Scientific Research Publishing

Advances in Lung Cancer, 2022, 11, 51-60
https://www.scirp.org/journal/alc
ISSN Online: 2169-2726
ISSN Print: 2169-2718

Targeting TIGIT in NSCLC—Is There Light on the Horizon?

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How to cite this paper: Reuther, S. and Dempke, W.C.M. (2022) Targeting TIGIT in NSCLC—Is There Light on the Horizon? *Advances in Lung Cancer*, **11**, 51-60.
https://doi.org/10.4236/alc.2022.114005

Received: October 5, 2022
Accepted: December 3, 2022
Published: December 6, 2022

Abstract

Non-small cell lung cancers (NSCLCs) represent over 80% of all malignant lung tumours and are one of the leading causes of cancer death throughout the world. First- and second-line treatment of advanced or metastatic NSCLCs has changed dramatically during the last two decades with the development of novel immunotherapies (e.g., checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4) sparing NSCLC patients from the toxic effects of chemotherapy. However, only 15% - 20% of all patients respond to treatment. In order to improve response rates, experimental and clinical evidence has provided the basis for further evaluating the combination of co-stimulatory and inhibitory monoclonal antibodies to improve the anti-tumour immune response. Innovative second- and third-generation immuno-oncology drugs are currently evaluated in ongoing phase I-III trials (either alone or in combination) including the new checkpoint inhibitor target TIGIT (T cell immunoreceptor with Ig and ITIM domains). TIGIT functions as an inhibitory immunoglobin receptor which is overexpressed by different immune cells including effector and memory $CD4^+$ T and $CD8^+$ T cells, regulatory T cells (T_{regs}), follicular T helper cells (T_{fh}), and natural killer cells. Targeting the interaction between the receptors of the TIGIT receptors (e.g., CD96, CD112R, CD226, TIGIT and their corresponding binding partners) has become an innovative strategy for the next concepts of cancer immunotherapy that has the potential to synergize with PD-1/PD-L1checkpoint inhibition. Currently, four anti-TIGIT monoclonal antibodies are currently being studied in phase III trials in NSCLCs: 1) tiragolumab (SKYSCRAPER programme); 2) vibostolimab (KEYVIVE programme); 3) domvanalimab (ARC programme), and 4) ociperlimab (AdvanTIG programme). The vast majority of these studies are ongoing; however, the SKYSCRAPER-01 trial (tiragolumab in NSCLC) and the SKYSCRAPER-02 trial (tiragolumab in SCLC) were negative and did not meet their primary endpoint. The underlying preclinical and clinical mechanisms of these unexpectedly negative studies are currently far from being clear and the results

from currently recruiting clinical studies are eagerly awaited to shed some additional light on these results. From 2021 onwards different TIGIT family receptors are currently evaluated in over 25 clinical trials (phase I-III), however, a lot of preclinical and clinical research is ongoing at different research sites which will help to identify novel immune checkpoint targets with improved activity against malignancies across all histologies.

Keywords

NSCLC, TIGIT, SKYSCRAPER Trials, KEYVIVE Studies, Domvanalimab, Ociperlimab

1. Introduction

Non-small cell lung cancers (NSCLCs) represent over 80% of all malignant lung tumours and are one of the leading causes of cancer death worldwide [1]. First-line treatment of advanced or metastatic NSCLCs has changed dramatically during the last two decades, and novel treatment strategies such as immunotherapies (e.g., anti-immune checkpoint monoclonal antibodies targeting CTLA-4, PD-1, and PD-L1), and tyrosine kinase inhibitors (TKIs) have demonstrated significant benefit for several NSCLC patients sparing them from the toxic effects of chemotherapy [2].

During the last decades, systemic treatment options for patients with different types of malignancies including NSCLCs have emerged from chemotherapy through targeted-therapies to the more recently developed immune checkpoint inhibitors, and increasing evidence for the role of the anti-tumour activity of the immune system has sparked great interest in the concept of immunotherapy even for tumours that were generally known to be non-responsive to immuno-oncology treatments [3].

