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Anti-TIGIT Antibody Tiragolumab Alone or With Atezolizumab in Patients With Advanced Solid Tumors
A Phase 1a/1b Nonrandomized Controlled Trial

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IMPORTANCE Inhibition of the T-cell immunoreceptor with Ig and ITIM domains (TIGIT)/poliovirus receptor pathway may amplify the antitumor immune response of atezolizumab in programmed death ligand 1–selected tumors.

OBJECTIVE To evaluate the safety and antitumor activity of the anti-TIGIT antibody tiragolumab and its combination with atezolizumab in patients with advanced solid tumors.

DESIGN, SETTING, AND PARTICIPANTS The GO30103 open-label, first-in-human phase 1a/1b dose-escalation and dose-expansion nonrandomized controlled trial was conducted at 13 sites in 6 countries (Australia, Canada, France, Korea, Spain, and the US). The start dates were May 23, 2016, for phase 1a and October 11, 2016, for phase 1b. Patients were aged 18 years or older with measurable disease at baseline. The clinical cutoff date was October 1, 2021. Data analysis was performed on January 24, 2022.

INTERVENTIONS Patients received fixed-dose intravenous tiragolumab on day 1 of each 21-day cycle (2 mg escalating to 1200 mg) in phase 1a, plus fixed-dose intravenous atezolizumab (1200 mg every 3 weeks) in phase 1b. Patients were treated until disease progression, loss of clinical benefit, or development of unacceptable toxicity.

MAIN OUTCOMES AND MEASURES The primary end points included the safety, tolerability, and recommended phase 2 dose (RP2D) of tiragolumab or combination tiragolumab plus atezolizumab. The secondary end point included the investigator-assessed objective response rate (ORR). Counts and percentages are used for categorical variables, and medians and ranges are used for continuous variables.

RESULTS Among the phase 1a (n = 24) and 1b (n = 49) dose-escalation cohorts, the median age was 60 (range, 40-77) and 54 (range, 25-81) years, respectively. More than half of patients were women (14 of 24 [58%] and 25 of 49 [51%]), and more than a third (10 [42%] and 18 [37%]) had received 4 or more prior cancer therapies. No dose-limiting toxicities occurred, and the maximum tolerated dose of tiragolumab was not reached (NR). The most frequent treatment-related adverse events (AEs) were fatigue (5 of 24 [21%]) in phase 1a and pruritus (5 of 49 [10%]) in phase 1b; the majority of AEs were grade 1 or 2. Immune-mediated AEs occurred in 4 of 24 (17%) and 29 of 49 (59%) patients during phases 1a and 1b, respectively (primarily grade 1 or 2). The RP2D of tiragolumab was 600 mg intravenously every 3 weeks, which was tested in phase 1b dose expansion. The confirmed ORR was 0% during phase 1a, with evidence of antitumor activity in 6% of patients (n = 3) during phase 1b. The safety profile of combination tiragolumab plus atezolizumab in phase 1b was similar in the dose-escalation and dose-expansion cohorts. The confirmed ORR was 46% (6 of 13) in the non–small cell lung cancer (NSCLC) cohort (median duration of response [DOR], NR) and 28% (5 of 18) in the esophageal cancer (EC) cohort (median DOR, 15.2 [95% CI, 7.0 to NR] months).

CONCLUSIONS AND RELEVANCE In this nonrandomized controlled trial, tiragolumab was well tolerated with or without atezolizumab; no new safety signals were observed. Preliminary antitumor activity was demonstrated for the combination regimen in patients with cancer immunotherapy–naive metastatic NSCLC or EC.

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Supplemental content

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A number of immunotherapies, including cytotoxic T-lymphocyte-associated protein-4, programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1) inhibitors, are approved for the treatment of solid and hematologic tumors such as advanced non-small cell lung cancer (NSCLC), renal cell cancer, and melanoma.[1-3] However, their use can be limited by lack of response, resistance, and tumor heterogeneity.[2,4] Novel therapies or combination regimens are needed to induce complete or durable antitumor responses in most cancers.

The T-cell immunoreceptor with Ig and ITIM domains (TIGIT) is a novel inhibitory immune checkpoint expressed on activated T cells and natural killer cells in multiple cancers that binds with high affinity to CD155 (the poliovirus receptor [PVR]).[5-8] The TIGIT checkpoint is overexpressed in the microenvironment of many human tumors, is coexpressed with PD-1 (especially in tumor-infiltrating lymphocytes [TILs]), and is associated with impaired T-cell and natural killer cell function as well as antitumor immunity.[6-8] Both TIGIT and PD-1 converge to negatively regulate CD226, with TIGIT preventing CD226 homodimerization and PD-1 mediating CD226 dephosphorylation. In previous studies, inhibition of both TIGIT and PD-1 led to a mechanistic synergy and effective antitumor immune response in preclinical models.[8,9]

Tiragolumab is an anti-TIGIT monoclonal antibody with an intact Fc region that blocks the binding of TIGIT to PVR. In mouse tumor models,[9] combined inhibition of the TIGIT/PVR and PD-L1/PD-1 pathways improved antitumor activity compared with blockade of either pathway alone.[6] Simultaneous inhibition of both pathways also increased in vitro proliferation, cytokine production, and antitumor function of $CD8^+$ TILs from patients with NSCLC[6] or melanoma.[10] Tiragolumab was well tolerated in cynomolgus monkeys when administered by weekly intravenous bolus injection at doses up to 100 mg/kg for 26 weeks or less; exposures at this dose level in repeat-dose studies were up to or more than 25 and 15 times higher than the mean clinical exposure at 600 and 1200 mg, respectively.

