A Phase II Trial of the CD40 Agonistic Antibody Sotigalimab (APX005M) in Combination with Nivolumab in Subjects with Metastatic Melanoma with Confirmed Disease Progression on Anti-PD-1 Therapy

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ABSTRACT

Purpose: Disease progression during or after anti-PD-1-based treatment is common in advanced melanoma. Sotigalimab is a CD40 agonist antibody with a unique epitope specificity and Fc receptor binding profile optimized for activation of CD40-expressing antigen-presenting cells. Preclinical data indicated that CD40 agonists combined with anti-PD1 could overcome resistance to anti-PD-1.

Patients and Methods: We conducted a multicenter, open-label, phase II trial to evaluate the combination of sotigalimab 0.3 mg/kg and nivolumab 360 mg every 3 weeks in patients with advanced melanoma following confirmed disease progression on a PD-1 inhibitor. The primary objective was to determine the objective response rate (ORR).

Results: Thirty-eight subjects were enrolled and evaluable for safety. Thirty-three were evaluable for activity. Five confirmed partial responses (PR) were observed for an ORR of 15%. Two PRs are ongoing at 45.9+ and 26+ months, whereas the other three responders relapsed at 41.1, 18.7, and 18.4 months. The median duration of response was at least 26 months. Two additional patients had stable disease for >6 months. Thirty-four patients (89%) experienced at least one adverse event (AE), and 13% experienced a grade 3 AE related to sotigalimab. The most common AEs were pyrexia, chills, nausea, fatigue, pruritus, elevated liver function, rash, vomiting, headache, arthralgia, asthenia, myalgia, and diarrhea. There were no treatment-related SAEs, deaths, or discontinuation of sotigalimab due to AEs.

Conclusions: Sotigalimab plus nivolumab had a favorable safety profile consistent with the toxicity profiles of each agent. The combination resulted in durable and prolonged responses in a subset of patients with anti-PD-1-resistant melanoma, warranting further evaluation in this setting.

See related commentary by Wu and Luke, p. 9

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Introduction

Antagonistic antibodies against programmed death-1 (PD-1) administered alone or in combination with anti-cytotoxic T-lymphocyte associated protein-4 (CTLA-4) in advanced melanoma produce durable responses in a large subset of patients. The 6.5-year survival rate for ipilimumab plus nivolumab approaches 50%, with a median overall survival (OS) of 72.1 months (1). The mechanisms responsible for primary or acquired resistance to these immune checkpoint inhibitors (ICI) remain poorly defined, and immunotherapy options in the second-line setting or beyond remain limited.

Preclinical animal model data and correlative studies from prior human trials suggest that enhancing tumor antigen presentation by antigen-presenting cells (APC) and enabling recruitment of T cells into the tumor microenvironment (TME) could overcome resistance to ICI. Cluster of differentiation 40 (CD40) is a costimulatory receptor of the TNF receptor superfamily expressed on numerous cell types including APCs such as dendritic cells (DC) and macrophages and is a fundamental component of the T-cell and B-cell activation pathway. CD40 ligand (CD40L) is a transmembrane protein expressed on activated $CD4^+$ T cells, B cells, and platelets. CD40–CD40 L binding promotes the transformation of immature DCs into fully functional mature DCs and induces upregulation of MHC, T-cell costimulatory molecules, and key immune cell stimulatory cytokines such as IL12. These features are optimal for processing and presenting tumor antigens to T cells and activating T-cells. Agonistic mAb to CD40 can mimic the CD40–CD40 L effects and can also stimulate DCs

Translational Relevance

This study describes results from a phase II trial of nivolumab combined with the CD40 agonist sotigalimab in patients with melanoma whose disease had progressed on anti-PD-1 therapy alone or with anti-CTLA-4. The objective response rate was modest (15%); however, a majority of the responders achieved prolonged treatment-free periods. The safety profile of the combination was favorable. On the basis of the activity of this combination and the prolonged durable responses, studies of sotigalimab and nivolumab in other settings or tumor types is warranted. The combination could be investigated in patients with melanoma with primary resistance to ipilimumab/nivolumab and relatlimab/nivolumab or in patients who cannot be rechallenged with ipilimumab due to prior toxicity, and sotigalimab could be combined with other immune checkpoint inhibitor doublets in patients who are not responding to those regimens early on or who have a very low chance of responding.

to activate cytotoxic $CD8^+$ T cells in the absence of $CD4^+$ T-cell help (2–4). A similar cell-surface phenotypic change occurs in B cells upon CD40–CD40 L binding (5). In addition, agonists of CD40 reprogram macrophages to kill tumor cells in a T-cell independent fashion while also activating cytotoxic NK cells and neutrophils (6).

