptor-related immunoglobulin domain-containing; PVRL2, Poliovirus receptor-related 2; TGF-β, transforming growth factor-beta; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains; TROP2, trophoblast antigen 2.

DISCLOSURE

FB declares no personal financial interests (since August 2021); institutional financial interests with AbbVie, ACEA, Amgen, Astra-Zeneca, Bayer, Bristol-Myers Squibb, Boehringer—Ingelheim, Eisai, Eli Lilly Oncology, F. Hoffmann—La Roche Ltd, Genentech, Ipsen, Ignyta, Innate Pharma, Loxo, Novartis, Medimmune, Merck, MSD, Pierre Fabre, Pfizer, Sanofi-Aventis and Takeda; nonfinancial interests as the principal investigator for Astra-Zeneca, BMS, Innate Pharma, Merck, Pierre Fabre and F. Hoffmann-La Roche, Ltd-sponsored trials (or investigator-sponsored trails). The other authors have no conflicts of interest to declare.

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