We hypothesized that inhibition of TIGIT/PVR might potentiate the antitumor immune response of PD-L1 inhibitor atezolizumab in patients with PD-L1–selected tumors and enhance the clinical benefit associated with immune checkpoint blockade. Here, we report the results of a first-in-human phase 1a/1b study (GO30103) evaluating the safety, pharmacokinetics (PK), and preliminary antitumor activity of tiragolumab administered alone (phase 1a) or with atezolizumab (phase 1b) in patients with advanced solid tumors. We also describe results from phase 1b dose-expansion cohorts in cancer immunotherapy (CIT)–naive patients with metastatic NSCLC or metastatic esophageal cancer (EC).

Key Points

Question Can inhibition of the TIGIT/poliovirus receptor pathway by tiragolumab potentiate the antitumor immune response of atezolizumab in patients with advanced solid tumors?

Findings In this nonrandomized controlled trial including 73 patients, no dose-limiting toxicities occurred in phase 1a or 1b and the recommended phase 2 dosage of tiragolumab was identified as 600 mg given once every 3 weeks. There were no objective responses with single-agent tiragolumab, but some patients experienced tumor shrinkage; combination tiragolumab plus atezolizumab showed promising activity in patients with immunotherapy-naive non–small cell lung cancer and esophageal cancer.

Meaning These findings support the continued investigation of dual TIGIT/programmed death ligand 1 inhibition in patients with advanced solid tumors.

Methods

Study Design and Patients

GO30103 was a multicenter, open-label, dose-escalation and dose-expansion phase 1a/1b nonrandomized controlled trial (eFigure 1 in Supplement 2) of tiragolumab and its combination with atezolizumab administered to patients with advanced solid tumors for whom standard treatment did not exist or was ineffective (NCT02794571). The trial protocol (Supplement 1) was approved by the institutional review board or ethics committee at each participating center and complied with good clinical practice guidelines, the principles of the Declaration of Helsinki,[11] and local laws. All patients provided written informed consent. The study followed the Transparent Reporting of Evaluations With Nonrandomized Designs (TREND) reporting guideline.

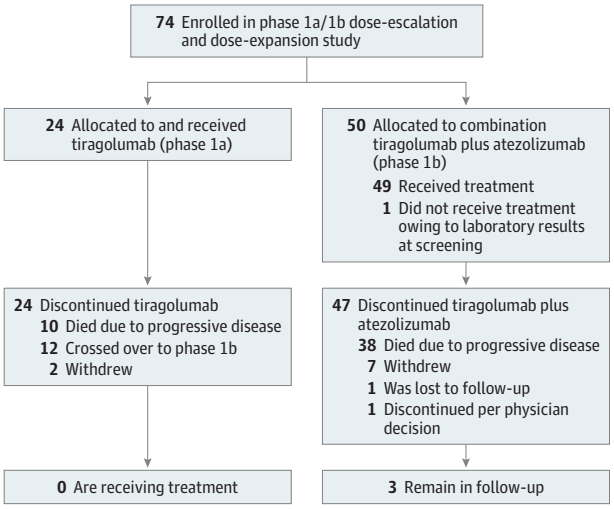
Patients were enrolled at 13 sites across 6 countries (Australia, Canada, France, Korea, Spain, and the US). The start dates were May 23, 2016, for phase 1a and October 11, 2016, for phase 1b. Eligible patients were aged 18 years or older, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. When permitted per country regulations, race and ethnicity was self-reported as Asian, Black or African American, White, or unknown. These data were available for all countries except France, for which race was reported as unknown for all patients. Patients were excluded if they had received prior anti-TIGIT therapy, anticancer therapy within 3 weeks, or palliative radiation within 2 weeks of study treatment; had discontinued immunotherapy due to immune-mediated adverse events (AEs; grade ≥3); had active or untreated central nervous system metastases; or had a history of autoimmune disease (eMethods in Supplement 2). The clinical cutoff date was October 1, 2021.

For the phase 1b dose-expansion cohorts reported herein, patients must not have received prior CIT. Patients in the NSCLC cohort had to have PD-L1–positive tumors (tumor cell or immune cell expression ≥1%) as determined with the VENTANA PD-L1 SP142 and/or SP263 immunohistochemistry assays (Roche Diagnostics). The EC cohort included all-comers, regardless of PD-L1 status, as immunotherapy has demonstrated antitumor activity in unselected patients with EC.[12] These 2 cohorts were summarized separately due to differing histology, organ of origin, prior treatments, prognoses, and available therapies.