In preclinical studies, CD40 agonists alone (7) and in combination with chemotherapy (8) demonstrated antitumor activity in several tumor types (9, 10). In poorly T-cell-infiltrated murine tumors such as pancreatic cancer, addition of a CD40 agonist to PD-1 and CTLA-4 inhibitors was shown to prime T-cell responses (4). The combination of a CD40 agonist and PD-(L)1 inhibitors also produced additive or synergistic antitumor effects in several tumor models, including tumors highly resistant to PD-1 antagonists, and induced protective immunity against rechallenge (11, 12).

Agents targeting CD40 entered clinical trials more than two decades ago. The CD40 agonistic antibodies currently in clinical development have variable isotype properties and epitope specificity that impact their potency (2, 13). The first anti-CD40 agonist studied in the clinic, selicrelumab (CP-870,893), showed activity as a single agent in solid tumors and melanoma (14). In ICI-naïve patients with advanced melanoma, selicrelumab combined with anti-CTLA-4 produced an objective response rate (ORR) of 27.3%, including two complete responses, and a median OS of 23.6 months (15). The results provided the foundation for development of subsequent agonistic anti-CD40 antibodies designed to enhance activity and improve the therapeutic ratio.

Sotigalimab (APX005M) is a humanized IgG_1 mAb targeting CD40, which uniquely binds within the human CD40 L binding domain on CD40 with high affinity (1.2×10^{-10} M) to mimic natural CD40 L signaling and effect. Potency of sotigalimab was increased by enhancing its binding to FcγRIIb, thereby increasing crosslinking by Fc-bearing cells and CD40 signaling. It was also designed to eliminate binding to FcγRIIIa, which could mediate antibody-dependent cellular cytotoxicity effects on CD40-expressing APCs and consequently abrogate the intended immune stimulatory effects (16, 17). Mechanistically, sotigalimab is predicted to stimulate both innate and adaptive immune responses, activate APCs to process and present antigens to T cells, prime antitumor T cells, modulate the TME by targeting tumor-associated macrophages (TAM), and convert uninflamed ("immunologically cold") tumors to inflamed ("hot") tumors (**Fig. 1A**). Sotigalimab demonstrated single-agent activity and an

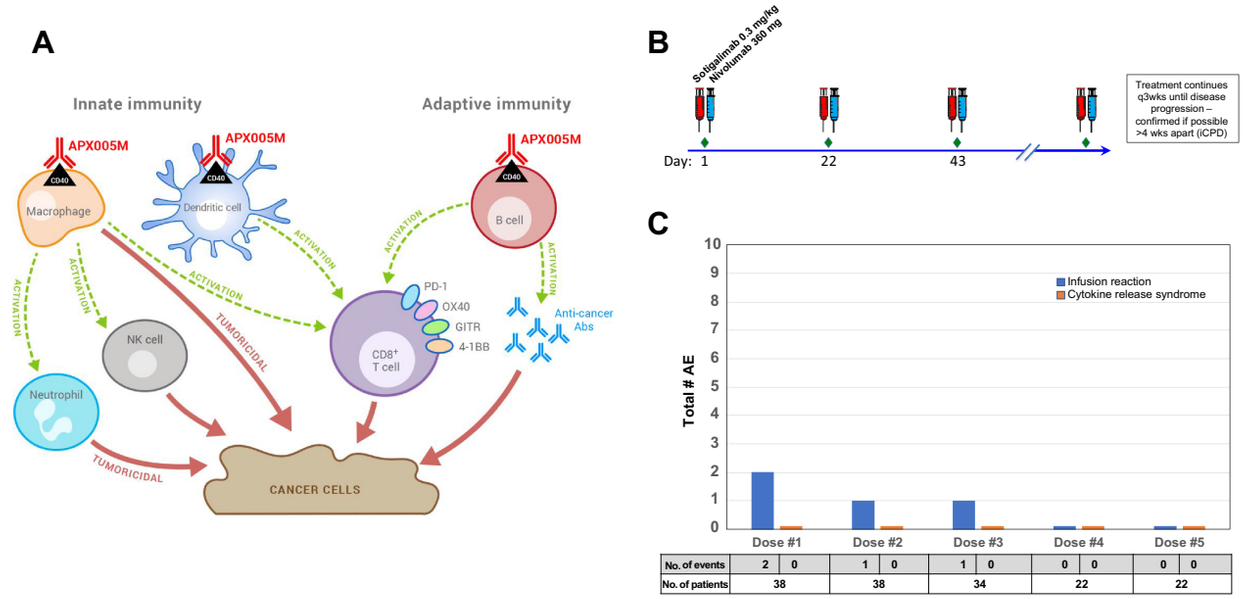

Figure 1.

