

Tiragolumab (Anti-TIGIT) in SCLC: Skyscraper-02, a Towering Inferno

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Abstract: Small cell lung cancer (SCLC) is characterized by rapid progression and poor prognosis. Although the phase II CITYSCAPE-02 trial found objective response rate (ORR) and progression-free survival (PFS) of non-small cell lung cancer (NSCLC) patients improved when tiragolumab was added to atezolizumab and chemotherapy, the phase III SKYSCRAPER-02 failed to find PFS or OS benefit in patients with SCLC. Atezolizumab was the first immunotherapy to show survival benefit in extensive SCLC based on the phase III IMpower133 study. Given that immunotherapy has become the standard of care for SCLC patients, further research is needed into ways to augment the immune system to better treat these patients.

Keywords: tiragolumab, TIGIT, immunotherapy, small cell lung cancer

Introduction

Small cell lung cancer (SCLC) is characterized by rapid progression and poor prognosis. It is typically associated with tobacco smoking. SCLC management depends on whether the disease is classified as limited or extensive stage, with 56.6% of patients presenting with extensive stage disease at diagnosis.¹ Extensive-stage small cell lung carcinoma remains difficult to treat. Current standard of care is chemotherapy plus immunotherapy.

Immunotherapy with monoclonal antibodies against programmed cell death 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) are now standard of care for a number of cancers. Atezolizumab was the first immunotherapy to show survival benefit in extensive SCLC based on the phase III IMpower133 study.² Additionally, the CASPIAN study utilizing chemotherapy and durvalumab, another PDL1 inhibitor, also showed comparable results to those of the IMpower133 study.³

Cluster of differentiation 155 (CD155) is involved in the cellular adhesion, migration, differentiation, proliferation, survival, and metastases of tumor cells^{4,5} as well as immune regulation.⁶ The role of CD155 in immune regulation of the tumor microenvironment is not well understood but has been shown to interact with T cell receptor and TIGIT domains to inhibit lymphocyte cytotoxicity and proliferation. Previous studies found CD155/T-cell immunoreceptor with Ig and ITIM domains (TIGIT) and PD-L1/PD-1 are highly expressed in SCLC tumors and that elevated expression of PD-L1 or CD155 portends worse overall survival.⁷ The receptors of CD155 and PD-L1 were constitutively expressed on both CD8 tumor infiltrating lymphocytes and on SCLC cells. These findings suggest that tumor cells may upregulate CD155 and PD-L1 to evade immune detection.

Tiragolumab (Genentech) is an anti-TIGIT antibody that was given breakthrough therapy designation by the US Food and Drug Administration (FDA) in February 2021 for treatment of PD-L1-high metastatic NSCLC. This was based off of the promising phase II CITYSCAPE study. In this review, we discuss the role of TIGIT inhibition in solid tumors, early clinical trials, and recently released results of tiragolumab in SCLC.

Structural Characteristics and Mechanism of Action

TIGIT is a transmembrane glycoprotein composed of an immunoglobulin variable domain, a transmembrane domain, and a cytoplasmic tail.^{8–10} TIGIT initiates an inhibitory signaling cascade via the cytoplasmic tail. When ligand binds, the tail is phosphorylated, ultimately inhibiting the phosphoinositide 3 kinase (PI3K)/mitogen-activated protein kinase (MAPK) signaling cascades.¹¹ Additionally, through recruitment of Src-containing inositolphosphate-1 (SHIP-1) to inhibit tumor necrosis factor (TNF) and nuclear factor kappa B (NF- κ B) activation.^{11,12} TIGIT has multiple ligands but seems to have a greater affinity for PVR (Necl-5 or CD155) which is upregulated in several types of cancer^{13,14} and is associated with poor prognosis.^{15,16}

TIGIT is found on T cells and natural killer (NK) cells. TIGIT expression is known to strongly correlate with PD-1 expression.¹⁷

Pharmacodynamics/Kinetics

Exposure of tiragolumab increased with increasing dose followed by nonlinear pharmacokinetics at doses greater than or equal to 100 mg every 3 weeks.¹⁸ Pharmacokinetics were unchanged when administered in combination with atezolizumab. Peripheral TIGIT receptors on cluster of differentiation 8 (CD8) cells were completely occupied for sustained periods at tiragolumab doses at least 30 mg every 3 weeks. Clinical activity was observed at 400 mg to 600 mg doses every 3 weeks.