Dose Escalation and Dose Expansion

Cohorts of 3 to 6 patients were treated at escalating doses of tiragolumab alone (phase 1a) or with a fixed dose of atezolizumab (phase 1b) to determine the maximum tolerated dose and/or

Figure 1. Study Flow Diagram



the maximum administered dose. In phase 1a dose escalation, tiragolumab was administered intravenously as a fixed dose on day 1 of each 21-day cycle, starting at 2 mg (based on preclinical in vivo data) and escalating to 8, 30, 100, 400, 600, and 1200 mg. Dose-limiting toxicities (DLTs) were assessed during cycle 1 (eMethods in Supplement 2).

Phase 1b was activated after DLT and safety evaluation of at least 2 dose levels of single-agent tiragolumab in phase 1a (2 and 8 mg were deemed safe). In phase 1b dose escalation, tiragolumab was administered intravenously at a fixed dose on day 1 of each 21-day cycle (starting at 2 mg and escalating to 8, 30, 100, 400, 600, and 1200 mg) in combination with atezolizumab (1200 mg intravenously) every 3 weeks. Tiragolumab was administered before atezolizumab. In the phase 1b dose-expansion cohorts, we evaluated tiragolumab (400 and 600 mg) administered every 3 weeks in combination with atezolizumab (1200 mg) every 3 weeks. The dose-expansion cohort was still enrolling when the recommended phase 2 dose (RP2D) was identified as 600 mg in the dose-escalation cohort. Thus, some patients were enrolled at the 400-mg dose level in the dose-expansion cohort.

Patients with progressive disease in phase 1a could cross over to phase 1b (eMethods in Supplement 2). All patients received tiragolumab or tiragolumab plus atezolizumab until death, unacceptable toxicity, loss of benefit, or patient or investigator decision to discontinue. Patients could continue study treatment in phase 1a/1b after they met RECIST criteria, version 1.1, for progressive disease.

Outcomes

In phase 1a, the primary objective was to assess the safety, tolerability, and RP2D of single-agent tiragolumab every 3 weeks. In phase 1b, the primary objective was to assess the safety, tolerability, and RP2D of tiragolumab every 3 weeks plus atezolizumab every 3 weeks. Secondary objectives were to assess the PK and preliminary antitumor activity of tiragolumab and combination tiragolumab plus atezolizumab. The PK data will be published separately. No survival analyses were performed.

Assessments

Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. An internal monitoring committee periodically reviewed the safety data. Tumor assessments were performed after cycles 2, 4, 6, and 8, and every 4 cycles thereafter, or as indicated. Response was determined by investigators using RECIST criteria, version 1.1. The objective response rate (ORR) was determined in patients with measurable disease at baseline and defined as complete response or partial response, confirmed by repeat assessment after 4 or more weeks. The disease control rate (DCR) was defined as the proportion of patients achieving complete response, partial response, or stable disease.

Statistical Analysis

Sample size determinations are described in the eMethods in Supplement 2. Summaries of study conduct and activity analyses were performed for all enrolled patients in phases 1a and 1b. Safety analyses were performed for the safety-evaluable population, which comprised all patients who received any study drug. Safety was assessed through DLTs and AEs. Patients with missing baseline or no response assessments were classified as nonresponders. We present data separately for the phase 1a dose-escalation (single-agent tiragolumab), phase 1b dose-escalation (tiragolumab plus atezolizumab), and phase 1b dose-expansion (tiragolumab plus atezolizumab) cohorts. Data analysis was performed on January 24, 2022, using SAS software, version 9.3 (SAS Institute).

Results

Phase 1a/1b Dose Escalation

Patients

A total of 24 patients (median age, 60 [range, 40-77] years) were treated in phase 1a dose escalation and 49 (median age, 54.0 [range, 25-81] years) were treated in phase 1b dose escalation (**Figure 1** and **Table 1**). The phase 1a cohort comprised 14 women (58%) and 10 men (42%); 17 patients (71%) had an ECOG performance status of 1, and 10 (42%) had received 4 or more prior cancer therapies (2 [8%] had received prior immunotherapy) (Table 1). The phase 1b cohort comprised 25 women (51%) and 24 men (49%); 36 patients (74%) had an ECOG performance status of 1, and 18 (37%) had received 4 or more prior cancer therapies (15 [31%] had received prior immunotherapy). Patients in the phase 1a and phase 1b dose-escalation cohorts self-reported their race and ethnicity as Asian (7 of 24 [29%] and 13 of 49 [27%], respectively), Black or African American (1 [4%] and 3 [6%], respectively), White (15 [63%] and 30 [61%], respectively), or unknown (1 [4%] and 3 [6%], respectively) (Table 1).

At the cutoff date (October 1, 2021), 12 patients (50%) had discontinued treatment in phase 1a and 12 (50%) had crossed over to phase 1b. Data for the phase 1b dose-escalation cohort included patients who crossed over from phase 1a. Three patients (6%) in phase 1b remain in follow-up (Figure 1). The primary reason for discontinuation was death due to progressive disease (10 of 24 [42%] in phase 1a and 38 of 49 [76%] in phase 1b). The number of patients evaluable for safety and

antitumor activity was 24 and 23, respectively, in phase 1a and 49 and 44, respectively, in phase 1b (eTable 1 in Supplement 2).