A, Mechanism of action of sotigalimab (APX005M). Sotigalimab is a humanized IgG_1 mAb targeting CD40 that uniquely binds within the human CD40 L binding domain on CD40 with high affinity. Sotigalimab stimulates both innate and adaptive immune responses, activates antigen presenting cells, primes antitumor T cells, and targets TAMs. **B,** Study schema. Nivolumab 360 mg as a 30-minute i.v. infusion was administered first on day 1 of each cycle, followed by sotigalimab 0.3 mg/kg as a 60-minute i.v. infusion. Cycles were every 3 weeks. **C,** Low incidence of reported infusion reactions and no reported cytokine release syndrome (CRS). The incidence of infusion reactions decreased with subsequent doses, and a similar trend has been seen in other studies. Other AEs reported as at least possibly related to sotigalimab and considered possibly part of an infusion reaction or CRS (which was a separate question to investigators in the database) but not reported as such (preferred term) include pyrexia (grade 1/2), hypotension (grade 1, 1 event), and rash/rash maculopapular (grade 1/2, all transient <1 day).

acceptable safety profile in immunotherapy-näive patients with advanced melanoma (NCT04337931). Here we present the phase II results of a trial evaluating the combination of sotigalimab and nivolumab in patients with anti-PD-1-resistant advanced melanoma.

Patients and Methods

A multicenter dose escalation phase I/II study was initially conducted at sites in the United States and Spain to determine the safety, activity, and MTD of sotigalimab in combination with nivolumab in patients with advanced melanoma or non–small cell lung cancer and confirmed disease progression during or following treatment with anti-PD-1. Subjects in the melanoma cohort had to have histologically confirmed unresectable or metastatic melanoma with confirmed progressive disease (PD) during treatment with anti-PD-(L)1 therapy as documented by at least two consecutive tumor assessments performed at least 4 weeks apart. Study treatment had to start no later than 8 weeks following the last dose of anti-PD-(L)1, with no intervening therapy. Informed written consent was obtained from each subject. This study was approved by the participating sites' institutional review boards and was conducted in accordance with ethical guidelines as outlined by the Declaration of Helsinki and with an assurance filed with and approved by the U.S. Department of Health and Human Services, where appropriate.

Sequential cohorts of patients received sotigalimab doses of 0.03, 0.1, and 0.3 mg/kg i.v. in combination with nivolumab 360 mg i.v. every 3 weeks using a 3+3 design. Sotigalimab 0.3 mg/kg was the recommended phase II dose (RP2D), which was also the RP2D established in a phase I single-agent study of sotigalimab in advanced solid tumors (manuscript in preparation). Here we present the results of the phase II expansion cohort of patients with melanoma whose disease progressed on anti-PD-1 therapy (NCT03123783). The study started on July 10, 2017, and completed on November 16, 2020. After the completion of the study and with IRB and/or site regulatory approval, site investigators reported de-identified long-term follow-up data beyond the end of study on patients who achieved an objective response.

The primary objective was to determine the ORR of the combination by RECIST v1.1. Secondary objectives were to evaluate the safety, 6-month progression-free survival (PFS) rate, median PFS, and duration of response (DOR) by RECIST v1.1. Thirty-seven patients were planned to be enrolled according to a Simon's two-stage design, testing the null hypothesis that the true response rate is 5% against a one-sided alternative. In the first stage, 12 patients were planned to be accrued. If there were no responses in the 12 subjects, the enrollment in this cohort would be stopped. Otherwise, if 1 or more responses were observed, 25 additional subjects would be accrued in the second stage for a total of 37 subjects. Enrollment could continue into stage 2 whereas the planned number of subjects for stage 1 were followed for efficacy. By the end of stage 2, if three or fewer responses were observed in 37 subjects, then no further investigation would be warranted. If 4 or more responses were observed, then the null hypothesis would be rejected.