Preclinical Studies

In mouse tumor models, decreased TIGIT delays growth of both B16F10 cells, MC38 cells, and lung metastases of B16 cells.^{19,20} Further, anti-TIGIT antibodies inhibit mouse T cell proliferation and cytokine production without antigen presenting cells.^{21,22}

Anti-TIGIT antibodies appear to work synergistically with anti-PD-1 antibodies through CD8+ responses.²³ Within ex vivo cell cultures of CD3+ TILs and Mel-624 cells, anti-TIGIT antibodies promote interferon gamma and interleukin-2 production.²⁴ These findings were seen in a variety of solid tumor types.

Based on the biochemical mechanism and preclinical studies, investigators sought to utilize TIGIT-mediated immune regulation to enhance T and NK cell activity.

Clinical Trials

Approximately 10 human anti-TIGIT monoclonal antibodies with varying isotypes or forms have entered clinical trials. Tiragolumab is being studied alone or in combination with atezolizumab in phase I to III trials of solid tumors such as cervical cancer, SCLC, and blood cancers (Table 1).

Phase I Solid Tumors

In a phase Ia/Ib trial of tiragolumab in 73 patients with solid tumors were treated in dose-escalation.¹⁸ Only 4% of patients experienced grade 3 or higher treatment-related adverse events, with the most commonly reported adverse events including fatigue (38%) and anemia (31%). No dose-limiting toxicities were observed. Within the metastatic NSCLC expansion cohort 9 (n=14), ORR was 50% with DCR 79%. Based on maximum receptor occupancy and clinical activity observed in the phase I results, the recommended dose of tiragolumab was determined to be 600 mg every 3 weeks.

Phase II NSCLC

The phase II CITYSCAPE (NCT03563716) studied tiragolumab in combination with atezolizumab in PD-L1 positive advanced/metastatic NSCLC without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations.²⁵ A total of 135 patients were randomized to the combination tiragolumab 600 mg plus atezolizumab 1200 mg IV every 3 weeks or atezolizumab plus placebo. At a median follow-up of 10.5 months, the trial showed significant improvement in ORR (37% vs 21%) and PFS (5.6 vs 3.9 months; hazard ratio (HR) 0.59). When further stratified by high PD-L1 status, defined as PD-L1 expression at least 50%, the ORR increased to 66% in the combination vs 24% with

Table I Ongoing Studies Utilizing Tiragolumab

Clinical Trial	Study Drugs	Disease	Patients	Phase	Primary Outcome	Status
Lung Cancer						
NCT03977467	Atezolizumab + Tiragolumab	NSCLC or advanced solid tumors	N=80, prior PD-I inhibitor treatment	2	ORR	Recruiting
NCT04308785	Atezolizumab ± Tiragolumab	SCLC	N=150, limited stage disease	2	PFS	Recruiting
NCT04958811	Tiragolumab + Atezolizumab + Bevacizumab	NSCLC	N=42, previously treated	2	ORR	Recruiting
NCT04294810 SKYSCRAPER-01	Tiragolumab + Atezolizumab	NSCLC	N=635, advanced or metastatic, PD-L1 positive	3	PFS and OS	Recruiting
NCT04513925 SKYSCRAPER-03	Atezolizumab + Tiragolumab vs Durvalumab	NSCLC	N=800, locally advanced stage III	3	PFS	Recruiting
NCT0483285	Tiragolumab + Atezolizumab ± platinum-based chemotherapy	NSCLC	N=82, untreated stage II=IIIB	2	Surgical disease, Perioperative complications, Rate AEs, pathological response	Recruiting
NCT03563716	Tiragolumab + Atezolizumab	NSCLC	N=135, advanced or metastatic, chemotherapy naive	2	ORR and PFS	Active, not recruiting
NCT0461979 SKYSCRAPER-06	Tiragolumab + Atezolizumab + Pemetrexed and Carboplatin/Cisplatin vs Pembrolizumab + Carboplatin/Cisplatin	NSCLC	N=500, untreated advanced disease	2/3	ORR and PFS and OS	Recruiting
Head and Neck Malignancies						
NCT04665843 SKYSCRAPER-09	Atezolizumab + Tiragolumab	Head and neck	N=120, metastatic or recurrent	2	ORR	Active, not recruiting
NCT03708224	Atezolizumab + Tiragolumab	Head and Neck	N=55	2	Increased CD3 counts and R0 resection rate	Recruiting

(Continued)

Table I (Continued).

