A Phase 1a/b Open-Label, Dose-Escalation Study of Etigilimab Alone or in Combination with Nivolumab in Patients with Locally Advanced or Metastatic Solid Tumors

Niharika B. Mettu[1], Susanna V. Ulahannan[2,3], Johanna C. Bendell[3], Ignacio Garrido-Laguna[4], John H. Strickler[1], Kathleen N. Moore[2], Robert Stagg[5], Ann M. Kapoun[5], Leonardo Faoro[5], and Sunil Sharma[6]

ABSTRACT

Purpose: TIGIT (T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain) is a co-inhibitory receptor of T-cell and natural killer cell activity. Targeting TIGIT with or without PD-1/PD-L1 checkpoint inhibition may enhance antitumor immunity.

Patients and Methods: This Phase 1a/b trial was a first-in-human, open-label, multicenter, dose-escalation and -expansion study in patients with locally advanced or metastatic solid tumors. Using 3 + 3 design, patients underwent 14-day treatment cycles with anti-TIGIT antibody etigilimab alone (Phase 1a; 0.3, 1.0, 3.0, 10.0, 20.0 mg/kg intravenously) or in combination with anti–PD-1 antibody nivolumab (Phase 1b; 3.0, 10.0, 20.0 mg/kg etigilimab and 240 mg nivolumab). Primary objective was safety and tolerability.

Results: Thirty-three patients were enrolled (Phase 1a, $n = 23$; Phase 1b, $n = 10$). There were no dose-limiting toxicities (DLT). MTD for single and combination therapy was not determined; maximum administered dose was 20 mg/kg. The most commonly reported adverse events (AE) were rash (43.5%), nausea (34.8%), and fatigue (30.4%) in Phase 1a and decreased appetite (50.0%), nausea (50.0%), and rash (40%) in Phase 1b. Six patients experienced Grade ≥3 treatment-related AEs. In Phase 1a, 7 patients (30.0%) had stable disease. In Phase 1b, 1 patient had a partial response; 1 patient had prolonged stable disease of nearly 8 months. Median progression-free survival was 56.0 days (Phase 1a) and 57.5 days (Phase 1b). Biomarker correlative analyses demonstrated evidence of clear dose-dependent target engagement by etigilimab.

Conclusions: Etigilimab had an acceptable safety profile with preliminary evidence of clinical benefit alone and in combination with nivolumab and warrants further investigation in clinical trials.

Introduction

T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) is emerging as a novel target in the field of cancer immunotherapy (1). TIGIT (also called WUCAM, Vstm3, VSIG9) is a receptor of the immunoglobulin (Ig) superfamily that participates in a complex regulatory network involving multiple inhibitory receptors (CD96/TACTILE and CD112R/PVRIG), a competing costimulatory receptor (DNAM-1/CD226), and multiple ligands [CD155 (PVR/NECL-5), CD112 (Nectin-2/PVRL2)]. This complex network plays a critical role in mediating adaptive and innate immunity (2, 3) in an antitumor setting. TIGIT is expressed by activated CD8 and CD4 T cells, natural killer (NK) cells, and follicular T helper cells (4, 5), and is highly expressed on T-regulatory cells (Tregs; refs. 4, 6). TIGIT mediates an inhibitory effect on T cells and NK cells and increases the suppressive capacity of Treg cells (5, 7–10), thereby promoting an immunosuppressive environment that serves to dampen antitumor immunity (11–14).

In humans, expression of TIGIT and CD155 correlates with poor clinical outcomes in various cancers. For example, high levels of CD155 are associated with poor prognosis in melanoma, cervical cancer, and pancreatic cancer, cholangiocarcinoma, small cell lung cancer, and lung adenocarcinoma (15–20). Furthermore, expression of TIGIT on tumor-infiltrating lymphocytes (TIL) of patients with melanoma, or $CD8^+$ T cells of patients with gastric cancer, has been associated with development of metastatic disease and poor survival (14, 21). In addition, high TIGIT expression on tumor NK cells in endometrial cancer is associated with disease severity, while TIGIT expression on $CD8^+$ T cells correlates strongly with acute myelogenous leukemia relapse post-transplantation (22, 23). Mice deficient in TIGIT have significantly delayed tumor growth in two different tumor models, suggesting that TIGIT dampens antitumor responses (1, 13).

Preclinical data with a murine antibody functionally comparable with anti-TIGIT antibody etigilimab showed selective depletion of Tregs and activation of CD8 T cells, TILs, and NK cells (24). This antibody suppressed tumor growth in multiple syngeneic tumor models, including colon (CT26), breast (4T1), melanoma (B16F10), and kidney (RENCA), and inhibited growth of patient-derived melanoma in mice reconstituted with human hematopoietic stem cells,

[1]Division of Medical Oncology, Duke University Medical Center, Durham, North Carolina. [2]Department of Internal Medicine, Hematology-Oncology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma. [3]Drug Development Unit, Sarah Cannon Research Institute at Tennessee Oncology, Nashville, Tennessee. [4]Department of Internal Medicine, Utah School of Medicine, Salt Lake City, Utah. [5]OncoMed Pharmaceuticals/Mereo BioPharma, Redwood City, California. [6]Hematology and Medical Oncology, Honor Health, Scottsdale, Arizona.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Current address for L. Faoro: Exelixis, Inc., Alameda, California.

Corresponding Author: Niharika B. Mettu, Duke University Medical Center, DUMC Box 3505, Durham, NC 27710. Phone: 919-668-1861; Fax: 919-613-5228; E-mail: mettu002@mc.duke.edu

Clin Cancer Res 2022;28:882–92

doi: 10.1158/1078-0432.CCR-21-2780

Translational Relevance

T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) is emerging as a novel target in the field of cancer immunotherapy. This Phase 1a/b study evaluated the safety, tolerability, and preliminary efficacy of the novel anti-TIGIT antibody etigilimab alone (Phase 1a) and in combination with the anti–PD-1 inhibitor nivolumab (Phase 1b) in patients with refractory solid tumors. Treatment with etigilimab was well tolerated, with no dose-limiting toxicities reported in either phase of the study. Seven (30.4%) patients had stable disease in Phase 1a; in Phase 1b, 1 (10%) patient had stable disease and 1 (10%) had a partial response. This first-in-human clinical trial lays the foundation for evaluating etigilimab in combination with anti–PD-1 therapies in patients with solid tumors.

providing mechanistic insights into the activity of etigilimab. Thus, inhibition of TIGIT activity in patients with solid tumors may result in activation of the immune system and promote antitumor activity. Etigilimab is a humanized IgG1 monoclonal antibody that binds TIGIT, blocks its interaction with CD155, and inhibits downstream signaling. The IgG1 backbone of etigilimab activates antibody-dependent cellular cytotoxicity (ADCC); this backbone may thus have advantages over other anti-TIGIT antibodies in development that lack ADCC (25, 26). It has been proposed that binding of anti-TIGIT IgG backbones to Fc receptors on myeloid cells brings these cells in close proximity to the tumor, where they release tumor cell–killing substances (such as cytokines, granzymes, and perforins), highlighting a unique mechanism associated with enhanced antitumor activity of IgG1 antibodies (26).

