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Tiragolumab Plus Atezolizumab and Chemotherapy for Advanced Nonsquamous Non–Small Cell Lung Cancer
The Phase 3 SKYSCRAPER-06 Randomized Clinical Trial

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IMPORTANCE Programmed cell death 1 ligand 1/programmed cell death protein 1 inhibitors, with or without chemotherapy, are standard first-line treatment for patients with advanced non–small cell lung cancer (NSCLC); however, survival benefit is limited, and many patients experience disease progression.

OBJECTIVE To evaluate the efficacy and safety of tiragolumab plus atezolizumab plus chemotherapy vs placebo plus pembrolizumab plus chemotherapy in patients with advanced nonsquamous NSCLC.

DESIGN, SETTING, AND PARTICIPANTS SKYSCRAPER-06 was a phase 3 randomized clinical trial that recruited patients with previously untreated, locally advanced unresectable or metastatic NSCLC at 129 sites in 21 countries between December 15, 2020, and September 14, 2023 (data cutoff, April 19, 2024).

INTERVENTION Patients were randomized 1:1 to receive either tiragolumab, 600 mg, plus atezolizumab, 1200 mg, plus chemotherapy (pemetrexed, 500 mg/m^2, and carboplatin [area under the curve 5], or cisplatin, 75 mg/m^2) or placebo plus pembrolizumab, 200 mg, plus chemotherapy via intravenous infusion on day 1 of each 21-day cycle until disease progression, loss of clinical benefit, unacceptable toxic effect, or withdrawal of consent.

MAIN OUTCOMES AND MEASURES Primary end points were investigator-assessed progression-free survival and overall survival. The safety and tolerability of the study drugs were also evaluated.

RESULTS Of 542 patients in the full analysis set (mean [SD] age, 63.6 [9.3] years; 353 [65.1%] male), 269 were randomized to tiragolumab plus atezolizumab plus chemotherapy and 273 to placebo plus pembrolizumab plus chemotherapy. Overall, baseline demographics were similar between treatment groups. At data cutoff (median follow-up, 11.8 months), median investigator-assessed progression-free survival was 8.3 months (95% CI, 7.1-9.6 months) with tiragolumab plus atezolizumab plus chemotherapy vs 9.9 months (95% CI, 8.7-11.9 months) with placebo plus pembrolizumab plus chemotherapy (hazard ratio, 1.27; 95% CI, 1.02-1.57; P = .99); median overall survival was 18.9 months (95% CI, 15.2-23.8 months) vs 23.1 months (95% CI, 20.7-33.0 months) in each treatment group, respectively (hazard ratio, 1.33; 95% CI, 1.02-1.73; P = .98). Grade 3 to 4 adverse events occurred in 164 of 267 patients (61.4%) in the tiragolumab plus atezolizumab plus chemotherapy group and 165 of 272 patients (60.7%) in the placebo plus pembrolizumab plus chemotherapy group, with grade 5 AEs occurring in 27 of 267 patients (10.1%) and 16 of 272 patients (5.9%) in each group, respectively.

CONCLUSIONS AND RELEVANCE In the phase 3 SKYSCRAPER-06 randomized clinical trial, the primary end points were not met and the study has been terminated.

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Visual Abstract

Supplemental content

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Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases and is the leading cause of cancer deaths worldwide.[1-3] Around 75% of all NSCLC cases are histologically nonsquamous (large cell carcinoma or adenocarcinoma), with squamous cell carcinoma accounting for the remaining cases.[4]

Programmed cell death 1 ligand 1 (PD-L1)/programmed cell death protein 1 (PD-1) inhibitors in combination with chemotherapy have demonstrated meaningful improvement in survival compared with chemotherapy alone and are a standard first-line treatment for patients with advanced nonsquamous NSCLC without known actionable genomic alterations.[5-10] Despite the robust activity observed with anti-PD-L1/PD-1 antibodies, durable clinical benefit appears limited to a subset of patients due to both primary and acquired resistance.[11,12] Given that most patients will eventually experience disease progression, there is a need for more effective treatments for patients with advanced NSCLC.[11,12]