Immuno-oncology is a novel therapeutic approach which is currently investigated for many tumours with objective responses seen across different histologies. Clearly, this approach differs from former modalities, which target the tumour directly or try to disrupt tumour angiogenesis, as it has been developed to maximize the patient's immune response to tumour cells. Immunotherapy is now regarded to be a major modality in cancer treatment focusing on development of inhibitors or co-stimulatory agents of the cellular mediators of cancer-induced immunosuppression (immune checkpoints) to boost anti-tumour immune responses [4].

Different immunologic approaches inhibiting immune checkpoint pathways have been shown promise in development, and preclinical and clinical evidence provides the rationale for investigating the combination of co-stimulatory and inhibitory monoclonal antibodies to establish a novel or re-activate a pre-existing anti-tumour immune response ("cold-versus-hot-tumours"). In addition, novel bi- and tri-specific monoclonal antibodies are also being developed which may al-

so significantly contribute to the growing armamentarium of immune-oncology drugs.

Immune checkpoints encompass a myriad of inhibitory and co-stimulatory pathways that counteract certain critical steps of T cell-mediated immunity to maintain self-tolerance and modulate the duration and magnitude of the immune responses [5]. Recently, the understanding of several immune checkpoints that shut down the immune system as an immunosuppressive mechanism in tumours has led to a substantial paradigm shift in the treatment of human cancers. Immune checkpoints are activated primarily through T cell inhibiting and stimulating receptors and their ligands, including cytotoxic T lymphocyte-associated protein 4 (CTLA-4, CD152), PD-1 (programmed cell death-1, CD279) and PD-L1 (CD274) or PD-L2 (CD273; programmed cell death ligand-1, -2), amongst many others [6].

Several lines of preclinical and clinical research have provided evidence that the immune system plays a dual role in cancer: it is able to suppress cancer growth by destroying tumour cells or blocking their proliferation and survival, but is also capable to stimulate tumour progression either by selectively foster tumour cells that are fitter to survive in an immune-competent cellular environment or by establishing conditions within the tumour micro-environment (TME) that facilitate tumour proliferation and survival (so-called "cancer immune-editing") [7].

To improve response rates following treatment with immune checkpoint inhibitors and to overcome resistance, novel second- and third-generation immuno-oncology drugs (checkpoint inhibitors and co-stimulatory molecules) are currently evaluated in ongoing phase I-III trials (either alone or in combination) including innovative checkpoint inhibitors (e.g., TIM-3, VISTA, LAG-3, IDO, KIR, TIGIT) and novel co-stimulatory monoclonal antibodies (e.g., CD40, GITR, OX40, CD137, ICOS) [8] [9] (**Figure 1**).

2. TIGIT

TIGIT (T cell immunoreceptor with Ig and ITIM domains) family receptors represent a group of immunoglobulin super-family receptors that interfere with nectin and nectin-like molecules. It is only recently that these members have been identified to be a potential innovative target for immune-oncology (checkpoint inhibitor) [10]. These receptors include TIGIT, CD226 (formerly DNA X-associated molecule 1), CD96 (TACTILE: T cell activation, increased late expression), and CD112R (also known as PVRIG, PVR-related Ig domain). These molecules interfere with PVR (CD155), nectin-1 (CD111), nectin-2 (CD112), nectin-3 (CD113), and/or nectin-4 (known as PVRL4) [11].

TIGIT functions as an inhibitory immunoglobin receptor which is expressed by different immune cells including effector and memory $CD4^+$ T and $CD8^+$ T cells, regulatory T cells (T_{regs}), follicular T helper cells (T_{fh}), and natural killer cells. Several lines of research from experimental studies have provided evidence