Safety

No DLTs occurred in phase 1a/1b, and the maximum tolerated dose was not reached (NR). The maximum administered dosage was tiragolumab (1200 mg intravenously) every 3 weeks as monotherapy or in combination with atezolizumab (1200 mg) every 3 weeks.

The most common AEs were fatigue in phase 1a (9 of 24 [38%]) and anemia in phase 1b (15 of 49 [31%]) (eFigure 2 in Supplement 2). The majority of treatment-related AEs were grade 1 or 2, and the most frequent in phases 1a and 1b included fatigue (5 of 24 [21%] and 4 of 49 [8%]), pruritus (3 [13%] and 5 [10%]), and arthralgia (2 [8%] and 3 [6%]) respectively (eFigure 2 in Supplement 2). A similar proportion of patients experienced treatment-related AEs of grade 3 or greater in phase 1a (1 patient [4%] with increased grade 3 blood creatinine) and phase 1b (2 patients [4%]: 1 with grade 3 hyperlipasemia and 1 with decreased grade 3 lymphocyte count; **Table 2**). There were no grade 5 AEs related to tiragolumab and/or atezolizumab during dose escalation. Serious AEs occurred in 4 of 24 patients (17%) during phase 1a and 24 of 49 patients (49%) during phase 1b. Small intestinal obstruction was the most frequent serious AE in phase 1a (2 of 24 [8%]), whereas pulmonary embolism was the most frequent serious AE in phase 1b (4 of 49 [8%]). Two patients in phase 1b experienced grade 5 pulmonary embolism but this was not considered to be related to tiragolumab or atezolizumab.

Immune-mediated AEs occurred in 4 of 24 patients (17%) during phase 1a and in 29 of 49 patients (59%) during phase 1b. Among these were rash (2 of 24 [8%] vs 14 of 49 [29%]) and hepatitis (including clinical diagnosis and laboratory abnormalities: 1 [4%] vs 10 [20%]; Table 2), which were primarily grade 1 or 2. There were no grade 4 or 5 immune-mediated AEs associated with tiragolumab and/or atezolizumab in dose escalation during phase 1a/1b. Adverse events led to the withdrawal of 2 patients from phase 1b only (Table 2), due to gastrointestinal complaints related to clinical progression and pemphigoid. No additional safety concerns were identified in the 12 patients who crossed over from phase 1a.

The RP2D of tiragolumab, as monotherapy and with atezolizumab (1200 mg intravenously every 3 weeks), was identified as 600 mg intravenously every 3 weeks. This dosage was based on complete and sustained peripheral receptor occupancy at doses of 30 mg or greater and activity at doses of 400 to 600 mg in phase 1b (eFigure 3 in Supplement 2). The RP2D of tiragolumab plus atezolizumab was tested in phase 1b dose expansion; the PK profile of tiragolumab was unaltered in the presence of atezolizumab.

Antitumor Activity

There were no objective responses in phase 1a, but 4 patients experienced prolonged stable disease with tumor shrinkage (**Figure 2**A and B). One patient had metastatic microsatellite instability-high colon cancer that had progressed on 2 prior lines of chemotherapy (best response progressive disease). This patient was enrolled in phase 1a, received tiragolumab (1200 mg), and had prolonged stable disease with a decline in the carcinoembryonic antigen tumor marker over 5 months. This patient crossed over into phase 1b, received combination tiragolumab

Table 1. Baseline Demographic and Clinical Characteristics in the Safety-Evaluable Population

Characteristic	Dose-escalation cohort[a]	
	Phase 1a tiragolumab (n = 24)	Phase 1b tiragolumab plus atezolizumab (n = 49)
Age, y, median (range)	60 (40-77)	54 (25-81)
Sex		
Men	10 (42)	24 (49)
Women	14 (58)	25 (51)
ECOG performance status at screening		
0	7 (29)	13 (27)
1	17 (71)	36 (74)
Race and ethnicity		
Asian	7 (29)	13 (27)
Black or African American	1 (4)	3 (6)
White	15 (63)	30 (61)
Unknown	1 (4)	3 (6)
Prior cancer therapies		
1	2 (8)	7 (14)
2	6 (25)	14 (29)
3	6 (25)	10 (20)
≥4	10 (42)	18 (37)
Prior immunotherapy[b]	2 (8)	15 (31)
Primary cancer type		
Colon	4 (17)	8 (16)
Rectum	4 (17)	4 (8)
Breast	2 (8)	9 (19)
NSCLC	0	6 (12)
HNSCC	0	4 (8)
Ovarian	1 (4)	3 (6)
Esophagus	0	2 (4)
Other	13 (54)[c]	13 (27)[d]
PD-L1 status (per VENTANA central test)		
SP263 TC or IC ≥1	Not reported[e]	Not reported[e]
SP142 TC or IC ≥1	10 (42)	29 (59)
Country of enrollment[f]		
Australia	2 (8)	1 (2)
Canada	2 (8)	10 (20)
France	0	1 (2)
Korea	7 (29)	14 (28)
Spain	0	1 (2)
US	13 (54)	23 (46)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HNSCC, head and neck squamous cell carcinoma; IC, immune cell; NSCLC, non–small cell lung cancer; PD-L1, programmed death ligand 1; TC, tumor cell.