In numerous murine (27) and human tumors, TIGIT is co-expressed with PD-1 on CD8 T cells (14, 28) suggesting co-involvement of multiple immune checkpoint inhibitors (ICI) in tumor resistance mechanisms. Supporting this, multiple lines of evidence have demonstrated synergy between anti-TIGIT antibodies and anti–PD-L1 antibodies in preclinical studies (29). For example, although inhibition of either TIGIT or PD-L1 did not slow the growth of CT26 tumors in a murine model, their co-inhibition enhanced antitumor $CD8^+$ T cells, resulting in improved survival (27). Similarly, in mice bearing gastric tumors, cotargeting TIGIT and PD-1 further enhanced CD8 T-cell activation and improved survival (30) in a synergistic manner compared with inhibition of TIGIT alone. Furthermore, in human subjects with bladder cancer, PD-1 blockade-mediated cytokine production by $CD8^+$ TILs was enhanced by TIGIT co-blockade (31). Finally, in patients with PD-L1 selected non–small cell lung cancer (NSCLC), targeting TIGIT and PD-L1 together as first-line treatment demonstrated improved activity over PD-L1 blockade alone (32), supporting the importance of developing combination therapy strategies targeting dual blockade of TIGIT and PD-1/PD-L1.

This study was designed to evaluate the safety, tolerability, and preliminary efficacy of etigilimab alone (Phase 1a) and in combination with the anti–PD-1 antibody nivolumab (Phase 1b) in patients with locally advanced or metastatic solid tumors.

Patients and Methods

Study design

This was a first-in-human, open-label, multicenter, dose-escalation and -expansion study of etigilimab alone or in combination with nivolumab conducted at five study centers in the United States. In Phase 1a, etigilimab was evaluated as a single agent in a 3+3 dose-escalation stage followed by a dose-expansion stage (**Fig. 1**). In the dose-escalation stage, dose levels evaluated were 0.3, 1.0, 3.0, 10.0, and 20.0 mg/kg. Etigilimab was administered by intravenous infusion on day 1 of 14-day cycles. Dosing was based on the patient's weight at baseline (day 1). The first patient in the first cohort had an intrapatient dose-escalation period: first dose was 0.03 mg/kg, second dose (given on day 14) was 0.1 mg/kg, and third and subsequent doses were 0.3 mg/kg. The initial dose of 0.03 mg/kg ensured a cautious approach to initial clinical investigation of etigilimab in the Phase 1a dose-escalation stage. In the Phase 1a dose-expansion stage, patients received a 20.0 mg/kg dose of etigilimab, which was the maximum administered dose (MAD) in the dose-escalation stage.

In Phase 1b, etigilimab in combination with nivolumab was evaluated using a 3+3 dose-escalation design. On the basis of available nonclinical toxicity data as well as the safety and tolerability data from the Phase 1a portion of the study, the starting dose of etigilimab for Phase 1b was 3 mg/kg, followed by 10 and 20 mg/kg dose levels (**Fig. 1**). All patients in Phase 1b received a flat dose of nivolumab 240 mg administered over 60 minutes through an intravenous line. For the first cycle only, etigilimab was given on cycle 1 day 1 and nivolumab was

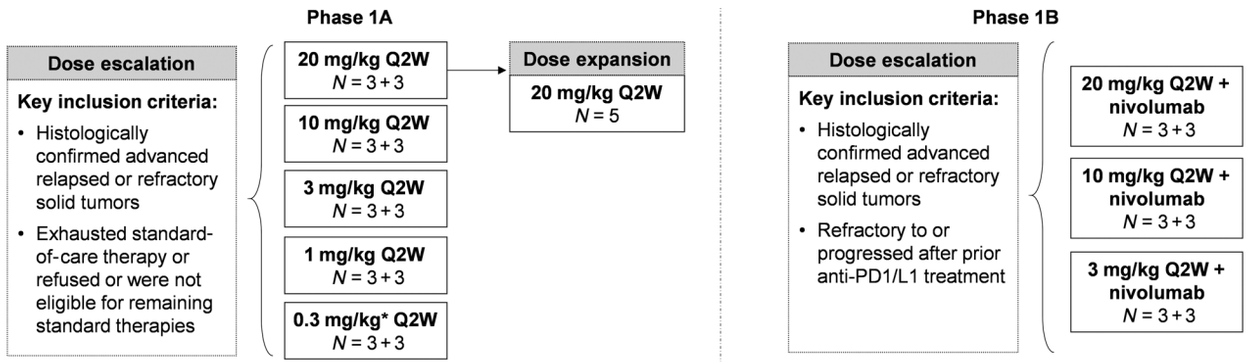

Figure 1.

Study schema. Using a 3+3 dose-escalation design, patients in the Phase 1a dose-escalation stage were treated with 0.3, 1, 3, 10, or 20 mg/kg of etigilimab intravenously every 2 weeks (Q2W). The first patient in the first cohort had an intrapatient dose-escalation period: first dose was 0.03 mg/kg; second dose was 0.1 mg/kg; third and subsequent doses were 0.3 mg/kg. In the Phase 1a dose-expansion stage, patients received a 20.0 mg/kg dose of etigilimab, which was the MAD in the dose-escalation stage. Patients in Phase 1b were treated with 3, 10, or 20 mg/kg of etigilimab and 240 mg of nivolumab intravenously Q2W.

given 48 hours later on cycle 1 day 3. For all other cycles, etigilimab and nivolumab were given on the same day (day 1 of each 14-day cycle).

In both Phase 1a and 1b, enrollment of the first 2 patients in each dose-escalation cohort was staggered such that their respective Cycle 1 Day 1 treatments were administered 72 hours or more apart. Treatment for all patients continued at the discretion of the investigator until disease progression, unacceptable toxicity, initiation of a new anticancer therapy, withdrawal of patient consent, or death.

The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki, and was approved by the institutional review boards (IRB) at the participating sites or a central IRB (ClinicalTrials.gov identifier NCT03119428). All patients provided written informed consent to participate in the trial.

Patient eligibility

Patients with histologically confirmed advanced relapsed or refractory solid tumors who had exhausted standard-of-care therapy or who refused or were not considered candidates for any remaining standard therapies were eligible for the Phase 1a and 1b dose-escalation cohorts. For the Phase 1a expansion cohort, patients were eligible if they had histologic documentation of locally advanced, recurrent, or metastatic incurable solid malignancies that had progressed after all available standard therapy or for which standard therapy had proven to be ineffective, intolerable, or considered inappropriate. Patients must have been ≥18 years old, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria (33), and adequate organ function. Phase 1b participants must have progressed after treatment with anti–PD-1 or anti–PD-L1 therapy; prior use of anti–PD-1 or anti–PD-L1 was permitted in Phase 1a provided that the patient did not discontinue these therapies due to immune-related adverse events (irAE). Key exclusion criteria were receipt of anticancer therapy within 3 weeks or five half-lives (whichever was shorter) before initiation of study treatment, AEs from prior anticancer therapy that had not resolved to Grade ≤1, primary central nervous system (CNS) malignancy or untreated/active CNS metastases, autoimmune disease (excluding autoimmune hypothyroidism, vitiligo, and minor autoimmune disease), and recent treatment with immunostimulatory agents or systemic immunosuppressive medications.

Endpoints and assessments

The primary objective was to evaluate the safety and tolerability of etigilimab alone (Phase 1a) or in combination with nivolumab (Phase 1b), and secondary safety objectives included estimation of the MTD and characterization of dose-limiting toxicities (DLT). Safety endpoints included AEs, serious AEs (SAE), physical examination, ECOG performance status, vital signs, clinical laboratory testing, and immunogenicity testing. AEs were graded according to the National Cancer Institute Common Terminology Criteria for AEs, Version 4.03 (NCI CTCAE v4.03). Patients were considered as having irAEs if they showed rash, pruritus, oral mucositis, or other immune system disorders. The DLT assessment window was 28 days (days 1 to 29). Immunogenicity was assessed by measuring the formation of anti-drug antibodies (ADA). All patients were followed after treatment discontinuation for survival and subsequent anticancer therapy approximately every 3 months for up to 2 years or until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor.