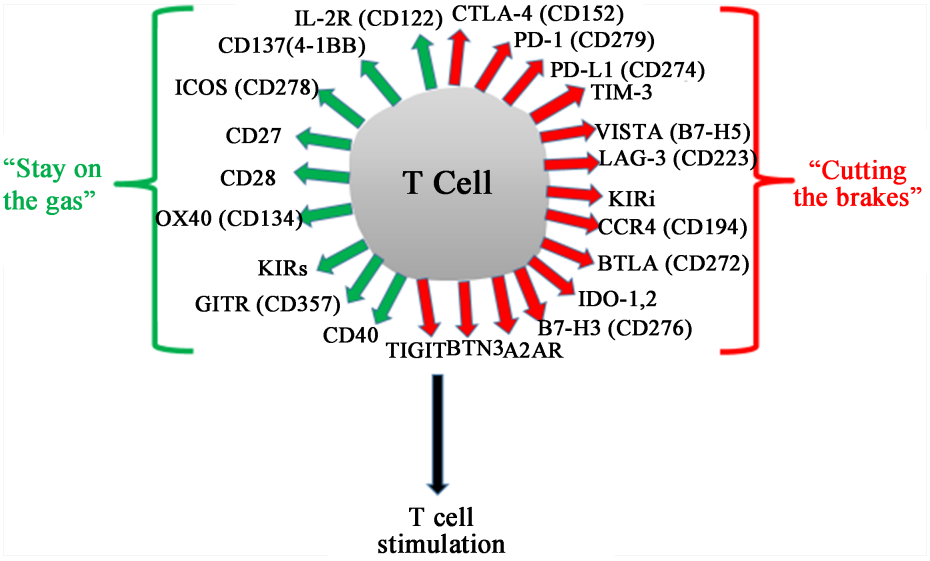

Figure 1. Checkpoint inhibitors (red arrows) and co-stimulatory targets (green arrows). IDO: indoleamine-pyrrole 2,3 dioxygenase; BTN3: butyrophilin 3A1-3; CCR: cellular chemokine receptor; GITR: glucocorticoid-induced TNF-R-related protein; ICOS: inducible T-cell co-stimulator; LAG-3: lymphocyte-activation gene 3; TIGIT: T cell immunoreceptor with Ig and ITIM domains; VISTA: V-domain Ig suppressor of T-cell activation; PD-(L)1: programmed cell death (ligand) 1; A2AR: adenosine-A2A-receptor; CTLA-4: cytotoxic T lymphocyte associated protein 4; BTLA: B- and T-lymphocyte attenuator; TIM-3: T-cell immunoglobulin and mucin-domain containing 3; KIR: killer cell immunoglobulin-like receptor.

that the cytoplasmic tail of TIGIT is comprised of an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoglobulin tail tyrosine (ITT)-like motif, which then in turn activate an inhibitory downstream signaling cascade. It is also known that the TIGIT receptor facilitates several different binding partners, including PVR, nectin-2, nectin-3, and nectin-4 (Figure 2). Of note, knockdown of TIGIT expression in human $CD4^+$ T cells was found to enhance the interferon-γ-secretion, which could be overcome by inhibiting CD226 signaling, suggesting that TIGIT blocks T cells by competing with CD226 for binding to the same PVR ligand [12].

TIGIT receptors are overexpressed on a subset of T_{reg} cells and are associated with a distinct immune-suppressive phenotype. TIGIT-expressing T_{reg} subclones were found to specifically suppress proinflammatory T_{h1} and T_{h17} cells, but not T_{h2}-type T cell responses in experimental systems [12].

3. Results of Clinical Trials

Several randomized clinical trials are currently ongoing with anti-TIGIT monoclonal antibodies, amongst them the most advanced are tiragolimab (SKYCRAPER programme) and vibostolimab (KEYVIBE programme). In the majority of these trials TIGIT inhibition is administered together with either anti-PD-(L)1 monoclonal antibodies or with adenosine-A2A receptors antagonists (Table 1).

The CITYSCAPE phase II clinical trial (N = 135, first-line NSCLC patients) provided the first evidence that the anti-TIGIT monoclonal antibody tiragolumab