T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) is an immune checkpoint receptor expressed on the surface of activated T cells and natural killer (NK) cells and binds with high affinity to its ligand, CD155, which has an activating counter receptor, CD226.[13-15] Activation of TIGIT on T cells and NK cells limits proliferation, effector cytokine production, and killing of tumor cells.[14,15] TIGIT is frequently coexpressed with PD-1 in the tumor microenvironment, and its expression is associated with T-cell exhaustion, impaired cytotoxicity, and poor clinical outcomes in various cancers, including NSCLC.[14,15] In preclinical models, coinhibition of the TIGIT and PD-L1/PD-1 pathways demonstrated superior efficacy compared with inhibition of either pathway alone, representing an attractive treatment strategy due to the complementary actions of anti-TIGIT and anti-PD-L1 antibodies.[15]

Atezolizumab, an anti-PD-L1 antibody, is approved as first-line monotherapy or in combination with chemotherapy with or without bevacizumab for metastatic NSCLC, and as an adjuvant therapy in patients with resected stage II to IIIA NSCLC.[5,9,16-20] Tiragolumab is an anti-TIGIT antibody that prevents TIGIT interacting with its receptor, CD155, which is expressed on several cell types, including tumor cells and antigen-presenting cells.[21] Results from early-phase clinical trials suggested that coinhibition of the TIGIT and PD-L1/PD-1 pathways by tiragolumab and atezolizumab, respectively, could improve outcomes for patients with advanced NSCLC.[22,23] Furthermore, immune modulation achieved through PD-L1/PD-1 inhibition can also amplify the immunogenic effects of chemotherapy through direct cytotoxicity (leading to increased tumor antigen release and enhanced tumor immunogenicity) and increased PD-L1 expression in the tumor microenvironment.[24-26] At the time this study was initiated, we hypothesized that checkpoint blockade with an anti-TIGIT antibody could enhance the efficacy of an anti-PD-L1/PD-1 antibody in combination with chemotherapy in patients with advanced nonsquamous NSCLC. Unfortunately, since this time, several major anti-TIGIT programs have been discontinued despite showing initial promise in early-phase trials.[27-29] Herein, we report results from the SKYSCRAPER-06 trial, assessing the efficacy and safety of tiragolumab plus atezolizumab plus chemotherapy compared with standard-of-care pembrolizumab plus chemotherapy in patients with advanced or metastatic nonsquamous NSCLC.

Key Points

Question Can treatment with the combination of tiragolumab plus atezolizumab plus chemotherapy improve outcomes for patients with advanced nonsquamous non–small cell lung cancer (NSCLC)?

Findings In this phase 3 randomized clinical trial of 542 patients with previously untreated, locally advanced unresectable or metastatic NSCLC, tiragolumab plus atezolizumab plus chemotherapy did not demonstrate a progression-free or overall survival benefit vs placebo plus pembrolizumab plus chemotherapy. Tiragolumab plus atezolizumab plus chemotherapy demonstrated a safety profile that was generally similar to that of pembrolizumab plus chemotherapy.

Meaning Treatment with the combination of tiragolumab plus atezolizumab plus chemotherapy did not improve outcomes for patients with advanced nonsquamous NSCLC compared with pembrolizumab plus chemotherapy.

Methods

Study Design and Participants

SKYSCRAPER-06 was a global, phase 2/3, double-blind, placebo-controlled, randomized clinical trial (eFigure 1 in Supplement 1). Patients were enrolled at 129 sites in 21 countries between December 15, 2020, and September 14, 2023. After patients were initially enrolled in the study, an interim safety and efficacy review by an independent data monitoring committee (IDMC) confirmed that the prespecified threshold (progression-free survival [PFS]; hazard ratio [HR] ≤1) for expansion was met and phase 3 enrollment was ungated.

Eligible patients were 18 years or older with previously untreated locally advanced unresectable or metastatic nonsquamous NSCLC and had an Eastern Cooperative Oncology Group Performance Status of 0 or 1; measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; and known PD-L1 status. All patients were assessed for tumor *EGFR* alteration or *ALK* gene rearrangement and were excluded from the study if found to have these variations. Full eligibility criteria can be found in the redacted protocol (Supplement 2).

The study protocol was approved by the institutional review board at each participating center and complied with Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and local laws. All patients provided written informed consent. The study followed Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Randomization and Masking

Patients were randomly assigned 1:1 using an interactive voice or web-based response system (S-CLINICA) to receive either

atezolizumab plus tiragolumab plus chemotherapy or placebo plus pembrolizumab plus chemotherapy. A permuted-block randomization method was used to ensure balanced assignment to each treatment group, and randomization was stratified by PD-L1 expression (tumor cell/tumor proportion score <1% vs 1%-49% vs ≥50% by local or central assay [central assay results were used for stratification if available prior to randomization]), geographic region (Asia vs another region), and Eastern Cooperative Oncology Group Performance Status (0 vs 1). Study site personnel and patients were blinded to treatment assignment during the study except for the pharmacist, who needed to remain unblinded due to differences in dose preparation. The final volume, rate of administration, and appearance of atezolizumab/pembrolizumab and placebo/tiragolumab were identical.