[a] Unless indicated otherwise, values are presented as No. (%) of patients.

[b] Immune checkpoint inhibitors.

[c] Includes endometrial (n = 2), melanoma (n = 2), and appendiceal, bladder, cervical, cholangiocarcinoma, kidney, neuroendocrine, peritoneal, sarcoma, and stomach (n = 1 each) cancer types.

[d] Includes sarcoma (n = 4), stomach (n = 2), melanoma (n = 2), and anal, appendiceal, bladder, Merkel cell, and peritoneal (n = 1 each) cancer types.

[e] The majority of patients in dose escalation in phases 1a and 1b were selected using the SP142 assay.

[f] Country of enrollment data are provided for all 50 patients allocated to tiragolumab plus atezolizumab in phase 1b.

Table 2. Safety Summary

AE type	Dose-escalation cohort[a]	
	Phase 1a tiragolumab (n = 24)	Phase 1b tiragolumab plus atezolizumab (n = 49)
Any AE	24 (100)	46 (94)
Leading to any study drug interruption	4 (17)	14 (29)
Leading to any study drug withdrawal	0	2 (4)
Grade 3-5 AE	5 (21)	27 (55)
Grade 3 treatment related	1 (4)[b]	2 (4)[c]
Serious AE	4 (17)	24 (49)
Grade 3-4	2 (8)	17 (35)
Grade 5	0	2 (4)[d]
Any immune-mediated AE[e]	4 (17)	29 (59)
Grade 3-5[f]	0	2 (4)
Infusion-related reaction	2 (8)	4 (8)
Rash	2 (8)	14 (29)
Hepatitis (diagnosis or laboratory abnormalities)	1 (4)	10 (20)
Pancreatitis (laboratory abnormality)	1 (4)	1 (2)
Hyperthyroidism	0	4 (8)
Hypothyroidism	0	3 (6)
Anemia	0	1 (2)

Abbreviation: AE, adverse event.

[a] Values are presented as No. (%) of patients.

[b] Blood creatinine increased (n = 1).

[c] Hyperlipasemia (n = 1) and lymphocyte count decreased (n = 1).

[d] Pulmonary embolism (n = 2) not considered related to tiragolumab or atezolizumab treatment.

[e] Clinical diagnosis unless specified.

[f] No grade 5 AEs or immune-mediated AEs were associated with tiragolumab or tiragolumab plus atezolizumab in phase 1a or 1b.

(600 mg) and atezolizumab (1200 mg), and experienced a prolonged partial response (>45 months).

The best ORR in phase 1b was 6% (n = 3), including 1 complete response and 1 partial response in patients with NSCLC, 1 partial response in a patient with head and neck squamous cell carcinoma, and 1 in a patient with microsatellite instability-high colon cancer (Figure 2C). The median duration of treatment in phase 1b was 2 (range, 0-49) months (Figure 2D). These findings led to the initiation of the phase 1b dose expansion in CIT-naive patients.

Phase 1b Dose Expansion

Baseline characteristics of patients with CIT-naive metastatic NSCLC (n = 13) or EC (n = 21) who received tiragolumab plus atezolizumab in the expansion cohorts are shown in eTable 2 in Supplement 2. The safety profile of combination treatment in the dose-expansion cohort (eTable 3 in Supplement 2) was similar to the phase 1b dose-escalation cohort. The most common immune-mediated AE was rash (7 patients [54%] with NSCLC and 8 [38%] with EC). The majority of treatment-related AEs were grade 1 or 2. There were no grade 5 AEs or immune-mediated AEs related to tiragolumab and/or atezolizumab.

In the metastatic NSCLC cohort, the confirmed ORR was 46% (6 of 13), with a DCR of 77% (10 of 13). The median duration of response (DOR) was 24.2 (95% CI, 9.7 to NR) months (**Figure 3**A and B). Of the 6 responders, all had tumors with PD-L1 tumor cell or immune cell expression of 1% or greater per the VENTANA SP263 assay. Four patients had a response to tiragolumab plus atezolizumab that lasted longer than 12 months (2 complete responses and 2 partial responses).

In the metastatic EC cohort, the confirmed ORR was 28% (5 of 18) and the DCR was 50% (9 of 18). The median DOR was 15.2 (95% CI, 7.0 to NR) months (Figure 3C and D). Reponses were observed in patients with tumors of squamous or adenocarcinoma histology. One patient with metastatic esophageal adenocarcinoma had received multiple prior therapies (first-line 5-fluorouracil, leucovorin, and oxaliplatin [mFOLFOX6]) with stable disease as best response before progressive disease, then second-line paclitaxel plus ramucirumab with progressive disease as best response. This patient was enrolled in the expansion cohort and had a partial response at the first tumor assessment, which continued for 2 years (eFigure 4 in Supplement 2). A summary of responses in the phase 1b expansion cohort is shown in eTable 4 in Supplement 2. Exploratory analysis of antitumor activity by PD-L1 expression was limited by the low patient numbers for each indication, and no meaningful association with response was observed.