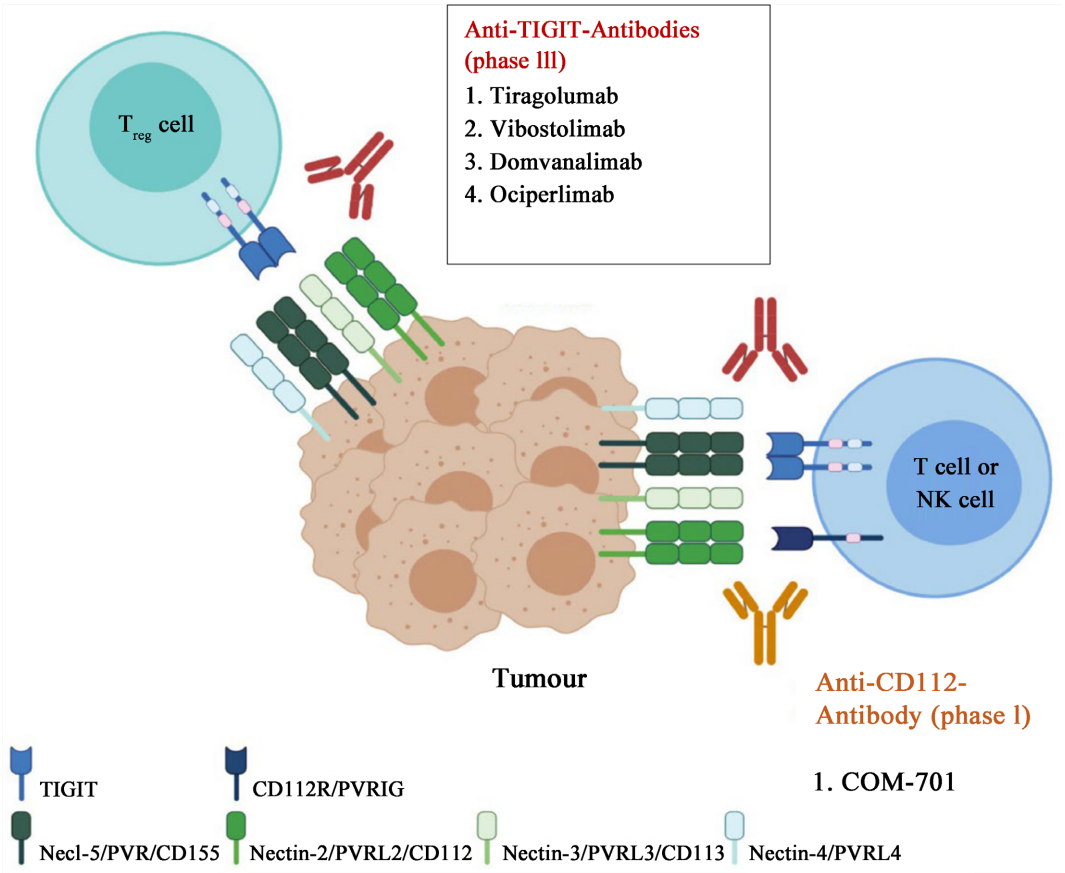

Figure 2. Summary of inhibitory TIGIT and CD112R monoclonal antibodies undergoing clinical trials (modified after Jin and Park [10]).

Table 1. Relevant phase II and phase III studies with TIGIT inhibitory monoclonal antibodies. NR: not reached. EP: etoposide plus platinum.

Drug	Trial Design	NCT Number	Outcome
Tiragolumab	*CITYSCAPE*: Atezolizumab + Tiragolumab vs. Atezolizumab, Phase II (N = 135), NSCLC	NCT03563716	mPFS: 5.6 vs. 3.9 months, for patients with PD-L1 ≥ 50%: NR vs. 4 months.
Tiragolumab	*SKYSCRAPER*-01: Similar design as CITYSCAPE in NSCLC, Phase III (N = 635)	NCT04294810	Trial failed to meet its primary endpoint.
Tiragolumab	*SKYSCRAPER*-02: EP chemotherapy + Atezolizumab and Tiragolumab vs. EP chemotherapy + Atezolizumab, Phase III, SCLC (N = 400)	NCT04256421	Trial failed to meet its primary endpoint.
Tiragolumab	*SKYSCRAPER*-03: Tiragolumab + Atezolizumab vs. Duravalumab following radio-chemotherapy (Stage III NSCLC, N = 800), Phase III	NCT04513925	ongoing
Tiragolumab	*SKYSCRAPER*-04: Tiragolumab + Atezolizumab vs. Atezolizumab in cervical cancer (N = 172, Phase III)	NCT04300647	active, but not recruiting