Secondary efficacy endpoints aimed at evaluating preliminary efficacy included overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Patients were assessed for overall response using RECIST v1.1 (33) as the primary method of assessment and immune-related modified RECIST (as exploratory method of assessment) criteria every 8 weeks (34). Objective response was defined as a complete response (CR) or partial response (PR) confirmed ≥4 weeks after initial documentation. The best ORR (BOR) was defined as the number of patients per dose group who had either a CR or PR for best overall response divided by the number of patients in each of the respective dose groups. Patients without any tumor assessments were counted as non-responders. The Kaplan–Meier method was used to estimate the DOR, PFS, and OS. Screening and subsequent tumor assessments included CT scans or MRI of the chest, abdomen, and pelvis. Brain imaging (either MRI or contrast-enhanced CT) was required at screening for all patients. Further investigations such as bone scans and CT scans of the neck were performed if there was any clinical suspicion of disease at any site that was not demonstrated by the other assessments listed.

In Phase 1a, serum samples were taken at pre-specified time points before and after dosing to characterize the pharmacokinetic (PK) properties of etigilimab, including study drug area under the curve (AUC), half-life, volume of distribution, and clearance. Compartmental analysis was conducted on the composite of the cohort mean data from the intrapatient escalation (first enrolled patient), 0.3, 1, 3, 10, and 20 mg/kg dose groups, and parameter estimation was conducted using PK/pharmacodynamic modeling software ADAPT 5 (35). In the Phase 1b cohorts, etigilimab was measured at 15 minutes post-infusion and pre-infusion during each dosing cycle. Blood samples were also assessed for pharmacodynamic biomarkers, TIGIT and immune-related gene expression by mRNA detection (e.g., CD226, T-cell genes), and changes in peripheral blood mononuclear cell (PBMC) populations and activation. Detailed PK methods are available in the Supplementary Methods, and in Supplementary Tables S1 and S2.

Biomarker assessments

Flow cytometry

Whole blood was collected in two 10-mL Na Heparin tubes. Samples were sent overnight to Primity Bio for PBMC isolation; flow cytometry analysis was performed on cryopreserved PBMCs. For phenotypic characterization of different immune cell subsets described herein, monoclonal antibodies against CD3 (UCHT1), CD4 (RPA-T4), CD8 (RPA-T8), CD19 (HIB19), IL-2 (MQ1–17H12), CCR7 (G043H7), TIGIT (A15153G), and FOXP3 (206D) were obtained from BioLegend, whereas CD3 (SK7), CD45 (HI30), CD45RA (HI100), and Ki-67 (B56) were from BD Biosciences, and viability dye (DL800) and IL-17a (eBio64Dec17) were from Thermo Fisher Scientific.

Briefly, cryopreserved PBMCs were thawed in a 37°C water bath and washed by centrifugation with pre-warmed complete RPMI (10% FBS) medium containing Benzonase (Sigma). After washing, cells were stained with fixable viability dye DL800 followed by cell surface staining with fluorochrome tagged antibodies and fixation. For intracellular staining, such fixed cells were permeabilized and stained with antibodies against Ki-67 and FOXP3, or IL-2 and IL-17a. Note: for cytokine analysis, after thawing, PBMCs were stimulated first with 50 ng/mL phorbol myristate acetate and 1 μmol/L ionomycin for 4 hours in the presence of GolgiStop (BD Biosciences) followed by

surface and intracellular staining. Stained samples were acquired on a BD LSRFortessa X-20 equipped with (minimally) 372, 405, 488, 561, and 640 nm lasers and 14 fluorescence channels.

Manual gating and data analysis was performed using CellEngine (Primity Bio) software. After exclusion of debris and dead cells (DL800 positive), B cells and T cells were identified on the basis of the expression of CD19 and CD3, respectively. T cells were further classified as $CD4^+$ or $CD8^+$ cells and FOXP3 expression was used to identify Tregs while Ki-67 expression was used to determine the extent of proliferating cells. In addition, $CD4^+$ and $CD8^+$ cells were analyzed for the expression of CD45RA and CCR7 that allowed the discrimination (36, 37) of $CD45RA^+$ $CCR7^+$ naïve (TN), $CD45RA^-$ $CCR7^+$ central memory (TCM), $CD45RA^-$ $CCR7^-$ effector memory (TEM), and $CD45RA^+$ $CCR7^-$ effector memory re-expressing CD45RA (TEMRA) subsets; cytokine (IL-2 and IL-17a) production within each of these memory populations was determined.

Epigenetic immunophenotyping

Blood was collected in Paxgene tubes (Qiagen). Epigenetic immune cell quantification was performed at the Berlin laboratory of Precision for Medicine as described previously in ref. 38 with the distinction that the whole protocol has been adapted for a fully automated sample processing using the EpMotion 5075T liquid handling system (Eppendorf). Laboratory personnel were blinded to the status of the samples received.

In brief, 75 µL whole blood was lysed by adding 67 µL lysis solution (Invitrogen) containing 270 ng Proteinase K (Sigma-Aldrich) and heated to 56°C for 20 minutes. Bisulphite conversion of genomic DNA was achieved by adding 90 µL tetrahydrofurfuryl alcohol (Merck) and 270 µL 70% ammonium bisulphite (TIB chemicals) to the lysate and heated to 80°C for 55 minutes. The Dynabeads SILANE Genomic DNA Kit chemistry (Invitrogen) was used for a subsequent purification of converted DNA, which was recovered from the magnetic beads with 56 µL of elution buffer.

For epigenetic quantitative PCR analysis, 3 µL of template was mixed with 7 µL LightCycler 480 Probes Master (Roche) containing 15 pmole methylation-specific forward and reverse primer, 2.5 pmole hydrolysis probe, and 50 ng of l-DNA. Thermal cycling was performed on a LightCycler 480 II instrument (Roche) applying the following profile: 35 minutes pre-incubation at 95°C for thermal desulfonation followed by 50 cycles of 15 seconds at 95°C and 1 minute at 61°C with signal acquisition. Total cell count determination and calculation of relative frequencies of Treg and $CD8^+$ T cells were carried out as described previously in refs. 38, 39. All measurements were performed in duplicates and were subjected to rigorous quality controls according to the laboratory's quality management system that is accredited under ISO 17025. All plate runs conformed with performance limits set for standards, calibrators and reference samples that monitor standard linearity, bisulfite conversion, and quantitative PCR efficiency.

Optional biopsy of skin rash

The expression of immune infiltrate was assessed by hematoxylin and eosin (H&E) staining and/or immunohistochemistry (IHC).

Statistical analysis

As this was a Phase 1a/b study, the general analytical approach for evaluating all endpoints was descriptive in nature, and no formal statistical hypothesis testing was conducted. Baseline characteristics, demographics, efficacy, immunogenicity, and biomarker data were analyzed using the intent-to-treat (ITT) population, which included all patients who received at least one partial or complete dose of etigilimab. All safety endpoints were summarized using the safety population, which included all patients who received at least one partial or complete dose of etigilimab and who had at least one post-dose safety evaluation. The dose group used for analysis for each patient was based on the dose assigned at enrollment. Antitumor activity analyses were based on investigator assessment by RECIST v1.1. Patients without any tumor assessments were categorized as not evaluable for efficacy assessments. Statistics describing time-to-event variables utilized the Kaplan–Meier method. No adjustments were made for multiplicity, and missing values were not imputed. All analyses and tabulations were performed using SAS software, Version 9.4 or higher (SAS Institute Inc.; Statistical Analysis System, RRID:SCR_008567).

Data availability

Data were generated by the authors and included in the article.

Results

Patient characteristics

A total of 33 patients were enrolled in the study (23 patients in Phase 1a and 10 patients in Phase 1b) from May 2, 2017 to February 28, 2019. All 33 patients received study drug and were included in both the safety and the ITT populations. In Phase 1a, 20 of the patients were evaluable (19 with tumor assessments), and in Phase 1b, 8 of the patients were evaluable (7 with tumor assessments).