Clinical Trial	Study Drugs	Disease	Patients	Phase	Primary Outcome	Status
Melanoma						
NCT05116202 Morpheus-Melanoma	Tiragolumab + Atezolizumab or RO7247669	Melanoma	N=191	Ib/2	ORR and PCR	Recruiting
NCT03554083 NeoACTIVAT	Atezolizumab + Tiragolumab	Melanoma	N=30, high risk, stage III	Parallel assignment	PCR, RFS	Recruiting
Gastrointestinal Malignancies						
NCT03281369 Morpheus-Gastric and Esophageal	Atezolizumab + Tiragolumab + Cisplatin + 5-FU or Atezolizumab + Tiragolumab	Gastric cancer	N=410, advanced or metastatic	Ib/2	ORR, rate AEs	Recruiting
NCT04524871 Morpheus-Liver	Atezolizumab + Bevacizumab + Tiragolumab	Liver cancer	N=280, advanced disease	Ib/2	ORR	Recruiting
NCT03193190 Morpheus-Pancreatic cancer	Atezolizumab + Tiragolumab + Chemotherapy	Pancreatic cancer	N=290, metastatic	Ib/2	ORR and rate AEs	Recruiting
NCT04929223 INTRINSIC	Atezolizumab + Tiragolumab ± Bevacizumab	Colorectal cancer	N=220, metastatic	I/Ib	ORR	Recruiting
NCT05251948 Morpheus-Gastric	Atezolizumab + capecitabine + oxaliplatin + tiragolumab	Gastric cancer	N=90	Ib/2	ORR	Recruiting
NCT0493322	Atezolizumab + Tiragolumab + Chemotherapy	Gastric cancer	N=60, HER2 negative, unresectable, recurrent or metastatic	2	ORR	Recruiting
NCT0500906	Atezolizumab ± Tiragolumab	Rectal cancer	N=76, locally advanced	2	pCR	Recruiting
NCT04543617 SKYSCRAPER-07	Atezolizumab ± Tiragolumab	Esophageal Squamous Cell Carcinoma	N=750, unresectable	3	PFS and OS	Recruiting
Hematologic Malignancies						
NCT04045028	Tiragolumab	Multiple Myeloma or Non-Hodgkin Lymphoma	N=60, relapsed/refractory disease	Ia/Ib	Rate of AEs	Recruiting

(Continued)

Table I (Continued).

Clinical Trial	Study Drugs	Disease	Patients	Phase	Primary Outcome	Status
NCT05315713	Mosunetuzumab + Tiragolumab ± Atezolizumab	Non-Hodgkin Lymphoma	N=118, relapsed/refractory disease	Ib/2	Rate of AEs and ORR	Recruiting
All Solid Tumors						
NCT04632992 MyTACTIC	Atezolizumab + Tiragolumab	Solid tumors	N=260, advanced disease with biomarkers	2	ORR	Recruiting
NCT02794571	Tiragolumab ± Atezolizumab ± Anti-Cancer Therapies	Solid tumors	N=660, advanced or metastatic	Ia/Ib	Rate of AEs, dose limiting toxicities, anti-drug antibodies	Recruiting
Gynecologic/Genitourinary Malignancies						
NCT04486352 EndoMAP	Atezolizumab + Tiragolumab	Endometrial cancer	N=100, recurrent	Ib/2	ORR	Recruiting
NCT03869190 Morpheus-UC	Atezolizumab + Tiragolumab or Cisplatin + Gemcitabine + Atezolizumab + Tiragolumab	Urothelial carcinoma	N=645	Ib/2	ORR and pCR	Recruiting
NCT04300647 SKYSCRAPER-04	Tiragolumab + Atezolizumab and Atezolizumab Monotherapy	Cervical cancer	N=172, metastatic or recurrent PD-L1 positive disease	2	ORR	Active, not recruiting

Abbreviations: AEs, adverse events; CD3, cluster of differentiation 3; N, number; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; pCR, pathologic complete response; R0, radical resection; RFS, recurrence free survival.

atezolizumab alone.¹⁷ A 21% of patients in the combination group and 18% in the atezolizumab alone cohort had serious treatment-related adverse events. The most common grade 3 or higher adverse event was lipase increase (9% combination, 3% atezolizumab). Two treatment-related deaths (pyrexia and infection) occurred in the combination cohort. As a result of these findings, the phase III SKYSCRAPER-01 study was launched.