Key eligibility criteria included patients ≥18 years old, an ECOG performance status of 0 to 1, and biopsy-proven unresectable or metastatic melanoma with disease progression during treatment with anti-PD-(L)1, which was confirmed ≥4 weeks later. Prior anti-CTLA-4 was allowed provided there was no progression whereas on anti-CTLA-4 and the last treatment was >3 months prior to study start. The rationale for this criteria was to prevent the inclusion of patients with rapidly progressive disease on ipilimumab/nivolumab, which may represent a disease biology distinct from the other patients with anti-PD-1-resistant melanoma, and to avoid potential combined or overlapping toxicity at initiation of sotigalimab/nivolumab. Patients with a BRAF-activating mutation could have also received a BRAF and MEK inhibitor regimen prior to anti-PD-(L)1 therapy. Patients with ocular melanoma, autoimmune disease requiring treatment in the last 2 years, or active central nervous system metastases were excluded. Full inclusion and exclusion criteria can be found in the protocol provided in the Supplementary Materials and Methods.

The study schema is shown in **Fig. 1B**. Nivolumab was administered first as a 30-minute intravenous infusion on day 1. Sotigalimab was administered approximately 30 minutes following nivolumab as a 60-minute intravenous infusion. Because sotigalimab was developed as an every 3-week infusion, nivolumab was administered at 360 mg every 3 weeks as well for convenience. Oral premedication for sotigalimab was administered approximately 30 minutes prior to nivolumab and included H1 antagonist (H2 antagonist was optional), ibuprofen 400 mg, and acetaminophen 650 mg. Nonsteroidal anti-inflammatory drugs were often extended for a 24-hour period or longer at the discretion of the investigator for optimal control. Tumor assessments were performed within 21 days prior to the start of the investigational drugs and every 8 weeks thereafter. Tumor response required confirmatory imaging assessments at least 4 weeks later. When clinically feasible, progressive disease was also confirmed at least 4 weeks later.

All adverse events (AE) and serious AEs (SAE) related to nivolumab, sotigalimab, the combination, or unrelated to study drugs were recorded using CTCAE version 4.03. Data cut-off for response was November 16, 2020. Best overall response (BOR) by RECIST v1.1 was recorded as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). DOR was defined as the time from first documented PR to the earlier date of PD or last restaging studies prior to the end of study. Duration of SD was defined as the time from first study treatment to the earlier date of PD or end of study. Beyond the end of study, long-term follow-up data are reported for the responders as of July 2022.

Peripheral blood was collected from patients pre-start and 4 hours post-start of the first infusion to study changes in soluble analytes that may be associated with immune cell activation. Plasma was analyzed using proximity extension assay (PEA) technology for 92 protein biomarkers (Olink Target 96 Immuno-Oncology panel). Qualitative changes in the protein biomarkers are reported as Normalized Protein eXpression (NPX) values on a $\log_2$ scale.

Data availability

Data from the study can be accessed at https://clinicaltrials.gov/study/NCT03123783?cond=melanoma&term=apx005m&rank=4. Any additional deidentified raw data that are not posted on clinicaltrials.gov due to patient privacy restrictions can be requested from the study sponsor Apexigen, Inc., by first contacting the corresponding author.

Results

Baseline characteristics

Thirty-eight patients with confirmed anti-PD-1-resistant melanoma received at least one dose of sotigalimab and were evaluable for safety. Five of these patients were not evaluable for activity either due to a lack of posttreatment tumor assessments or were deemed ineligible based on major inclusion criteria violations. Two of the 5 patients were not evaluable due to lack of posttreatment tumor assessments. Of these two patients, one withdrew consent and the second died after bowel

Table 1. Baseline patient characteristics.