Procedures

Patients were initially treated during an induction phase for 4 cycles and received either tiragolumab, 600 mg, plus atezolizumab, 1200 mg, plus pemetrexed, 500 mg/m^2, and carboplatin (area under the curve 5)/cisplatin, 75 mg/m^2, or placebo, 600 mg, plus pembrolizumab, 200 mg, plus pemetrexed, 500 mg/m^2, and carboplatin (area under the curve 5)/cisplatin, 75 mg/m^2, all administered via intravenous infusion on day 1 of each 21-day cycle (eFigure 1 in Supplement 1). Selection of carboplatin or cisplatin was at the discretion of the investigator. The induction phase was followed by a maintenance phase (cycle 5 onward) in which patients continued to receive either tiragolumab plus atezolizumab plus pemetrexed or placebo plus pembrolizumab plus pemetrexed until disease progression, loss of clinical benefit, unacceptable toxic effect, withdrawal of consent, or death. Crossover between treatment groups was not allowed, and dose reductions were not permitted for the immunotherapies or placebo. Patients had tumor assessments at baseline, every 6 weeks for the first 48 weeks following treatment initiation, and every 9 weeks thereafter, regardless of dose delays, until radiographic disease progression per RECIST, version 1.1; withdrawal of consent; death; or study termination, whichever occurred first. Patients who were treated beyond disease progression had tumor assessments every 6 weeks after initial documentation of progression, or more frequently if clinically indicated, until treatment was discontinued. The clinical cutoff date was April 19, 2024.

Tumor PD-L1 expression was assessed via immunohistochemistry using a local health authority-approved assay (investigational VENTANA SP263 CDx Assay [preferred; Ventana Medical Systems]) or, if the SP263 assay was unavailable, using the PD-L1 immunohistochemistry 22C3 assay (Agilent Technologies). PD-L1 expression levels were assessed by a central assay (SP263) if local test results were unavailable. If both local and central test results were available prior to randomization, patient stratification was based on central test data.

Outcomes

The primary end points of SKYSCRAPER-06 were investigator-assessed PFS and overall survival (OS). Investigator-assessed PFS was defined as the time from randomization to the first occurrence of disease progression as determined by the investigator per RECIST, version 1.1, or death from any cause, whichever occurred first. OS was defined as the time from randomization to death from any cause. Secondary efficacy end points included landmark investigator-assessed PFS and OS analyses, investigator-assessed PFS and OS according to PD-L1 expression as determined by central testing, investigator-assessed confirmed objective response rate (ORR; defined as the proportion of patients with a complete response or partial response on 2 consecutive occasions ≥4 weeks apart), and duration of response (DOR; defined as the time from first occurrence of a documented objective response to disease progression or death from any cause). Subgroup analyses were performed to assess the consistency of investigator-assessed PFS and OS in clinically relevant subgroups defined by demographic and disease characteristics.

The safety and tolerability of the study drugs were evaluated throughout the study through the assessment of adverse events (AEs), vital signs, and laboratory test results. The severity of AEs was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