Phase III NSCLC

The phase III SKYSCRAPER-01 trial (NCT04294810) studied combination tiragolumab and atezolizumab in newly diagnosed metastatic NSCLC with PD-L1 expression of at least 50%. A total of 534 patients were randomized to this study. At interim analysis, the study did not meet its co-primary end point of improvement in PFS. At the time of analysis, data for overall survival (OS) was immature.²⁶ The study will continue until the next planned data analysis.

Phase III SCLC

In the SCLC space, the phase III SKYSCRAPER-02 (NCT04256421) is ongoing. In this study of newly diagnosed extensive-stage small cell lung cancer, 490 patients are randomized to atezolizumab 1200 mg IV every 3 weeks plus carboplatin and etoposide either with (n=243) or without (n=247) tiragolumab 600 mg IV every 3 weeks.²⁷ At a median follow-up of 14.3 months, 397 patients were analyzed for interim analysis. This study failed to meet its co-primary endpoint of PFS improvement. Median PFS was 5.4 months (95% CI 4.7–5.5) with tiragolumab vs 5.6 months without this agent.²⁸ The other co-primary endpoint of OS was unlikely to reach statistical significance by planned final analysis. The median OS was 13.6 months for both cohorts (95% CI 0.10.8–14.9). There was no significant difference in OS based on stratifying for factors including Eastern Cooperative Oncology Group (ECOG) performance status (PS), brain metastases or lactate dehydrogenase levels. Additionally, ORRs were similar between cohorts (70.8% (95% CI 64.6–76.3) with tiragolumab vs 65.6 (95% CI 59.3–71.4) with placebo). Duration of response (DOR) was also similar at 4.2 months (95% CI 4.1–4.4) with tiragolumab compared to 5.1 (95% CI 4.4–5.8) without. The study will continue until planned final OS analysis.

Adverse events were common in SKYSCRAPER-02, with 99.6% of patients in both cohorts reporting side effects. Grade 3 or higher adverse events occurred in 69.4% of patients receiving tiragolumab compared to 70.3% of patients receiving placebo. Toxicity resulted in withdrawal in 5.0% and 5.3% of patients receiving tiragolumab and placebo, respectively. The most common adverse events were anemia, neutropenia, and alopecia, though pruritus was more common in the tiragolumab group.

Discussion

Although studies have shown that patients with NSCLC and SCLC have better outcomes when immunotherapy is added to chemotherapy, it is unclear which patients will benefit the most or develop serious immune-related adverse effects. More research is needed and there is an unmet need for additional immune system targets/complementary pathways.

The IMpower133 trial showed a significant improvement in OS (12.3 months vs 10.3 months; HR death 0.70; 95% CI 0.54–0.91) with atezolizumab in extensive stage SCLC.² Median PFS was 5.2 months vs 4.3 months (HR 0.77; 95% CI 0.62–0.96). These findings showed the potential for immune regulation to alter clinical outcomes in extensive SCLC and received FDA approval in March 2019. Additionally, results from the CASPIAN study further backed up the synergistic effects of immunotherapy added onto chemotherapy in extensive stage SCLC patients and thus these two regimens became the standard of care. Table 2 compares these studies side by side in addition to the Skyscraper-02 study. Of note, KEYNOTE-604 studied pembrolizumab or placebo combined with platinum and etoposide in the first-line setting of extensive stage SCLC. Results showed improved PFS (HR 0.75; 95% CI 0.61–0.91) as well as 12-month PFS of 13.6% vs 3.1%.²⁹ OS was longer with the addition of pembrolizumab but did not reach statistical significance. The ORR was 70.6% vs 61.8% with similar rates of adverse events.

Table 2 Comparison of IMpower133, CASPIAN and SKYSCRAPER-02 Endpoints

	IMpower133	CASPIAN	SKYSCRAPER-02
Number participants	403	805	490
Stratification factors	PS, sex	Carboplatin/cisplatin	PS, brain metastases, LDH
OS (months)	12.3 vs 10.3	12.9 vs 10.5	13.6 vs 13.6
HR	0.76	0.71	1.04
P value	0.0154	0.003	0.79
Median follow up	22.9	39.4	14.3

Abbreviations: HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PS, performance status.

Nevertheless, extensive stage SCLC remains a difficult diagnosis to treat due to disease progression being ultimately inevitable with oftentimes limited therapeutic options. Unfortunately, the addition of tiragolumab to atezolizumab did not provide clinical benefit at interim analysis for either PFS or OS based on Skyscraper-02. But why?