Continued

Tiragolumab	*SKYSCRAPER*-05: Tiragolumab + Atezolizumab, platinum-based chemotherapy, Surgery, Tiragolumab, Atezolizumb vs. Platinum-based chemotherapy, Surgery, Platinum-based Chemotherapy (Phase II, N = 83)	NCT04832854	ongoing
Tiragolumab	*SYKSCRAPER*-06: Atezolizumab + Tiragolumab plus Pemetrexate/Platinum vs. Pembrolizumab + Pemetrexate/Platinum (N = 500, NSCLC), Phase II	NCT04619797	ongoing
Tiragolumab	*SKYSCRAPER*-07: Tiragolumab plus Atezolizumab vs. Atezolizumab following radio-chemotherapy (esophageal cancer, N = 750), Phase III	NCT04543617	ongoing
Vibostolimab	*KEYVIBE*-002: Vibostolimab + Pembrolizumab + Docetaxel vs. Vibostolimab + Pembrolizumab vs. Docetaxel (Phase II, N = 240, NSCLC)	NCT04725188	ongoing
Vibostolimab	*KEYVIBE*-003: Vibostolimab + Pembrolizumab vs. Pembrolizumab (Phase III, NSCLC, N = 1,246)	NCT04738487	ongoing
Vibostolimab	*KEYVIBE*-006: Vibostolimab + Pembrolizumab followed by radio-chemotherapy and Vibostolimab + Pembrolizumab vs. radio-chemotherapy followed by Durvalumab (NSCLC, N = 784, Phase III)	NCT05298423	ongoing
Vibostolimab	*KEYVIBE*-007: Vibostolimab + Pembrolizumab + Chemotherapy vs. Pembrolizumab + Chemotherapy (Phase III, NSCLC, N = 700)	NCT05226598	ongoing
Vibostolimab	*KEYVIBE*-008: Vibostolimab + Pembrolizumab + EP chemotherapy vs. Atezolizumab + EP chemotherapy (SCLC, Phase III, N = 450)	NCT05224141	ongoing
Domvanalimab	*ARC*-7: Zimberelimab vs. Zimberelimab + Domvanalimab vs. Zimberelimab + Domvanalimab + Entrumadenant (Phase II, N = 150, NSCLC)	NCT04791839	ongoing
Domvanalimab	*PACIFIC*-8: Durvalumab + Domvanalimab following radio-chemotherapy (NSCLC, N = 860, interventional)	NCT05211895	ongoing
Ociperlimab	*AdvanTIG*-301: Ociperlimab + Tislelizumab + concurrent chemo-radiotherapy followed by Ociperlimab or Tislelizumab + concurrent chemo-radiotherapy followed by Tislelizumab versus concurrent chemo-radiotherapy followed by Durvalumab in locally advanced and previously untreated and unresectable NSCLC (N = 900)	NCT04866017	ongoing
Ociperlimab	*AdvanTIG*-302: Ociperlimab + Tislelizumab versus Pembrolizumab + Placebo (NSCLC, first-line, Phase III, N = 600)	NCT04746924	ongoing

(Roche/Genentech, 600 mg every three weeks) in combination with the anti-PD-L1 monoclonal antibody atezolizumab (Roche/Genentech, 1200 mg every three weeks) could increase the overall response rate (ORR) (37.3% versus 20.6%)

and medium progression free survival (mPFS) (5.6 versus 3.9 months, HR = 0.57) in NSCLC patients with PD-L1 > 1%. Of note, in patients with PD-L1 ≥ 50% ORR was found to be 66% for the combination versus 24% for atezolizumab alone (HR = 0.30). The mPFS was not reached for the combination and was 4 months for atezolizumab. The combination of tiragolumab and atezolizumab was found to be safe and no additional safety signals were detected compared with atezolizumab alone [13].

Based on these encouraging results the SKYSCRAPER study programme was established since preclinical and early clinical data provide evidence that TIGIT family receptor members act synergistically with the PD-1 pathway, and, therefore, the combination of tiragolumab, atezolizumab, (and chemotherapy) may be able to augment the immune response of cancers. Interestingly, both phase III studies in these settings (NSCLC: SKYSCRAPER-01; SCLC: SKYSCRAPER-02) did not meet their co-primary endpoints of medium overall survival (mOS) and mPFS (**Table 1**) [14] [15]. Furthermore, despite the similar safety profiles of atezolizumab with placebo versus atezolizumab with tiragolumab, 80.6% of patients in the combination group and 72% of patients in the placebo-group experienced immune-related adverse events (irAEs). Amongst the most common irAEs in these trials, infusion reactions, diarrhea, hepatitis, rash, and thyroid abnormalities have been reported [13].