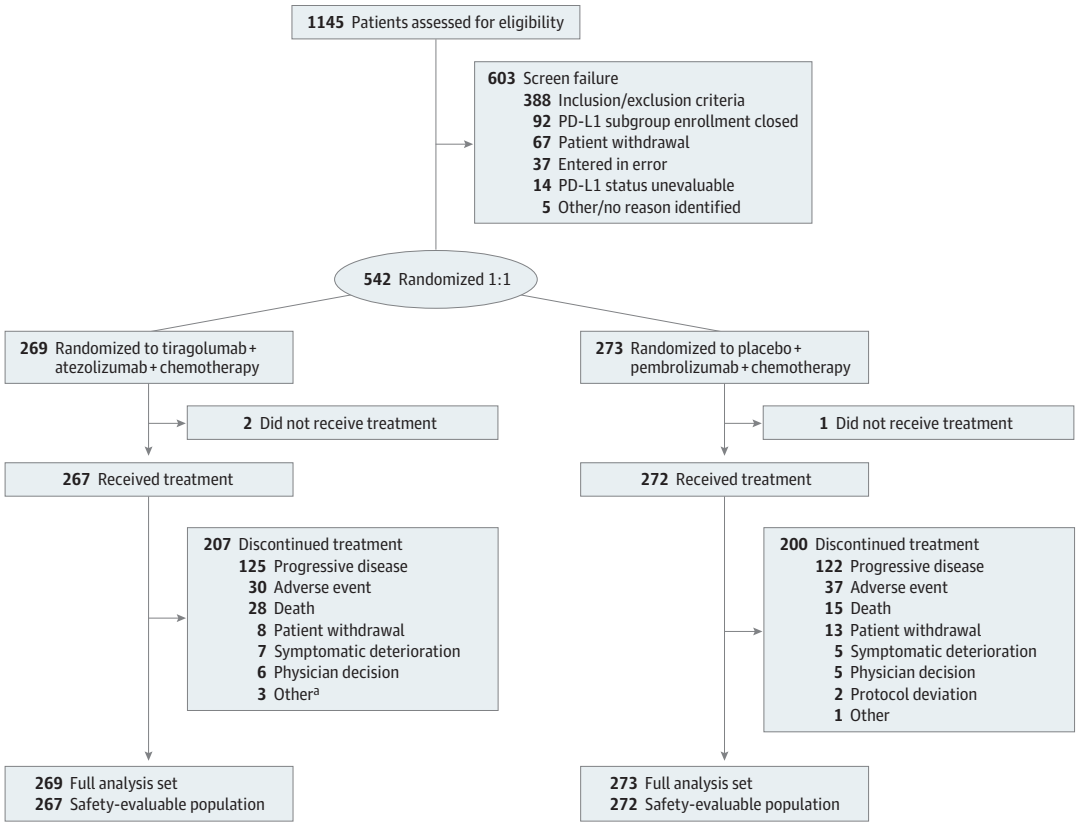
Statistical Analysis

Efficacy analyses were performed using the full analysis set, defined as all patients randomized to each treatment group, regardless of whether they received any study treatment. PD-L1 efficacy results were all based on central testing using the preferred assay. Safety analyses were assessed in the safety-evaluable population, defined as all randomized patients who received any amount of study treatment.

When the first 200 enrolled patients had completed at least 2 postbaseline tumor assessments, a nonbinding interim efficacy analysis was conducted by the IDMC (approximately 16 months after the first patient was enrolled) to enable the gating decision to continue into phase 3. The statistical analysis plan for the expanded phase 3 study specified that the primary analysis of investigator-assessed PFS was planned for when approximately 373 investigator-assessed PFS events were observed (or 232 OS events, whichever occurred later), providing 90% power to detect a target HR of 0.65 at a 2-sided significance level of .004. The overall type I error for the study was controlled at 0.05 (two-sided). To control the overall type I error rate at 0.05, a group sequential weighted Holm procedure was used where a 2-sided alpha of .004 and .046 were allocated to the primary comparisons for PFS and OS in all randomized patients, respectively (eFigure 2 in Supplement 1). The stopping boundary for the OS interim analysis was determined by the O'Brien-Fleming type α spending function.

The primary analyses of investigator-assessed PFS and OS were based on the inverse normal combination test where 1-sided *P* values were reported. Kaplan-Meier methodology was used to estimate the median investigator-assessed PFS and OS and to construct survival curves for each treatment group; Brookmeyer-Crowley methodology was used to estimate the 95% CIs. A stratified Cox proportional hazards model was used to estimate the HR and 95% CI for investigator-assessed PFS and OS (stratification factors were the same as those used for

Figure 1. CONSORT Diagram



PD-L1 indicates programmed cell death 1 ligand 1.

[a]In the tiragolumab plus atezolizumab plus chemotherapy group, there were 3 patients who discontinued tiragolumab for other reasons, and 2 patients who discontinued atezolizumab for other reasons.

randomization). Landmark investigator-assessed PFS and OS were estimated using Kaplan-Meier methodology, with 95% CIs calculated using the SE derived from the Greenwood formula. The 95% CI for ORR was calculated using the Wilson score method, while median DOR and its 95% CI were estimated using Kaplan-Meier methodology. All other analyses were performed using descriptive statistics. Analyses were completed using SAS, version 9.4 (SAS Institute).