Discussion

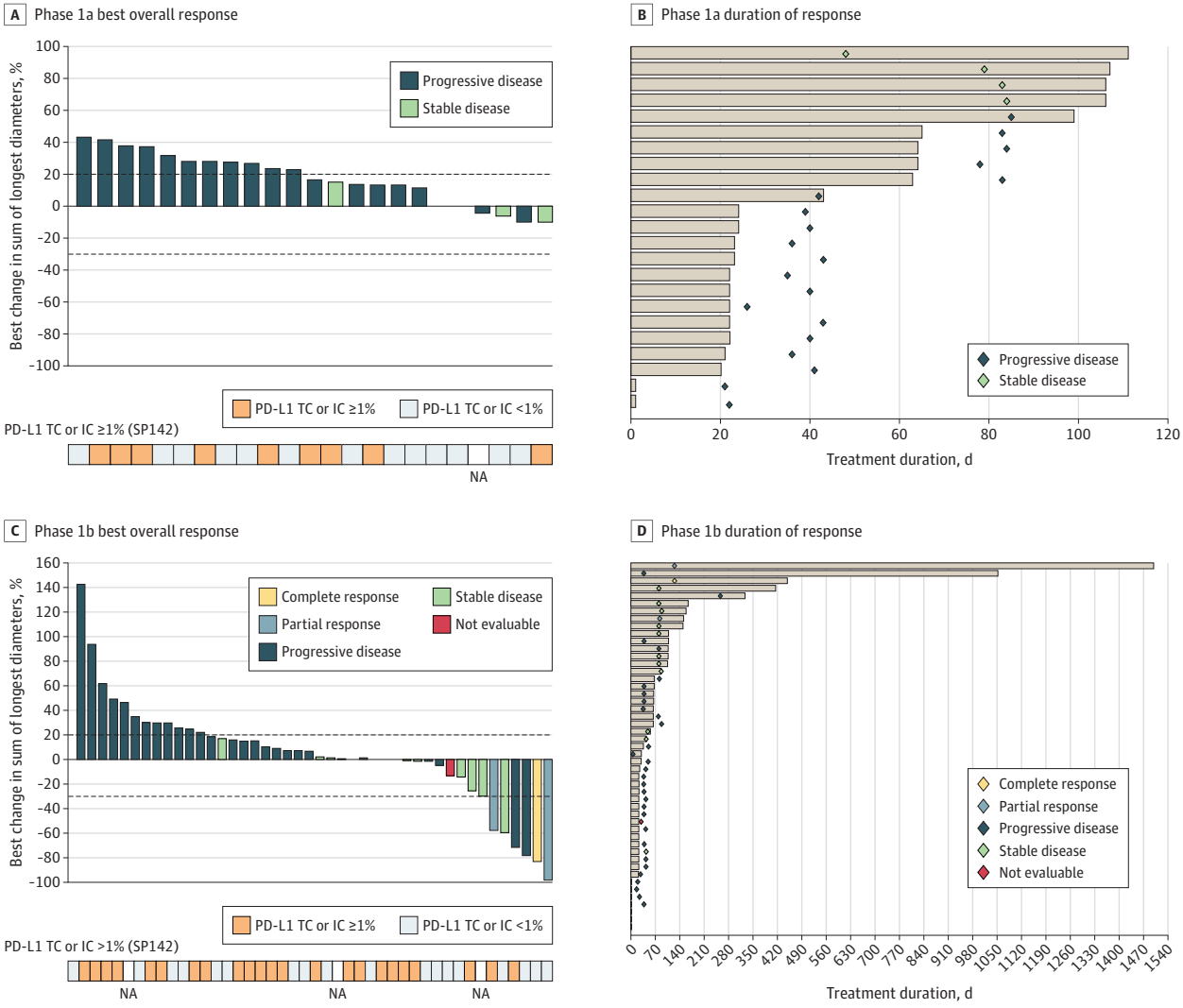
Inhibition of TIGIT by tiragolumab in combination with atezolizumab represents a treatment strategy that may amplify the magnitude and quality of tumor-specific T-cell responses and provide meaningful antitumor activity. GO30103 is a first-in-human study investigating tiragolumab and tiragolumab plus atezolizumab in advanced solid tumors.

Based on the proposed mechanism of action of tiragolumab, possible risks associated with TIGIT/PVR pathway inhibition include heightened immune responses and increased frequency or severity of immune-mediated AEs. However, tiragolumab was well tolerated as monotherapy and in combination with atezolizumab. There were no DLTs and the maximum tolerated dose was NR in phase 1a/1b; the maximum administered dose was determined as 1200 mg intravenously every 3 weeks. The RP2D of tiragolumab with or without atezolizumab (1200 mg intravenously) every 3 weeks was identified as 600 mg intravenously every 3 weeks.