The Phase 1b study was stopped prematurely due to business reasons. Patient demographics and baseline characteristics are summarized in **Table 1**. Approximately half of the patients were <65 years old (51.5%); 16 (48.5%) patients were male and 17 (51.5%) were female. The majority of patients were White (84.8%) and heavily pretreated (78.8% had received ≥3 prior therapies). Prior anti–PD-1 therapy was received by 9 (39.1%) patients in Phase 1a and the 8 evaluable patients (100%) in Phase 1b.

The median duration of treatment with etigilimab was 56.0 days (range, 28.0–226.0) per patient in Phase 1a and 49.5 days (range, 14.0–224.0) in Phase 1b, with the median number of doses administered per patient being 4 (range, 2–16) and 3 (range, 1–15), respectively. The median duration of treatment with nivolumab in Phase 1b was 47.5 days, with a median total dose of 720 mg per patient. The most common reason for discontinuation from the study was disease progression [20 patients (87.0%) in Phase 1a and 6 patients (60.0%) in Phase 1b]. Other reasons for discontinuation in Phase 1a were AE, clinical progression, and investigator decision due to clinical progression [1 patient (4.3%) each]. In Phase 1b, other reasons for study discontinuation included investigator decision to remove the patient from further treatment (2 patients, 20.0%), death (1 patient, 10.0%), and withdrawal of consent (1 patient, 10.0%). New enrollment was halted at the end of 2018 and all ongoing patients had treatment termination visits by February 28, 2019.

Safety and immunogenicity

No DLTs were reported in either the Phase 1a or 1b portions of the study; thus, the MTD was not determined. The MAD was 20 mg/kg every 2 weeks (Q2W); this was the dose used in the expansion phase of the trial. All patients in the study reported one or more treatment-emergent AE. The most commonly reported AEs were rash (43.5%), nausea (34.8%), and fatigue (30.4%) in Phase 1a and decreased appetite (50.0%), nausea (50.0%), and rash (40%) in Phase 1b.

Overall, AEs considered related to study drug were reported by 16 patients (69.6%) in Phase 1a and 7 patients (70.0%) in Phase 1b

Table 1. Patient demographics and baseline characteristics.

Characteristic, *n* (%)	Phase 1a *n* = 23	Phase 1b *n* = 10	Overall *n* = 33
Age (y)			
<65	11 (47.8)	6 (60.0)	17 (51.5)
≥65–<75	12 (52.2)	4 (40.0)	16 (48.5)
Sex			
Male	10 (43.5)	6 (60.0)	16 (48.5)
Female	13 (56.5)	4 (40.0)	17 (51.5)
Race			
White	18 (78.3)	10 (100)	28 (84.8)
Black or African American	3 (13.0)	0	3 (9.1)
Asian	1 (4.3)	0	1 (3.0)
American Indian or Alaska Native	1 (4.3)	0	1 (3.0)
Tumor type			
Head and neck	4 (17.4)	1 (10.0)	5 (15.2)
Uterine	4 (17.4)	0	4 (12.1)
Colorectal	6 (26.1)	1 (10.0)	7 (21.2)
Gastric	0	3 (30.0)	3 (9.1)
Triple-negative breast	2 (8.7)	0	2 (6.1)
Pancreatic	2 (8.7)	0	2 (6.1)
Other[a]	5 (21.7)	5 (50.0)	10 (30.3)
Microsatellite status			
MSI	1 (4.3)	1 (10.0)	2 (6.1)
MSS	5 (21.7)	3 (30.0)	8 (24.2)
Unknown	17 (73.9)	6 (60.0)	23 (69.7)
Number of prior therapies[b]			
1	2 (8.7)	0	2 (6.1)
2	3 (13.0)	2 (20.0)	5 (15.2)
3	6 (26.1)	1 (10.0)	7 (21.2)
4	5 (21.7)	1 (10.0)	6 (18.2)
5	2 (8.7)	2 (20.0)	4 (12.1)
>5	5 (21.7)	4 (40.0)	9 (27.3)
Current stage	*n* = 22	*n* = 9	*n* = 31
1	1 (4.5)	0	1 (3.0)
2	0	0	0
3	3 (13.6)	1 (11.1)	4 (12.1)
4	18 (81.8)	8 (88.9)	26 (78.8)
Prior anti–PD-1/L1 therapy			
Yes[c]	9 (39.1)	9 (90.0)	18 (54.5)
Pembrolizumab	4 (17.4)	5 (50.0)	9 (27.3)
Nivolumab	2 (8.7)	1 (10.0)	3 (9.1)
Pembrolizumab and nivolumab	0	1 (10.0)	1 (3.0)
Atezolizumab and pembrolizumab	0	1 (10.0)	1 (3.0)
Nivolumab and durvalumab	0	1 (10.0)	1 (3.0)
Other	3 (13.0)	0	3 (9.1)
No[d]	14 (60.9)	1 (10.0)	15 (45.5)

Abbreviations: MSI, microsatellite instability; MSS, microsatellite stable.
[a]Other tumor types included: Adenoid cystic, Ewing sarcoma, fallopian tube, gallbladder, lung, hepatocellular, NSCLC, ovarian, and renal cell.
[b]Chemotherapies, biologic therapies, or immunotherapies.
[c]Patients receiving more than 1 type of anti–PD-1/L1 therapy are counted once for each type of therapy they received. Median Phase 1b prior anti–PD-L1 therapy is 168 days, with the shortest being 42 days and the longest being 715 days.
[d]One patient in Phase 1b did not have anti–PD-1/L1 therapy before study start. This patient was not evaluable and did not have a tumor assessment.

Table 2. Treatment-related AEs.

	Phase 1a (*n* = 23)		Phase 1b (*n* = 10)	
Related AEs, *n* (%)[a]	All	Grade ≥3	All	Grade ≥3
Patients reporting ≥1 related AE	16 (69.6)	4 (17.4)	7 (70.0)	2 (20.0)
Rash[b]	8 (34.8)	2 (8.7)	4 (40.0)	2 (20.0)
Pruritus	4 (17.4)	0	2 (20.0)	0
Fatigue	3 (13.0)	0	3 (30.0)	0
Nausea	3 (13.0)	0	1 (10.0)	0
Chills	2 (8.7)	0	0	0
Cough	2 (8.7)	0	0	0
Abdominal pain	1 (4.3)	0	0	0
ALT increased	1 (4.3)	1 (4.3)	1 (10.0)	1 (10.0)
AST increased	1 (4.3)	1 (4.3)	1 (10.0)	1 (10.0)
Autoimmune hepatitis	0	0	1 (10.0)	0
Decreased appetite	1 (4.3)	0	1 (10.0)	0
Hypophosphatemia	1 (4.3)	1 (4.3)	0	0
Headache	1 (4.3)	0	0	0
Influenza-like illness	1 (4.3)	0	0	0
Pain	1 (4.3)	0	0	0
Skin disorder	1 (4.3)	0	0	0
Stomatitis	1 (4.3)	0	0	0
Thrombocytopenia	1 (4.3)	0	0	0
Vomiting	1 (4.3)	0	0	0
Dysgeusia	0	0	1 (10.0)	0
Myalgia	0	0	1 (10.0)	0
Vulvovaginal pruritus	0	0	1 (10.0)	0

[a]Patients reporting more than one event are counted only once for each preferred term.
[b]All preferred terms that included the term rash were consolidated into the term "rash." These included rash, rash maculopapular, rash macular, rash pruritic, and dermatitis psoriasiform.