Results

Patients

The full analysis set included 542 patients (mean [SD] age, 63.6 [9.3] years; 353 [65.1%] male) randomly assigned to receive either tiragolumab plus atezolizumab plus chemotherapy (n = 269) or placebo plus pembrolizumab plus chemotherapy (n = 273) (**Figure 1**). Overall, baseline characteristics were similar across treatment groups (**Table 1**), except there were more men (184 [68.4%] vs 169 [61.9%]), fewer patients with PD-L1 tumor cell/tumor proportion score lower than 1% (92 [34.5%] vs 112 [41.6%]), and more patients with baseline liver metastases (38 [14.1%] vs 25 [9.2%]) in the tiragolumab plus atezolizumab plus chemotherapy group than in the placebo plus pembrolizumab plus chemotherapy group.

Efficacy

The primary analysis of investigator-assessed PFS took place after 364 events had occurred. At the clinical cutoff date (April 19, 2024; median duration of survival follow-up, 11.8 months), median investigator-assessed PFS was 8.3 months (95% CI, 7.1-9.6 months) in the tiragolumab plus atezolizumab plus chemotherapy group vs 9.9 months (95% CI, 8.7-11.9 months) in the placebo plus pembrolizumab plus chemotherapy group (HR, 1.27; 95% CI, 1.02-1.57; P = .99; **Figure 2**A). The 6-month investigator-assessed PFS rate was 61.1% and 68.5% in the tiragolumab plus atezolizumab plus chemotherapy and placebo plus pembrolizumab plus chemotherapy groups, respectively, and the 12-month investigator-assessed PFS rate was 34.3% and 42.8% in each group, respectively.

The first interim analysis of OS was conducted after 230 events had occurred. Median OS was 18.9 months (95% CI, 15.2-23.8 months) in the tiragolumab plus atezolizumab plus chemotherapy group vs 23.1 months (95% CI, 20.7-33.0 months) in the placebo plus pembrolizumab plus chemotherapy group

Table 1. Summary of Baseline Patient Characteristics

Characteristic	No. (%)	
	Tiragolumab + atezolizumab + chemotherapy (n = 269)	Placebo + pembrolizumab + chemotherapy (n = 273)
Age		
Mean (SD), y	64 (9.4)	63 (9.3)
<65 y	146 (54.3)	146 (53.5)
Sex		
Female	85 (31.6)	104 (38.1)
Male	184 (68.4)	169 (61.9)
Race[a]		
American Indian or Alaska Native	10 (3.7)	12 (4.4)
Asian	87 (32.3)	89 (32.6)
Black or African American	4 (1.5)	2 (0.7)
Native Hawaiian or Other Pacific Islander	1 (0.4)	3 (1.1)
White	165 (61.3)	163 (59.7)
Unknown	2 (0.7)	4 (1.5)
ECOG Performance Status		
0	110 (40.9)	102 (37.4)
1	159 (59.1)	171 (62.6)
Smoking status		
Never smoked	41 (15.2)	54 (19.8)
Currently smoke	55 (20.4)	58 (21.2)
Formerly smoked	173 (64.3)	161 (59.0)
Locally advanced unresectable disease	19 (7.1)	28 (10.3)
PD-L1 by central laboratory testing[b]		
<1%	92 (34.5)	112 (41.6)
1%-49%	78 (29.2)	74 (27.5)
≥50%	84 (31.5)	78 (29.0)
Not done	13 (4.9)	5 (1.9)
Metastatic disease	253 (94.1)	248 (90.8)
No. of metastases, mean (SD)[c]	2.4 (1.2)	2.4 (1.3)
Brain metastases or history of brain metastases	46 (17.1)	46 (16.8)
Liver metastases	38 (14.1)	25 (9.2)
Investigator choice of chemotherapy		
Carboplatin	232 (86.2)	244 (89.4)
Cisplatin	35 (13.0)	28 (10.3)
Missing	2 (0.7)	1 (0.4)
Baseline sum of diameters for target lesions, mean (SD)[d]	88.1 (52.6)	83.4 (43.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death 1 ligand 1.

[a] Race data were collected on the electronic case report form and self-reported by the patient.

[b] Across 267 patients in the tiragolumab plus atezolizumab plus chemotherapy group and 269 patients in the placebo plus pembrolizumab plus chemotherapy group. The VENTANA SP263 CDx Assay (Ventana Medical Systems) was used to determine PD-L1 status.