Most treatment-related AEs with tiragolumab were grade 1 or 2 in phases 1a and 1b. The combination regimen was also well tolerated in the phase 1b dose-expansion cohort. As expected, immune-mediated AEs were more common during phase 1b than phase 1a but were mainly grade 1 or 2. No grade 4 or 5 immune-mediated AEs associated with tiragolumab and/or atezolizumab were reported in phase 1a/1b dose escalation. In addition, AEs leading to study drug discontinuation occurred in only 2 patients in phase 1b. Overall, the safety profile of tiragolumab appears similar to other checkpoint inhibitors, and no new safety signals were detected.[13]

Although we did not observe objective responses with single-agent tiragolumab in phase 1a, some patients experienced tumor shrinkage. Most of these patients had cancers

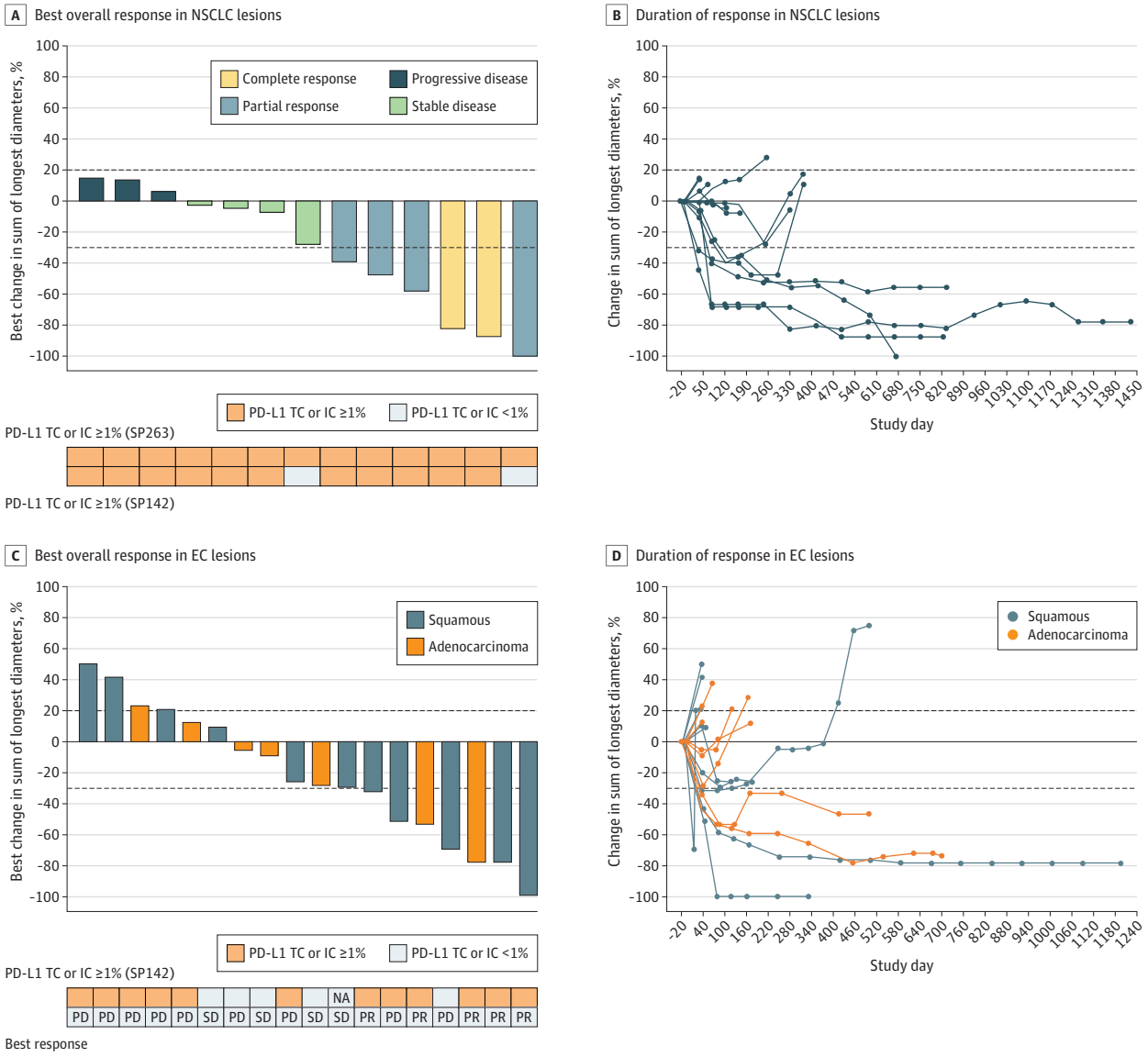
Figure 2. Waterfall and Swimmer Plots of Best Response and Duration of Response in Individual Patients



Waterfall plots of best response and PD-L1 status (A and C) and swimmer plots of duration of response (B and D) in individual patients. A and B, Phase 1a dose escalation of single-agent tiragolumab. Of the 24 patients, 23 had evaluable CT scans; 1 patient discontinued treatment without tumor assessment, but progressive disease was observed during follow-up (>100 days after discontinuation). C and D, Phase 1b dose escalation of combination tiragolumab plus atezolizumab. Of the 49 patients, 44 had evaluable CT scans; 5 patients discontinued treatment due to progressive disease in cycle 1, including 1 with a newly diagnosed brain metastasis. One patient (in C) had a postbaseline assessment with stable disease per investigator on study day 29; because the assessment was done earlier than expected per protocol, it was labeled "not evaluable." The clinical cutoff date was October 1, 2021. In A and C, the dashed line at 20% indicates the progression of the disease; the dashed line at −30% indicates the partial response if other criteria were met (no new lesions, no nontarget lesion progression, and response was confirmed after 40 days from the start of treatment). Response was determined by investigators using RECIST (Response Evaluation Criteria in Solid Tumors), version 1.1. CT indicates computed tomography; IC, immune cell; NA, not available; PD-L1, programmed death ligand 1; TC, tumor cell.