(**Table 2**). Grade ≥3 treatment-related AEs were reported by 4 patients (17.4%) in the Phase 1a portion of the study: 3 of these patients reported Grade 3 rashes (rash in a patient receiving 1.0 mg/kg, macular rash in a patient receiving 3.0 mg/kg, and maculopapular rash in a patient receiving 10.0 mg/kg) and 1 patient receiving 20.0 mg/kg reported four related Grade 3 AEs: hypophosphatemia, increased aspartate aminotransferase (AST) levels, and two events of increased alanine aminotransferase (ALT) levels, which led to discontinuation of the study drug. In addition, this patient was admitted to the hospital for suspected autoimmune hepatitis but was later determined post liver biopsy to have non-alcoholic steatohepatitis. This patient was treated with corticosteroids, which led to a decline in the liver function tests and the SAE of hepatitis was considered resolved 5 days after onset. In Phase 1b, Grade ≥3 treatment-related AEs were reported for 2 patients (20.0%): 1 patient receiving 3.0 mg/kg reported a related Grade 3 rash, and 1 patient receiving 20.0 mg/kg reported three related Grade 3 AEs (ALT increased, AST increased, and rash), which resolved after treatment with oral corticosteroids. This patient also experienced a related Grade 2 AE of autoimmune hepatitis; study treatment was temporarily held due to this AE, and it was considered unresolved at the time of database lock. One patient in Phase 1b had a Grade 1 infusion reaction of itchy throat that was considered related to nivolumab; no other infusion reactions were reported in the study.

SAEs occurred in 10 patients (43.5%) in Phase 1a and 4 patients (40.0%) in Phase 1b. None of these SAEs were considered to be related to etigilimab. AEs with a fatal outcome were reported for 3 patients (13.0%) in Phase 1a (malignant neoplasm progression, metastatic pancreatic carcinoma, and metastatic endometrial cancer) and 2 patients (20.0%) in Phase 1b (acute respiratory failure in a patient with NSCLC and hepatic failure in a patient with head and neck cancer); none of these were considered related to the study drug.

Table 3. Immune-related AEs.

Immune-related AEs, *n* (%)[a,b]	Phase 1a (*n* = 23)	Phase 1b (*n* = 10)
Rash	8 (34.8)	4 (40.0)
Pruritus	3 (13.0)	2 (20.0)
Skin disorder	1 (4.3)	0
Autoimmune hepatitis	0	1 (10.0)
Chills	2 (8.7)	0
Pyrexia	1 (4.3)	0
Arthralgia	1 (4.3)	0
Myalgia	1 (4.3)	0
Infusion-related reaction	0	1 (10.0)
ALT increased	0	1 (10.0)
AST increased	0	1 (10.0)

[a]Patients reporting more than one event are counted only once for each preferred term.
[b]Immune-related AEs were treatment-emergent AEs determined by the investigator to be immune-related adverse reactions. The investigator was to ensure adequate evaluation to confirm etiology or exclude other causes.

AEs leading to discontinuation of study drug occurred in 3 patients (13.0%) in Phase 1a: 1 patient receiving 20.0 mg/kg who had Grade 3 ALT increased (discussed above; considered related to etigilimab); 1 patient receiving 20.0 mg/kg who had Grade 3 non-cardiac chest pain (considered unrelated to etigilimab); and 1 patient receiving 0.3 mg/kg who had Grade 3 peripheral edema, hypoxia, decreased appetite, and fatigue, as well as Grade 2 dyspnea and abdominal pain (all considered unrelated to etigilimab). No patients in Phase 1b had an AE leading to discontinuation of study drug.

Immune-related AEs were reported for 10 (43.5%) patients in Phase 1a and 4 (40.0%) patients in Phase 1b (**Table 3**). Rash was reported as irAEs in 8 patients (34.8%) in Phase 1a and 4 patients (40.0%) in Phase 1b (Supplementary Table S3). Treatment-related autoimmune hepatitis in a patient in Phase 1b was also considered an irAE. None of the irAEs led to permanent discontinuation of study drug. Supplementary Fig. S1 depicts the H&E and IHC stains for a rash experienced by a patient receiving 3 mg/kg of etigilimab. There were no irAEs in the lowest dose (0.3 mg/kg in Phase 1a).

The most common NCI CTCAE Grade ≥3 laboratory test abnormalities were increases in lymphocytes (8 patients, 34.8%), alkaline phosphatase (3 patients, 13.0%), and ALT, and a decrease in sodium (each reported by 2 patients, 8.7%) in Phase 1a, and an increase in alkaline phosphatase (3 patients, 30.0%) and AST (2 patients, 20.0%) in Phase 1b.

All 33 patients had serum samples collected for immunogenicity analysis; of these, 24 patients had at least one post-dose sample analyzed and ADA analysis for the remaining samples was terminated due to closure of the study by the sponsor. On the basis of the partial data available, 23 of the 24 patients tested negative for ADAs and only 1 patient tested positive for ADAs (4% incidence of immunogenicity). This patient received single-agent etigilimab in Phase 1a at a dose of 1 mg/kg and tested positive for ADAs at the treatment termination visit (42 days after the last dose of etigilimab). One patient in the Phase 1b, 10 mg/kg cohort screened positive for ADAs pre-dose. Further confirmatory analysis of this sample was not conducted; this patient had one post-dose sample collected that was not analyzed because the patient was deemed ineligible for immunogenicity analysis.

Tumor response

In the Phase 1a portion of the study, 7 patients (30.4%) had stable disease (2 patients with colorectal cancer, 2 with endometrial, 2 with head and neck, and 1 with fallopian tube cancer; **Fig. 2**). No patients had a PR or CR and thus the DOR could not be calculated. In Phase 1b, 1 patient (10.0%) with ovarian cancer had a PR and was on study 224 days and 1 patient (10.0%) with gastric cancer had stable disease and was on study 218 days. The median PFS was 56.0 [95% confidence interval (CI), 51.0–112.0] days in Phase 1a, and 57.5 (95% CI, 14.0–224.0) days in Phase 1b.

PK

All 33 patients had serum concentration data sufficient for PK analysis; however, 19 out of 601 (3%) samples in Phase 1a and 8 out of 80 (10%) samples in Phase 1b were not analyzed due to study closure. A linear two-compartment model was found to best describe the Phase 1a cohort mean data simultaneously. Etigilimab exhibited linear PK characteristics typical of a monoclonal antibody (Supplementary Fig. S2), with a mean clearance of 8.4 mL/d/kg (95% CI, 8.1–8.7) and mean terminal half-life of 6.1 days (95% CI, 5.4–6.8). In Phase 1b, peak and trough concentrations of etigilimab were obtained for the assessment of whether the presence of nivolumab affected the PK of etigilimab. To conduct such an assessment, the linear two-compartment model established on the basis of the Phase 1a data was used to simulate the expected concentration-time profiles, taking into consideration patient-specific actual dose level and dosing frequency. Mean (±SD) concentrations of etigilimab in the presence of nivolumab from the Phase 1b portion were overlaid onto the "model simulation" and a visual comparison was conducted. Agreement between the "expected" based on single-agent PK and the "observed" from the combination with nivolumab indicated that the presence of nivolumab did not have an identifiable impact on the PK of etigilimab.

Biomarkers

Biomarker analyses were performed on 16 patients from the Phase 1a portion of the study, which showed a reduction of Tregs in circulation by immune profiling and an increase in the CD8/Treg ratio, primarily at the higher 3.0, 10.0, and 20.0 mg/kg dose levels (Supplementary Fig. S3). No substantial changes in CD8 cells were observed with etigilimab treatment. Activation of immune cells, as measured by increases in $Ki67^{+}TIGIT^{+}CD4$, and NK cells, and increased intracellular cytokines (IL-2 and IL-17) were observed (**Fig. 3**). Gene expression of RTKN2 and CTLA4 (Treg-associated genes) and TIGIT were significantly downregulated by etigilimab at the 10 and 20 mg/kg dose levels. Levels of PD-L1 in baseline tumor tissues could not be assessed due to lack of evaluable tumor tissues.