[c] Across 253 patients in the tiragolumab plus atezolizumab plus chemotherapy group and 248 patients in the placebo plus pembrolizumab plus chemotherapy group.

[d] Across 268 patients in the tiragolumab plus atezolizumab plus chemotherapy group and 268 patients in the placebo plus pembrolizumab plus chemotherapy group.

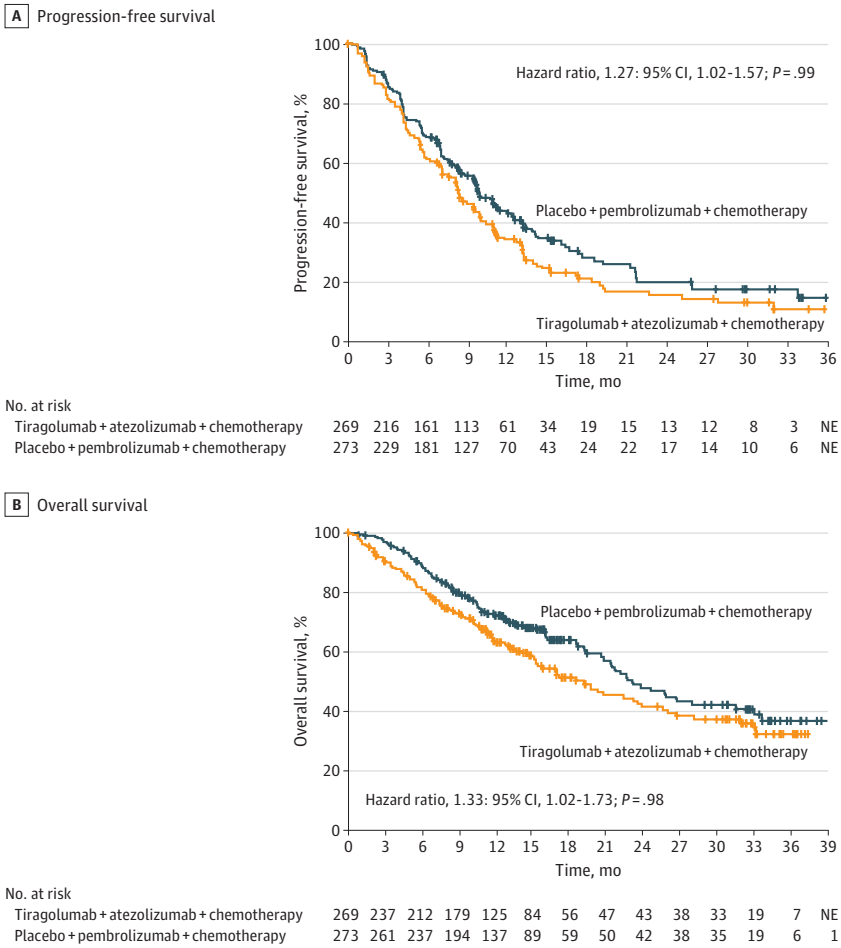
(HR, 1.33; 95% CI, 1.02-1.73; P = .98; Figure 2B). The 12-month OS rate was 63.4% for tiragolumab plus atezolizumab plus chemotherapy and 72.3% for placebo plus pembrolizumab plus chemotherapy.

There was no investigator-assessed PFS or OS benefit according to PD-L1 expression or any other clinically relevant subgroups for tiragolumab plus atezolizumab plus chemotherapy over placebo plus pembrolizumab plus chemotherapy (eFigures 3 and 4 in Supplement 1). Investigator-assessed confirmed ORR was 50.2% (95% CI, 44.1%-56.3%) in the tiragolumab plus atezolizumab plus chemotherapy group and 56.6% (95% CI, 50.5%-62.6%) in the placebo plus pembrolizumab plus chemotherapy group; among patients who responded to treatment, median DOR was 9.4 months (95% CI, 8.2-11.7 months) and 11.1 months (95% CI, 9.5-18.9 months) in each group, respectively.

Safety

The safety-evaluable population comprised 539 patients. Among 267 patients in the tiragolumab plus atezolizumab plus chemotherapy group, the median duration of treatment was 7.0 months for tiragolumab, 7.2 months for atezolizumab, 6.3 months for pemetrexed, and 2.1 months for carboplatin/cisplatin. Among 272 patients in the placebo plus pembrolizumab plus chemotherapy group, the median duration of treatment was 7.7 months for placebo, 7.9 months for

Figure 2. Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival and Overall Survival in the Full Analysis Set



NE indicates not estimable.

pembrolizumab, 6.5 months for pemetrexed, and 2.1 months for carboplatin/cisplatin.