Efficacy population		(*N* = 33)
Age	Median (range)	61 (32–83)
Gender: Female/male	*n* (%)	14 (42.4)/19 (57.6)
ECOG PS at baseline		
0	*n* (%)	25 (75.8)
1		8 (24.2)
Number of prior therapies[a]		
1	*n* (%)	26 (78.8)
2		5 (15.1)
3		2 (6.1)
Prior treatment with anti-PD-(L)1 agent	(%) (anti-PD-1/ anti-PD-L1)	(100/0)
Prior anti-CTLA-4	*n* (%)	8 (24)
Baseline elevated LDH > ULN	*n* (%)	14 (42.4)
Melanoma subtype		
Cutaneous, nonacral	*n* (%)	18 (54.5)
Acral lentiginous		6 (18.2)
Mucosal		1 (3)
Unknown subtype		8 (24.2)
Metastatic site(s) at study entry[a]		
Lung	*n* (%)	19 (58)
Lymph nodes		
Local-regional		9 (27)
Distant		11 (33)
Skin or subcutaneous		14 (42)
Liver		6 (18)
Bone		4 (12)
Brain		2 (6)
Other		10 (30)

[a]Patients may have more than one site of metastatic disease.

obstruction unrelated to the study drugs. The remaining 3 of 5 patients were deemed ineligible after it was discovered that their most recent anticancer therapy was not a PD-(L)1 inhibitor. Although these patients previously progressed on a PD-(L)1 inhibitor, no intervening therapy was allowed. Thirty-three patients were evaluable for efficacy. Baseline patient characteristics are listed in **Table 1**. Most patients (79%) had only one prior therapy, 24% (8/33) received prior anti-CTLA-4, and 42% (14/33) had an elevated LDH at baseline. Median time on prior anti-PD-1 therapy was 10.4 months (range, 1.9–37.8 months). Median number of cycles of sotigalimab plus nivolumab administered for the safety population ($n = 38$) was 6.

Safety of sotigalimab plus nivolumab

AEs of any grade whether treatment-related or unrelated were reported in 95% of patients. Most AEs were grade 1 to 2 and transient. Grade 3 AEs were reported in 29% of patients, although only 13% had grade 3 events related to sotigalimab. There were no grade 4 or 5 AEs. AEs related to sotigalimab or nivolumab or both occurring in >10% of patients are shown in **Table 2**. SAEs were reported in 15.8% of patients but were unrelated to either nivolumab or sotigalimab. There were no sotigalimab-related AEs that led to its discontinuation or to death. The incidence of immune-related AEs (irAE) was low and not greater than expected with nivolumab alone. Reported irAEs included grade 1 colitis ($n = 1$), grade 1 to 2 pneumonitis ($n = 2$), and grade 1 hyperthyroidism related to both sotigalimab and nivolumab or nivolumab alone. Grade 3 AEs attributed to sotigalimab alone and not to nivolumab were infrequent and included transient elevations in AST and ALT occurring in 1 patient, and pyrexia in 1 patient. Grade 3 AEs attributed to both sotigalimab and nivolumab included AST and ALT elevations in 2 patients and elevated amylase and lipase in 1 patient.

Infusion reactions and cytokine release syndrome (CRS)

No events of investigator-defined CRS were reported. In total, four infusion reactions occurred in 3 patients, all grade 2. The incidence of

Table 2. Treatment-related AEs occurring in ≥10% of patients.

N = 38	Related to sotigalimab alone, not related to nivolumab		Related to nivolumab alone, not related to sotigalimab		Related to both		Overall related AE	
							All grades	
Related AEs	Grade 1–2 subjects, *n* (%)	Grade 3+ subjects, *n* (%)	Grade 1–2 subjects, *n* (%)	Grade 3+ subjects, *n* (%)	Grade 1–2 subjects, *n* (%)	Grade 3+ subjects, *n* (%)	Events, *n*	Subjects, *n* (%)
Pyrexia	11 (28.94)	1 (2.63)	0 (–)	0 (–)	13 (34.21)	0 (–)	55	24 (63.16)
Fatigue/asthenia	4 (10.53)	0 (–)	1 (2.63)	0 (–)	15 (39.47)	0 (–)	41	20 (52.63)
Chills	8 (21.05)	0 (–)	2 (5.26)	0 (–)	13 (34.21)	0 (–)	48	19 (50.00)
Nausea	7 (18.42)	0 (–)	1 (2.63)	0 (–)	9 (23.68)	0 (–)	17	15 (39.47)
Pruritus	2 (5.26)	0 (–)	1 (2.63)	0 (–)	10 (26.32)	0 (–)	15	13 (34.21)
ALT increased	2 (5.26)	1 (2.63)	0 (–)	1 (2.63)	6 (15.79)	1 (2.63)	17	10 (26.31)
AST increased	1 (2.63)	1 (2.63)	0 (–)	0 (–)	6 (15.79)	1 (2.63)	14	8 (21.05)
Headache	2 (5.26)	0 (–)	0 (–)	0 (–)	6 (15.79)	0 (–)	17	8 (21.05)
Rash/maculo-papular rash	2 (5.26)	0 (–)	1 (2.63)	0 (–)	4 (10.53)	0 (–)	10	7 (18.42)
Vomiting	2 (5.26)	0 (–)	1 (2.63)	0 (–)	4 (10.53)	0 (–)	14	7 (18.42)
Arthralgia	0 (–)	0 (–)	3 (7.89)	0 (–)	4 (10.53)	0 (–)	14	6 (15.79)
GGT increased	1 (2.63)	0 (–)	0 (–)	0 (–)	4 (10.53)	1 (2.63)	16	6 (15.79)
Myalgia	1 (2.63)	0 (–)	1 (2.63)	0 (–)	4 (10.53)	0 (–)	10	6 (15.79)
Alk phos increased	1 (2.63)	0 (–)	0 (–)	0 (–)	5 (13.15)	0 (–)	10	5 (13.15)
Diarrhea	0 (–)	0 (–)	0 (–)	1 (2.63)	3 (7.89)	0 (–)	6	4 (10.53)