Discussion

TIGIT plays an important role in limiting adaptive and innate immunity against tumors through multiple mechanisms (2). This Phase 1a/b study demonstrated the safety and tolerability of the anti-TIGIT antibody etigilimab, both as a monotherapy and in combination with nivolumab. In Phase 1a, etigilimab was dose-escalated to 20 mg/kg Q2W and 20 mg/kg was established as the MAD. In Phase 1b, etigilimab was also dose-escalated to 20 mg/kg Q2W with standard dosing of nivolumab. There were no DLTs observed in the study. Treatment with etigilimab by itself or in combination with nivolumab showed a similar AE profile, with rash, pruritis, and transaminase elevations being the most common irAEs. Dermatologic AEs (primarily rash) were noted in 56.5% ($n = 13$) and 50.0% ($n = 5$)

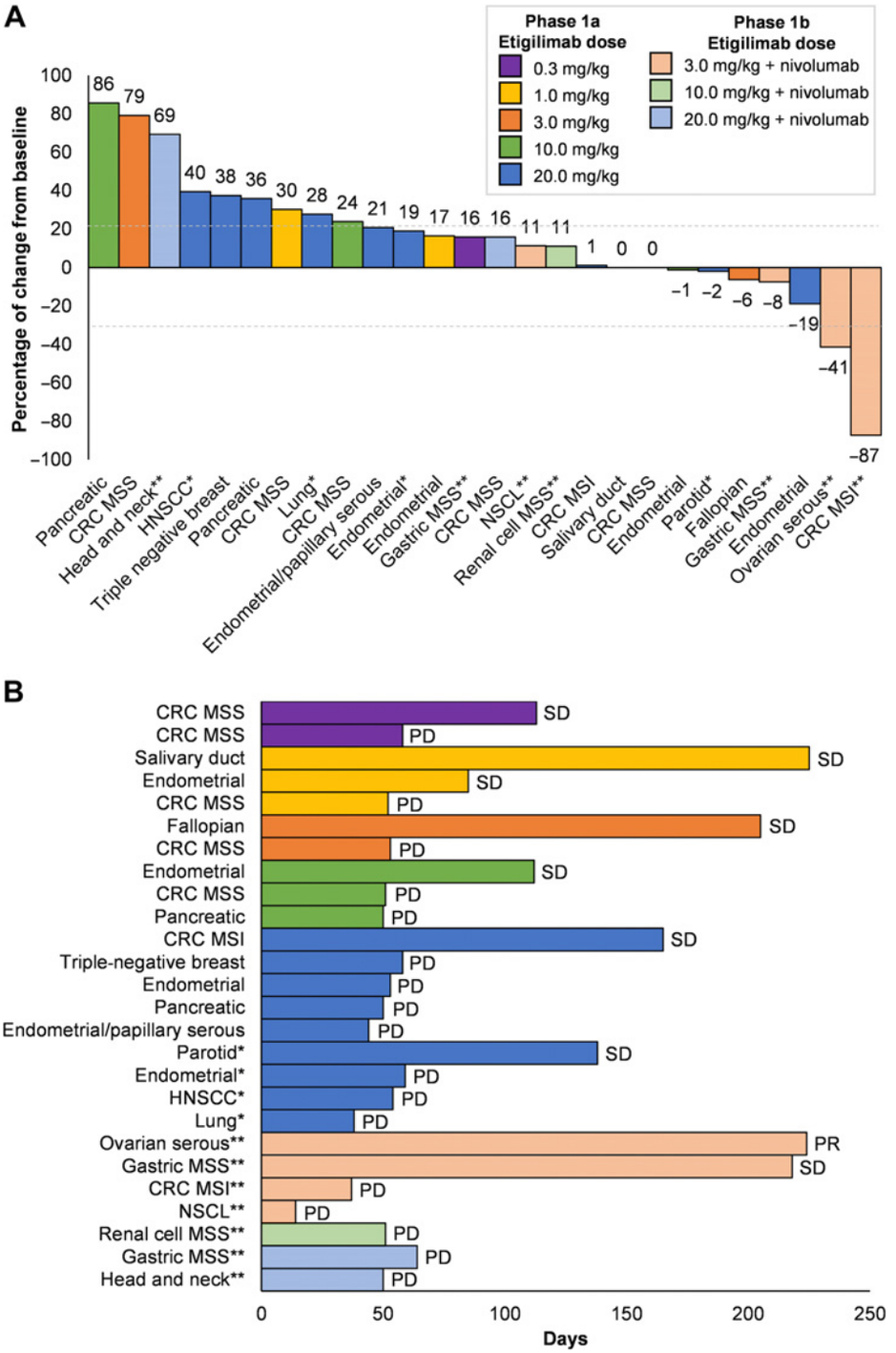

Figure 2.

A, Best percentage reduction in target lesion size. **B,** Duration on study. Figure includes evaluable patients with tumor assessments: Phase 1a, $n = 19$; Phase 1b, $n = 7$. *Phase 1a dose expansion; **Phase 1b. Patients without available tumor assessment data were not included. The Phase 1b patient with CRC MSI who had an 87% tumor reduction had a near CR of their primary target lesion but developed a new lesion and came off study after the first staging scan. CRC, colorectal cancer; HNSCC, head and neck squamous cell carcinoma; MSI, microsatellite instability; MSS, microsatellite stable; NSCL, non–small cell lung; PD, progressive disease; PR, partial response; SD, stable disease.

of Phase 1a and 1b patients, respectively. Although most of these were Grade 1, several patients experienced Grade 3 rashes due to the large surface area of the rash, and all were successfully treated with supportive care, antipruritic oral and topical corticosteroids. There was one case of treatment-related liver function test elevations (autoimmune hepatitis) that occurred in a patient receiving 20 mg/kg etigilimab and nivolumab. This event was successfully managed with systemic corticosteroids resulting in resolution of the elevated liver function tests. Importantly, no new safety signal was noted with etigilimab monotherapy or in combination with nivolumab, and all observed AEs were consistent with immune-mediated AEs noted with ICIs (40).

On the basis of the partial data available, the immunogenicity incidence was 4%, which is on the lower end of the range of 0.7%–48% ADA incidence observed with other ICIs such as pembrolizumab and atezolizumab (41). The linear PK characteristics of etigilimab in