Overall, 262 of 267 patients (98.1%) in the tiragolumab plus atezolizumab plus chemotherapy group and 267 of 272 patients (98.2%) in the placebo plus pembrolizumab plus chemotherapy group experienced at least 1 AE of any cause (**Table 2**), most commonly anemia (146 patients [54.7%] and 141 patients [51.8%], respectively) and nausea (105 patients [39.3%] and 107 patients [39.3%], respectively; eTable 1 in Supplement 1). The incidence of AEs related to any study treatment can be found in Table 2. Grade 3 to 4 AEs occurred in 164 patients (61.4%) in the tiragolumab plus atezolizumab plus chemotherapy group and 165 patients (60.7%) in the placebo plus pembrolizumab plus chemotherapy group, with anemia (62 patients [23.2%] and 60 patients [22.1%], respectively) and decreased neutrophil count (27 patients [10.1%] and 27 patients [9.9%], respectively) occurring most frequently in each treatment group. AEs resulting in treatment discontinuation occurred in 61 patients (22.8%) in the tiragolumab plus atezolizumab plus chemotherapy group and 72 patients (26.5%) in the placebo plus pembrolizumab plus chemotherapy group; grade 5 AEs were reported in 27 of 267 patients (10.1%) (treatment-related, 9 [3.4%]) and 16 of 272 patients (5.9%) (treatment-related, 7 [2.6%]) in each group, respectively.

Immune-mediated AEs (imAEs) were reported in 187 patients (70.0%) in the tiragolumab plus atezolizumab plus chemotherapy group and 170 patients (62.5%) in the placebo plus pembrolizumab plus chemotherapy group (Table 2); the most common (≥20% of patients) imAEs were immune-mediated rash (107 patients [40.1%] and 72 patients [26.5%], respectively), and immune-mediated hepatitis (mostly hepatic laboratory abnormalities; 78 patients [29.2%] and 80 patients [29.4%], respectively; eTable 2 in Supplement 1). imAEs requiring treatment with systemic corticosteroids occurred in 63 patients (23.6%) in the tiragolumab plus atezolizumab plus chemotherapy group and 50 patients (18.4%) in the placebo plus pembrolizumab plus chemotherapy group.

Discussion

To our knowledge, SKYSCRAPER-06 is the first phase 3 study investigating the activity of combined anti-TIGIT plus anti-PD-L1 antibodies plus chemotherapy in comparison with stan-

Table 2. Summary of Safety Events in the Safety-Evaluable Population

Adverse event	No. (%)	
	Tiragolumab + atezolizumab + chemotherapy (n = 267)	Placebo + pembrolizumab + chemotherapy (n = 272)
All-grade, any cause	262 (98.1)	267 (98.2)
Grade 3-4	164 (61.4)	165 (60.7)
Grade 5	27 (10.1)	16 (5.9)
Treatment related	251 (94.0)	255 (93.8)
Grade 3-4	135 (50.6)	139 (51.1)
Grade 5	9 (3.4)[a]	7 (2.6)[b]
Serious	144 (53.9)	135 (49.6)
Treatment related	77 (28.8)	75 (27.6)
Leading to treatment discontinuation	61 (22.8)	72 (26.5)
Chemotherapy	56 (21.0)	70 (25.7)
Immunotherapy/placebo	31 (11.6)	38 (14.0)
Leading to dose modification/interruption	179 (67.0)	176 (64.7)
Chemotherapy	167 (62.5)	169 (62.1)
Immunotherapy/placebo	170 (63.7)	157 (57.7)
All-grade AESIs	187 (70.0)	170 (62.5)
Grade 3-4	42 (15.7)	31 (11.4)
Grade 5	7 (2.6)	3 (1.1)
Requiring systemic corticosteroids	63 (23.6)	50 (18.4)

Abbreviation: AESI, adverse event of special interest.

[a] Includes colitis (n = 2), hematotoxicity (n = 1), infusion-related reaction (n = 1), acute pancreatitis (n = 1), pancytopenia (n = 1), pneumonia (n = 1), pneumonitis (n = 1), and Stevens-Johnson syndrome (n = 1).