Note: Events = Number of events.
Subjects = Number of subjects with highest severity.
Percentages in the patients column are based on the number of subjects (*N*) in a given study group or overall as the denominator.
For each row category, a subject with two or more AEs in that category is counted only once for the patients column.
Overall: AEs related to sotigalimab, related to nivolumab or related to both.

infusion reactions was highest with the first dose (2 events) and decreased with subsequent doses (**Fig. 1C**). Other treatment-related AEs, which can be part of an infusion reaction or CRS were reported as individual events in the database, and included grade 1 to 2 pyrexia in 34% of patients, grade 1 hypotension in 3%, and grade 1 to 2 rash in 8%.

BOR

Characteristics of response are depicted in **Fig. 2A** to **E**. For the 33 evaluable patients, 5 (15.2%; 90% CI, 6.2–29.3) achieved a PR (**Table 3**). Four of five PRs were ongoing at end of study as of November 2020 with individual DOR of 4.2+, 11+, 18.4+, 18.7, and 24.7+ months and did not require further systemic treatment for up to 16+ months (**Tables 3** and **4**). One additional patient achieved an unconfirmed radiologic PR including 64% reduction of target lesions and resolution of nearly all nontarget lesions, but developed new lesions on subsequent imaging. SD defined as nonprogression through at least one imaging at 8 weeks was observed in 10 patients (30.3%). Two patients had SD lasting >6 months, including one who remained progression-free at 14+ months at end of study data collection. Median PFS was 1.97 months.

Beyond the end of study, site investigators reported long-term follow-up on patients who achieved an objective response (**Table 4**; **Fig. 2E**). As of July 2022, 2 of 5 patients remained in PR (**Fig. 2E**). Both patients were off systemic therapy for 37.3+ and 21+ months with DOR of 45.9+ and 26+ months, respectively. Of the three PR patients whose disease progressed, one received stereotactic radiation for an isolated brain lesion 9.4 months after stopping sotigalimab/nivolumab and after experiencing a DOR of 18.7 months. Subsequently, three small solitary brain metastases were treated sequentially with stereotactic radiation sessions but the patient has not required systemic therapy. A second patient maintained a response for 41 months and was off sotigalimab/nivolumab for 36.9 months until PD which presented as bowel metastases. The third patient remained in PR for 18.4 months and was off sotigalimab/nivolumab for 6.6 months at the time of PD which presented as growing hilar adenopathy.

All patients who achieved a PR had confirmed disease progression while receiving prior anti-PD-1 therapy for a range of 3 to 12.5 months and were not expected to have delayed tumor responses to continued anti-PD-1 therapy. Two of the PR patients received prior anti-CTLA-4 and anti-PD-1 therapy but stopped anti-CTLA-4 therapy 6 and 12 months before the study start date. For the PR patients, median time on sotigalimab plus nivolumab was 11.2 months. Treatment was discontinued mainly due to deep clinical and radiographic responses.