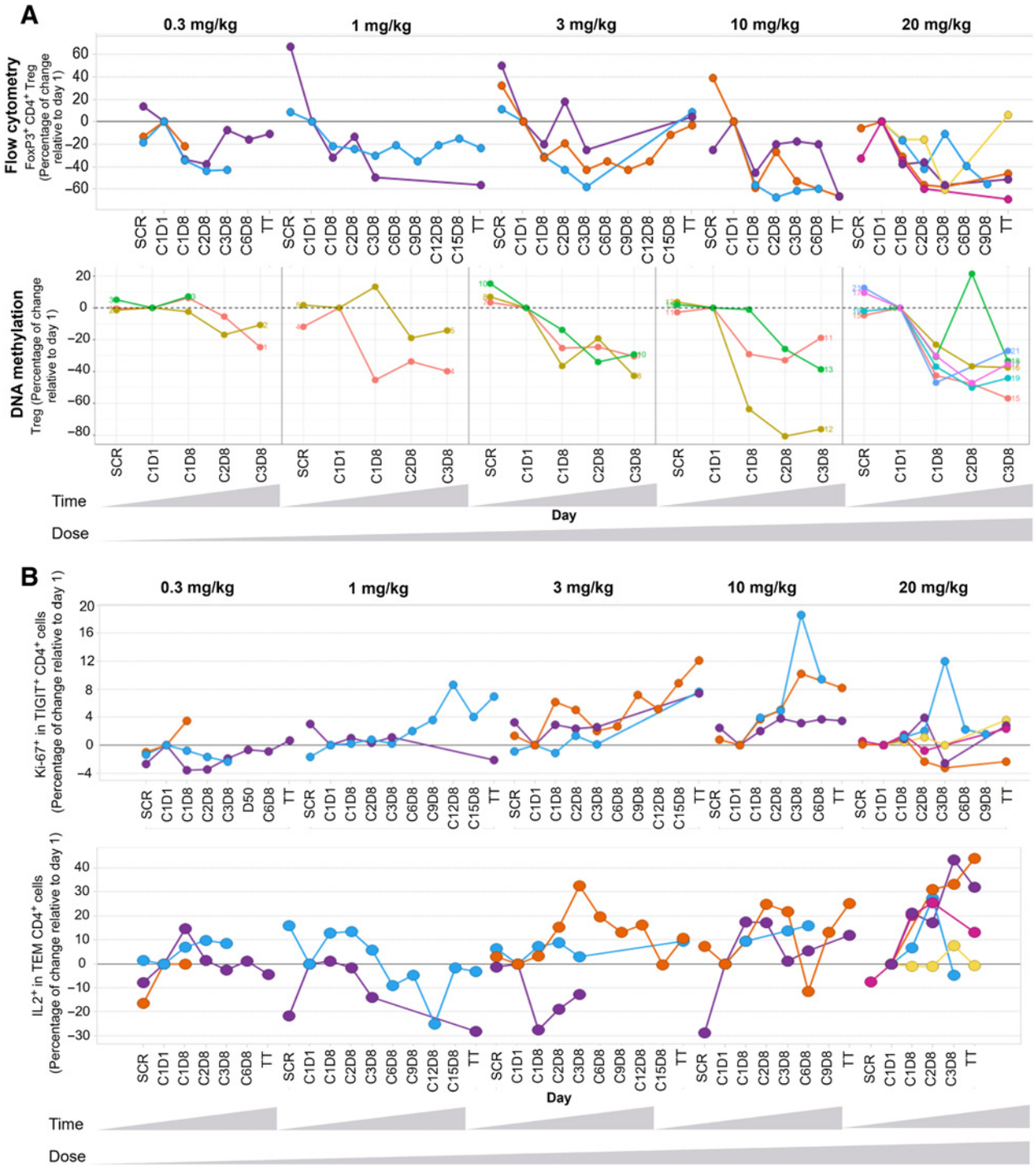

Figure 3.

Etigilimab reduces Tregs in circulation and enhances proliferation and intracellular IL-2 in immune subpopulations. Patients are grouped by dose cohort; each line represents results from an individual patient. One patient was excluded due to confounding chronic myeloid leukemia. **A,** Etigilimab treatment decreases Treg frequency ($FOXP3^+CD4^+$ cells) as measured by flow cytometry (top) and DNA methylation (bottom) immunophenotyping. Patients are grouped by dose cohort. **B,** Etigilimab increases Ki67 levels in $TIGIT^+/CD4^+$ cells by flow cytometry (top). Etigilimab increases intracellular IL-2 levels in $CD4^+$ TEM cells (bottom, similar data observed for IL-17, not shown).

this study were also comparable with those of established monoclonal antibodies, and the relatively slow clearance and half-life support dosing every 2 or 3 weeks. Combination treatment with nivolumab in Phase 1b did not appear to alter the PK of etigilimab.

Biomarker correlative analyses in this study demonstrated clear evidence of dose-dependent immune modulation by etigilimab. Treatment with etigilimab resulted in a reduction in Tregs, activation of immune cells, increased intracellular cytokines, and downregulation of Treg-associated genes. Importantly, treatment with etigilimab did not change the frequency of CD8 T cells and an increase in CD8/FOXP3 ratio was observed.

Most patients in this study were heavily pretreated, with nearly 80% having received ≥3 prior therapies, including receipt of prior ICI therapies in 39.1% of patients in Phase 1a and 100% in Phase 1b. Preliminary signals of clinical benefit (stable disease as the best response) were observed in 7 of the 23 patients treated with etigilimab monotherapy, even though the study enrolled most patients with tumor types that have historically not been known to respond to single-agent immunotherapy [e.g., serous ovarian, microsatellite stable (MSS) gastric, and other cancers]. Of note, one patient with endometrial cancer had a 19% decrease in tumor growth and another patient with fallopian tube cancer remained on study for 205 days.

Preclinical studies suggest that dual PD-1/PD-L1 and TIGIT inhibition is a promising combinatorial immunotherapy strategy in cancer (29–32). The Phase 1b portion of the study evaluated etigilimab in combination with nivolumab patients who had previously progressed after treatment with an anti–PD-1 or anti–PD-L1 agent. One patient with serous ovarian cancer had a PR and remained on study for nearly 8 months; this patient terminated treatment due to physician decision based on a modest increase in CA-125, despite stable PR at the time. In addition, one patient with microsatellite instability–high colorectal cancer had a near CR of their primary target lesion (87% decrease) but developed a new lesion and came off study after the first staging scan. In addition, a patient with MSS gastric cancer remained on study with stable disease for 7 months. These data suggest preliminary signals of clinical activity of the combination of etigilimab and nivolumab and are consistent with other Phase 1 trial data with combination anti-TIGIT and anti–PD-1/PD-L1 antibody therapy. In recent clinical trials, objective response rates of 5%–50% were observed when the anti-TIGIT antibodies tiragolumab and vibostolimab were combined with atezolizumab (anti–PD-L1) and pembrolizumab (anti–PD-1) in patients with solid tumors and NSCLC, respectively, with better outcomes noted in patients who were anti–PD-1/PD-L1 treatment-naïve and had tumors with PD-L1 expression (42–44). The safety, tolerability, and preliminary efficacy data noted in this Phase 1a/b study are consistent with recent data on other molecules targeting TIGIT as single agents or in combination with PD-1 inhibitors in patients with advanced solid tumors.

As is typical for early-phase trials, the small sample size limits the ability to draw conclusions about the efficacy of etigilimab as a monotherapy or the combination of etigilimab and nivolumab. The preliminary safety, target engagement, and antitumor data of etigilimab warrant further investigations of this agent, and a Phase 1b/2 study in combination with nivolumab is ongoing.

In summary, etigilimab monotherapy and the combination with nivolumab demonstrated acceptable safety and tolerability profile. Biomarker correlative analyses in this study demonstrated clear evidence of dose-dependent target engagement by etigilimab, including activation of immune T-cell subpopulations and reductions in peripheral Tregs. Preliminary efficacy data from the combination Phase 1b part of the study showed potential antitumor activity in solid tumor patients with recurrent, advanced/metastatic disease who had progressed after prior ICI therapy. These data support the development of future clinical trials with dual TIGIT/PD-1 blockade in patients with advanced solid tumors.