not typically known to respond to immunotherapy, had PD-L1-negative tumors, or had received heavy pretreatment (some with immunotherapy). Tiragolumab plus atezolizumab demonstrated promising antitumor activity in phase 1b, mainly in patients with CIT-naive and/or PD-L1-positive solid tumors. In the metastatic NSCLC expansion cohort, the confirmed ORR was 46%, with several responses showing durability (median DOR, NR; response for 4 patients lasted >12 months). In the metastatic EC cohort, the confirmed ORR was 28% and durable responses occurred independent of PD-L1 status or histology (median DOR, 15.2 [95% CI, 7.0 to NR] months). Enrollment into the EC cohort took place before the availability of emergent data in this setting, but we hypothesized that TIGIT inhibition by tiragolumab may potentiate atezolizumab activity in EC. This was because PD-L1 overexpression has been reported in EC[14] of both squamous and adenocarcinoma histology, and checkpoint inhibitors have shown resulting activity. In addition, TIGIT is often expressed with PD-1 on TILs in cancers, including EC.[10,15] Our data, while limited, are supportive of PD-L1 as a potential biomarker for combination tiragolumab plus atezolizumab in EC.

Figure 3. Waterfall and Spider Plots of Best Response in Target Lesions in the Phase 1b Tiragolumab Plus Atezolizumab Expansion Cohort



Waterfall plots of best response and PD-L1 status (A and C) and spider plots of change in response over time (B and D) in individual patients with CIT-naive metastatic NSCLC (n = 13; A and B) and CIT-naive metastatic EC (n = 21; C and D). The clinical cutoff date was October 1, 2021. In A and C, the dashed line at 20% indicates the progression of the disease; the dashed line at −30% indicates the partial response if other criteria were met (no new lesions, no nontarget lesion progression, and response was confirmed after 40 days from the start of treatment). Response was determined by investigators using RECIST (Response Evaluation Criteria in Solid Tumors), version 1.1. CIT indicates cancer immunotherapy; EC, esophageal cancer; IC, immune cell; NA, not available; NSCLC, non–small cell lung cancer; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; SD, stable disease; TC, tumor cell.

Our findings are consistent with recent data from other phase 1 studies of combined anti-TIGIT and anti-PD-L1 therapy. Niu et al[16] reported preliminary antitumor activity of anti-TIGIT antibody vibostolimab with PD-1 inhibitor pembrolizumab in advanced solid tumors. The confirmed ORR in phase 1a (n = 76) was 0% with vibostolimab and 7% with vibostolimab-pembrolizumab. In phase 1b, the ORR was 26% and the median DOR was NR (range, 4.1-≥21.1 months) in patients (n = 39) with NSCLC naive to PD-L1/PD-1 inhibitors. In patients (n = 12) with tumors that had a PD-L1 tumor proportion score of 1% or greater, the ORR was 33%.[14] Treatment-related AEs occurred in 85% of patients, with serious treatment-related AEs in 10%. Mettu et al[17] also reported preliminary evidence of clinical benefit with anti-TIGIT antibody etigilimab (n = 23; phase 1a) combined with anti-PD-1 antibody nivolumab (n = 10; phase 1b) in locally advanced or metastatic solid tumors. The best response was stable disease (7 [30%]) in phase 1a and partial response (1 [10%]) in phase 1b; 1 patient had prolonged stable disease of almost 8 months. Six patients experienced treatment-related AEs of grade 3 or higher.[17]

Limitations

The results of this phase 1 study are limited by the small sample size for each tumor type and by the poor prognosis of the study population, with many patients having received prior immunotherapy. Objective responses seen in metastatic NSCLC and EC appeared to be at least similar to single-agent anti-PD-1 and anti-PD-L1 agents. Whether the responses are indeed higher than single-agent checkpoint inhibitors, along with the durability of response, will be examined in larger studies.

Conclusions

Based on the preliminary safety and antitumor activity of tiragolumab demonstrated in this nonrandomized controlled trial, combination tiragolumab plus atezolizumab is being further investigated in phase 2 (CITYSCAPE: NCT03563716) and phase 3 (SKYSCRAPER-01: NCT04294810) studies in advanced PD-L1-positive NSCLC and in phase 3 studies (SKYSCRAPER-07: NCT04543617; and SKYSCRAPER-08: NCT04540211) in metastatic EC. Additional data analyses, including prognostic markers, will be reported separately. Primary analysis of the CITYSCAPE study showed that tiragolumab plus atezolizumab produced a statistically significant and clinically meaningful improvement in ORR and prolonged progression-free survival in patients with NSCLC whose tumors showed high PD-L1 expression (≥50% tumor proportion score) relative to placebo plus atezolizumab.[18] These data support the continued investigation of dual TIGIT/PD-L1 inhibition in advanced solid tumors.

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