Comparing IMpower133 and Skyscraper-02, the control arm outperformed expectations in the Skyscraper-02 study, which is likely the cause of negative endpoints, at least partially, in addition to the fact that enhanced benefit in the tiragolumab arm was not seen. However, the reason for this is unclear. Stratification factors in Skyscraper-02 included ECOG performance status, brain metastasis and LDH, whereas in IMpower133, patients were stratified based on ECOG performance status and sex. The distribution of both ECOG performance status and sex were largely similar in IMpower133 and Skyscraper-02. If anything, Skyscraper-02 study had a larger percentage of patients with brain metastasis at baseline (19.3% in the tiragolumab arm and 18.6% in the placebo arm), whereas IMpower133 had only 8.5% and 8.9% of patients in the investigational arm and placebo arm, respectively. While this observation was surprising, perhaps we are missing a more important factor in SCLC, which could be related to the molecular subtypes of SCLC.

Indeed, Gay et al reported differential survival benefits to the IMpower133 regimen based on the molecular subtypes of SCLC.³⁰ SCLC-I, or SCLC-inflamed subtype, had the best survival benefit when compared to other subtypes such as SCLC-A (SCLC-*ASCL1*), SCLC-N (SCLC-*NEUROD1*) and SCLC-P (SCLC-*POU2F3*). Characterized by the increased absolute number of immune cells including T-cells, NK cells and macrophages, the SCLC-I subtype had significant OS benefit relative to all other subtypes with an HR of 0.566 (95% CI: 0.321–0.998) with the chemotherapy and atezolizumab arm but not with the chemotherapy and placebo arm, which suggests that SCLC-I subtype may be predictive of benefit to immune checkpoint blockade.

Future Directions

Further research is needed on the association of cluster of differentiation 226 (CD226) activation with the efficacy of anti-TIGIT antibodies. Despite the lack of success in phase III trials, the preclinical and phase II data shows that PD-L1 complementary immune regulatory pathways may merit further investigation in lung cancer. In SCLC, more focus should be given on the molecular subtypes and perhaps utilization of anti-TIGIT combinations should be evaluated in cohorts enriched with the SCLC-inflamed subtype. For NSCLC, in addition to the SKYSCRAPER-01 study, phase II/III trials of tiragolumab are still ongoing including SKYSCRAPER-03 for unresectable stage 3 NSCLC and SKYSCRAPER-06 for treatment naïve nonsquamous NSCLC (Table 1).

Conclusion

Extensive stage SCLC remains difficult to treat. Although initial results of tiragolumab as a complement to PD-L1 inhibition were promising, the drug has failed to meet its endpoint in the phase III SKYSCRAPER-02 trial for SCLC. Phase III trials of this drug are still ongoing in NSCLC and other tumor types such as esophageal cancer. Given the positive results of IMpower133 and CASPIAN, there appears to be synergistic effects of chemotherapy and immunotherapy in SCLC. More research to understand ways to improve the immune regulation in SCLC patients is needed. Not all SCLC are created equal. Perhaps, it is time to look at the subtypes of SCLC and treat accordingly.

Abbreviations

ALK, anaplastic lymphoma kinase; CD8, cluster of differentiation 8; CD155, cluster of differentiation 155; CD226, cluster of differentiation 226; CTLA-2, cytotoxic T lymphocyte-associated antigen 4; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; FDA, Federal Drug Administration; HR, hazard ratio; MAPK, mitogen-activated protein kinase; NF- κ B, nuclear factor kappa beta; NK, natural killer; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PI3K, phosphoinositide 3 kinase; SCLC, small cell lung cancer; TIGIT, T-cell immunoglobulin and ITIM domain; TNF, tumor necrosis factor.

Funding

No funding was secured for this report.

Disclosure

SIO has stock ownership and was on the scientific advisory board of Turning Point Therapeutics Inc (until Feb 28, 2019); is a member of the SAB of Elevation Oncology and has stock ownership; honoraria from AstraZeneca, Caris Life Science, Daiichi Sankyo, DAVA Oncology LLP, Janssen/JNJ, Merck, Pfizer, Roche/Genentech, Takeda/ARIAD, BeiGene. MN reports honorarium/consulting from/for AstraZeneca, Daiichi Sankyo, Takeda, Novartis, EMD Serono, Janssen, Pfizer, Eli Lilly, Genentech, Mirati, Caris Life Sciences, Blueprint Medicines; travel support from AnHeart Therapeutics. The authors report no other conflicts of interest in this work.

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