[b] Includes hemoptysis (n = 1), interstitial lung disease (n = 1), pancytopenia (n = 1), pneumonia (n = 1), pneumonitis (n = 1), pneumoperitoneum (n = 1), and septic shock (n = 1).

dard-of-care pembrolizumab plus chemotherapy in patients with advanced, nonsquamous NSCLC. The primary end points of investigator-assessed PFS (primary analysis) and OS (first interim analysis [which was immature]) were not met in SKYSCRAPER-06, with no PFS or OS benefit observed with tiragolumab plus atezolizumab plus chemotherapy vs placebo plus pembrolizumab plus chemotherapy. No further analyses are planned, and the study has been terminated.[30]

In KEYNOTE-189, patients with metastatic nonsquamous NSCLC who were treated with pembrolizumab plus chemotherapy vs chemotherapy alone had improved PFS and OS outcomes, regardless of PD-L1 expression, resulting in the regimen being established as a standard first-line treatment option.[7,31,32] In SKYSCRAPER-06, tiragolumab plus atezolizumab plus chemotherapy did not cross the prespecified boundary for statistical significance for superiority or inferiority for the primary end points of PFS and OS compared with placebo plus pembrolizumab plus chemotherapy (per the statistical analysis plan). Additionally, no PFS or OS benefit was observed in clinically relevant subgroups, including PD-L1 expression. As tiragolumab activity is mediated through effects on myeloid and T-regulatory cells, it is possible that concurrent chemotherapy may have reduced the activity of tiragolumab via toxic effects on key myeloid cells[21]; however, data from other studies investigating combination anti-PD-L1/PD-1 plus anti-TIGIT antibodies in advanced NSCLC, without concurrent chemotherapy, have not shown any meaningful improvement in clinical benefit either.[27-29,33,34] The combined use of anti-PD-L1/PD-1 plus anti-TIGIT antibodies, with or without chemotherapy, have yielded inconsistent results so far in advanced NSCLC, with clinical activity seen in phase 2 trials yet to be translated into a PFS or OS benefit in phase 3 trials.[23,27-29,33-38] These data highlight the complex interplay of factors that influence the efficacy of combination regimens and the challenges in generating novel treatment regimens to help improve outcomes for patients.

At present, there is no validated predictive biomarker to guide patient selection for anti-TIGIT therapy. Mechanistically, TIGIT suppresses immune activation by competing with CD226 for binding to its shared ligand, CD155.[14,15] In NSCLC, CD226 is frequently downregulated, potentially disrupting costimulatory signaling even when TIGIT is inhibited.[39] This functional imbalance between inhibitory and activating signals may prevent sufficient T-cell or NK-cell activation, representing a key barrier to the success of anti-TIGIT strategies.[14,15,39] Furthermore, checkpoint blockade is believed to be more effective in tumors with an inflamed tumor microenvironment, characterized by abundant T-cell infiltration and preexisting immune activation (ie, high PD-L1 expression).[40-42] However, the presence of exhausted T cells does not necessarily indicate functional CD226 signaling, even among tumors with high PD-L1 expression, which may help explain the limited synergy observed with anti-TIGIT and anti-PD-L1/PD-1 antibodies.[13,43] More clinical data are needed to identify specific modulators within the tumor microenvironment that influence therapeutic response.

Overall, the safety profile of tiragolumab plus atezolizumab plus chemotherapy was generally consistent with that of placebo plus pembrolizumab plus chemotherapy. While the incidence of grade 5 AEs was higher in the tiragolumab-containing group, the rates of treatment-related grade 5 events were similar. Consistent with the addition of a second immune checkpoint inhibitor, a higher frequency of imAEs was reported, primarily driven by immune-mediated rash and infusion-related reactions. No new or unexpected safety signals were identified in either treatment group.

Limitations

Limitations of this study include the adaptive phase 2/3 study design, meaning that the trial was essentially a phase 3 trial with an early futility interim analysis. Although the phase 2 part of the study allowed preliminary safety and efficacy to be assessed by the IDMC, no formal hypothesis testing was conducted, analyses were descriptive, and a nonbinding interim analysis was conducted to expand the study to phase 3.

Conclusions

In the phase 3 SKYSCRAPER-06 randomized clinical trial, the primary end points of investigator-assessed PFS and OS were not met, with tiragolumab plus atezolizumab plus chemotherapy demonstrating no PFS or OS benefit over pembrolizumab plus chemotherapy in patients with advanced nonsquamous NSCLC.

ARTICLE INFORMATION

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