Authors' Disclosures

N.B. Mettu reports grants from Mereo BioPharma and OncoMed Pharmaceuticals during the conduct of the study; N.B. Mettu also reports grants and personal fees from Genentech, as well as grants from Amphivena Therapeutics, AstraZeneca, Biomed Valley Discoveries, Bristol Myers Squibb, Erytech Pharma, Incyte Corporation, Merck Sharp and Dohme, Repare Therapeutics, Revolution Medicines, Inc., Syros Pharmaceuticals, Amgen, Marc Lustgarten Pancreatic Cancer Foundation, Armo BioSciences/Eli Lilly, and NIH outside the submitted work. S.V. Ulahannan reports other support from Oncomed Pharmaceuticals during the conduct of the study, as well as other support from Array, Incyte, Bayer, Syros, Eisai, AbbVie, Arqule, AstraZeneca, Atreca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Ciclomed, Evelo Biosciences, Exelixis, G1 Therapeutics, GSK, IGM Biosciences, Incyte, Isofol, Klus Pharma, Macrogenics, Merck, Mersana, Pfizer, Regeneron, Revolution Medicine, Synermore Biologics, Takeda, Tarveda, Tesaro, Tempest, and Vigeo Therapeutics outside the submitted work. J.C. Bendell reports grants from Gilead, Genentech/Roche, Bristol Myers Squibb, Five Prime, Lilly, Merck, MedImmune, Celgene, EMD Serono, Taiho, GSK, Macrogenics, Novartis, OncoMed, LEAP, TG Therapeutics, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Bayer, Incyte, Apexigen, Koltan, SynDevRex, Forty Seven, AbbVie, Onyx, Array, Sanofi, Takeda, Eisai, Celldex, Agios, Nektar, Cytomx, ARMO, Boston Biomedical, Ipsen, Merrimack, Tarveda, Tyrogenex, Marshall Edwards, Oncogenex, Mersana, Pieris, Calithera, Blueprint, Evelo, FORMA, Merus, Jacobio, Effector, Novocare, Arrys, Tracon, Sierra, Innate, Arch Oncology, Prelude Oncology, Unum Therapeutics, Vyriad, Harpoon, ADC, Amgen, Pfizer, Millennium, Imclone, Acerta Pharma, Rgenix, Bellicum, Gossamer Bio, Arcus Bio, TempestTx, Seattle Genetics, Shattuck Labs, Synthorx, Inc., Revolution Medicines, Inc., Bicycle Therapeutics, Zymeworks, Relay Therapeutics, Scholar Rock, NGM Biopharma, Stemcentrx, BeiGene, CALGB, Cyteir Therapeutics, Foundation Bio, Innate Pharma, Morphotex, OncXerna, NuMab, AtlasMedx, Treadwell Therapeutics, MabSpace, IGM Biosciences, Hutchinson MediPharma, Repare Therapeutics, NeoImmune Tech, Regeneron, PureTech Health, Phoenix Bio, Cyteir, Molecular Partners, Innate, Torque, Janssen, Tizona, Tolero, Amgen, Moderna Therapeutics, Continuum Clinical, Agios, Pfizer, Samsung Bioepios, and Fusion Therapeutics during the conduct of the study, as well as grants from Gilead, Genentech/Roche, Five Prime, Bristol Myers Squibb, Lilly, Merck, MedImmune, EMD Serono, Celgene, Taiho, Macrogenics, GSK, Novartis, OncoMed, LEAP, TG Therapeutics, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Bayer, Incyte, Apexigen, Koltan, SynDevRex, Forty Seven, AbbVie, Array, Onyx, Sanofi, Takeda, Eisai, Celldex, Agio, Cytomx, Nektar, ARMO, Boston Biomedical, Ipsen, Merrimack, Tarveda, Tyrogenex, Oncogenex, Marshall Edwards, Pieris, Mersana, Calithera, Blueprint, Evelo, FORMA, Merus, Jacobio, Effector, Novocare, Arrys, Tracon, Sierra, Innate, Arch Oncology, Prelude Oncology, Unum Therapeutics, Vyriad, Harpoon, ADC, Amgen, Pfizer, Millennium, Imclone, Acerta Pharma, Rgenix, Bellicum, Gossamer Bio, Arcus Bio, Seattle Genetics, TempestTx, Shattuck Labs, Synthorx, Inc., Revolution Medicines, Inc., Bicycle Therapeutics, Zymeworks, Relay Therapeutics, Scholar Rock, NGM Biopharma, Stemcentrx, BeiGene, CALGB, Cyteir Therapeutics, Foundation Bio, Innate Pharma, Morphotex, OncXerna, NuMab, AtlasMedx, Treadwell Therapeutics, IGM Biosciences, Hutchinson MediPharma, Mabspace, Repare Therapeutics, NeoImmune Tech, Regeneron, PureTech Health, Phoenix Bio, Cyteir, Molecular Partners, Innate, Torque, Tizona, Janssen, Tolero, Amgen, Moderna Therapeutics, Continuum Clinical, Agios, Pfizer, Samsung Bioepios, and Fusion Therapeutics outside the submitted work. I. Garrido-Laguna reports other support from Oncomed during the conduct of the study; I. Garrido-Laguna also reports other support from Novartis, GSK, Bristol Myers Squibb, Lilly, Genmab, Navire, Amgen, Raphael, Trishula, Seattle Genetics, Repare, Tolero, and MedImmune, as well as personal fees and other support from SOTIO outside the submitted work. J.H. Strickler reports personal fees from Mereo and grants from Mereo during the conduct of the study. J.H. Strickler also reports grants and personal fees from AbbVie, AstraZeneca, SeaGen, Viatris, Silverback Therapeutics, Roche/Genentech, Amgen, and Bayer; personal fees from GSK, Natera, Inivata, and Pfizer; and grants from AStar D3, Curegenix, Daiichi Sankyo, Exelixis, Leap Therapeutics, Nektar, Sanofi Genzyme, Gossamer Bio, and Erasca. K.N. Moore reports personal fees from Aravive, AstraZeneca, Alkemeres, Blueprint Pharmaceuticals, Eisai, Elevar, EMD/Serono, GSK/Tesaro, Genentech/Roche, IMab, INXmed, Immunogen, Mereo, Merck, Myriad, Tarveda, VBL Therapeutics, and OncXerna outside the submitted work; K.N. Moore is also Associate Director GOG Partners NRG, Ovarian Cancer

Chair, and on the GOG Foundation Board of Directors. R. Stagg reports other support from OncoMed and Mereo during the conduct of the study, as well as other support from OncoMed and Mereo outside the submitted work. A.M. Kapoun reports other support from OncoMed and Mereo during the conduct of the study. L. Faoro reports other support from OncoMed Pharmaceuticals during the conduct of the study. S. Sharma reports other support from OncoMed during the conduct of the study, as well as other support from Celgene, Hengrui, Plexxikon, Toray, Tesaro, Syndax, AMAL, Ignyta, Nektar, Sirnaomics, Takeda, Dracen, Inhibrx, Merck, Aadi, Novartis, Celularity, Agastiya, Rappta Therapeutics, Stemline Therapeutics, Incyte, and Barricade outside the submitted work. S. Sharma reports a patent for neoantigen-informed TIL—cancer immunotherapy issued, Peptide Inhibitors Targeting the TBL1-Beta-Catenin Complex pending, Methods and Compounds for Neoantigen Vaccines pending, Imidazopyridazine and Imidazopyrazine Compounds and Methods of Use Thereof pending, and Compositions and Methods for the Treatment of Cancer pending; in addition, S. Sharma reports equity from Elevar (LSK BioPharma), Salarius Pharmaceuticals, Iterion Therapeutics, ConverGene, HLB-Korea, Stingray Therapeutics, and Barricade Therapeutics.

Authors' Contributions

N.B. Mettu: Investigation, writing–original draft, writing–review and editing. **S.V. Ulahannan:** Investigation, writing–review and editing. **J.C. Bendell:** Investigation. **I. Garrido-Laguna:** Investigation. **J.H. Strickler:** Investigation, writing–review and editing. **K.N. Moore:** Investigation. **R. Stagg:** Formal analysis, investigation, writing–review and editing. **A.M. Kapoun:** Data curation, formal analysis, writing–original draft, writing–review and editing. **L. Faoro:** Supervision, investigation. **S. Sharma:** Investigation.

Acknowledgments

This study was sponsored by Mereo BioPharma (formerly OncoMed Pharmaceuticals, Inc.). The authors would like to thank the patients and caregivers for their participation, and the research study team members at each participating institution for their contributions. Editorial and medical writing assistance was provided by Colleen Brown (Mark Consulting, Inc.) and funded by Mereo BioPharma. This study was registered at ClinicalTrials.gov under the trial number NCT03119428.

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Received August 2, 2021; revised October 13, 2021; accepted November 22, 2021; published first November 29, 2021.

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