The monoclonal antibody vibostolimab, another inhibitor of TIGIT, has been evaluated in cancer patients as monotherapy or together with pembrolizumab in the phase I trial (NCT02964013). The ORR for vibostolimab monotherapy was found to be significantly higher than that for combination therapy in the cohort of NSCLC patients with documented anti–PD-1/PD-L1–refractory cancers (7% versus 5%, $p < 0.05$) [16]. IrAEs were seen in 65% of patients in the same NSCLC cohort, including fatigue, pruritus, rash, decreased appetit. Furthermore, in 13% of patients treated lipase elevation and hypertension was recorded.

Albeit TIGIT expression appears to be highly associated with the PD-L1 expression in solid tumours, this preclinical observation did not translate into clinical benefit in lung cancer in these clinical trials. The underlying preclinical and clinical mechanisms of these negative studies are currently far from being clear and the results from currently ongoing clinical studies (**Table 1**) are eagerly awaited to shed some more light on these results. In this regard, the identification of suitable prognostic biomarkers of response to TIGIT inhibition alone or in combination with other checkpoint inhibitors is clearly warranted to improve the clinical benefit with reduced toxicity.

It should be noted that in the meantime even triplet immuno-oncology combinations ("triple threat") are under clinical development in NSCLSs. The currently recruiting ARC-7 study (**Table 1**) has demonstrated encouraging clinical activity in another interim analysis for the combinations with domvanalimab (TIGIT inhibitory monoclonal antibody). In addition, the zimberelimab (a novel PD-1 inhibitory monoclonal antibody) monotherapy arm showed activity comparable to that of

other anti-PD-1 antibodies studied in this setting [17]. The "the-more-the-better" treatment strategy might be appealing at the first glance; however, it remains to be seen how toxic these combinations may be in the longer term [6].

4. Conclusions

Targeting the interaction between the receptors of the TIGIT family (e.g., CD96, CD112R, CD226, TIGIT and their corresponding binding partners) has become an innovative strategy for the next concepts of cancer immunotherapy that has the potential to synergize with PD-1/PD-L1 checkpoint inhibition. Inhibition of TIGIT has provided promising results in various preclinical models and has now entered the clinic. Several phase I trials with these compounds are currently recruiting patients with refractory or relapsed advanced or metastatic tumours.

Moreover, inhibition of CD112R (PVRIG) (e.g., COM-701—first-in-class inhibitor) is also evaluated in ongoing phase I clinical trials (results have not been published to date) (NCT03667716) [18]. However, the mechanistic processes of the underlying signal cascades triggered by TIGIT and its family members (e.g., bypassing of family receptors, dynamics of receptor dimerization, receptor-associated immunity) is still not fully understood, and more preclinical research is clearly needed to shed light on the underlying molecular biology.

From 2021 onwards different TIGIT family receptors are currently evaluated in over 25 clinical trials (phase I-III) [11], however, a lot of preclinical and clinical research is ongoing at different research sites which will help to identify novel immune checkpoint targets with improved activity against malignancies across all histologies.

It is conceivable that increasing the therapeutic benefits of immune-modulatory agents in a heterogeneous patient population including NSCLCs can only be achieved by immune-oncology combination approaches (e.g., checkpoint inhibitors and co-stimulatory monoclonal antibodies). This concept then could help to overcome the immune-suppressive characteristics of the TME which is the nest where cancer-associated fibroblasts (CAFs) and tumour-associated macrophages (TAMs) together with other players as part for the immune system and tumour cells interact. In this regard, it remains to be seen whether the currently recruiting clinical studies with new-generation immune-oncology drugs can help to further clarify the role of novel immuno-oncology combinations for the treatment of lung and other malignancies.

Moreover, the development bi- and tri-specific monoclonal antibodies targeting immune checkpoints and/or co-stimulatory molecules might also significantly contribute to the growing armamentarium of novel immunotherapies for lung cancer patients in the not-too-distant future.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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