Figure 2D shows a radiographic response in a patient with mucosal melanoma who received three cycles of ipilimumab and nivolumab, transitioned to nivolumab monotherapy, and after 10 months of stable response on nivolumab alone, developed an elevated LDH and rapid

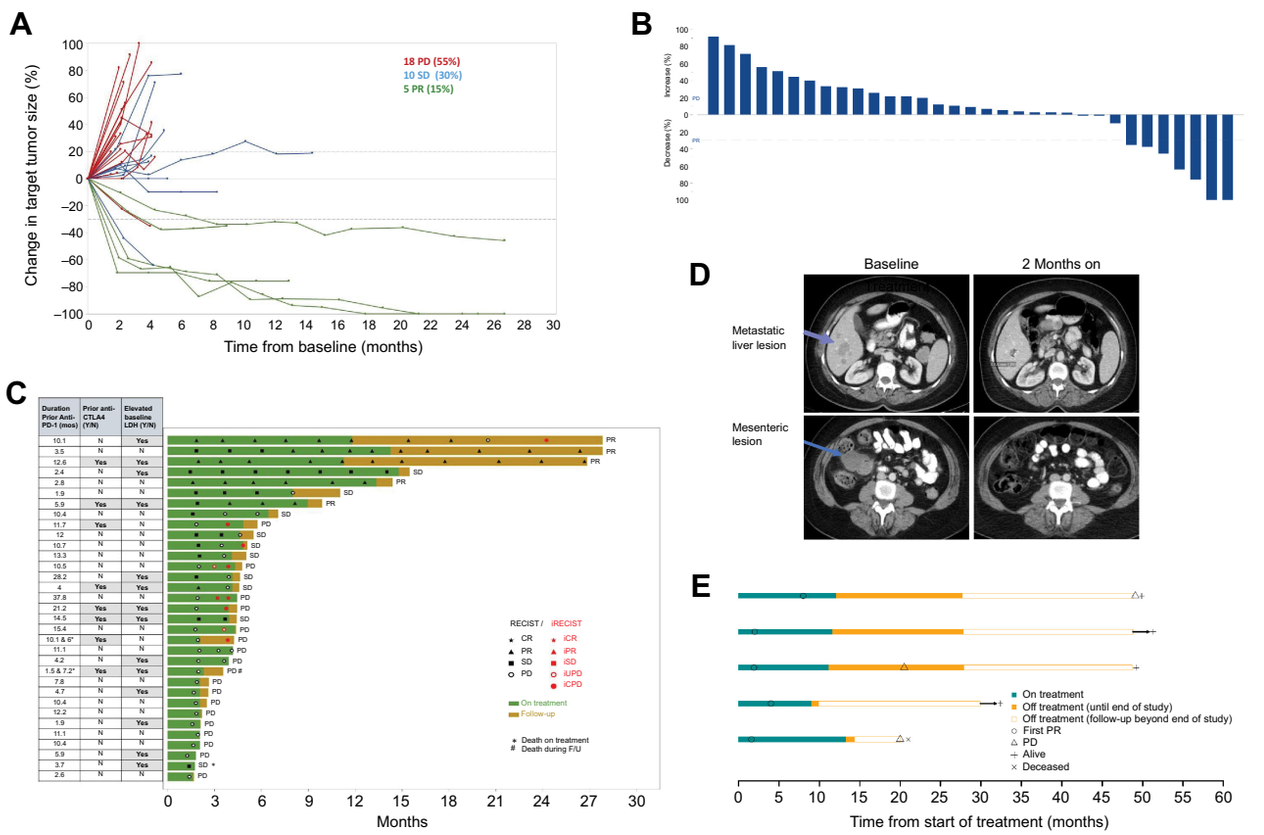

Figure 2.

A, Spider plot showing change in target tumor size over time. **B,** Waterfall plot demonstrating maximal change in sum of target lesions by RECIST v1.1 in 33 evaluable subjects. **C,** Swimmer plot showing tumor response per subject until end of study. Duration of prior anti-PD-1, whether prior anti-CTLA-4 therapy was received, and LDH level at baseline are reported for each patient and responses are documented through the end of the study as of November 2020. **D,** Response in a mucosal melanoma patient. This patient was previously treated with ipilimumab and nivolumab, became resistant to anti-PD-1 monotherapy, and has had an ongoing response to sotigalimab/nivolumab as of July 2022. **E,** Swimmer plot showing DOR and time off systemic therapy for patients with PR beyond end of study. Two patients have an ongoing response as of July 2022.

Table 3. BOR and DOR for evaluable patients through the end of study (November 2020).

BOR		Evaluable patients ($N = 33$)
PR	*n* (%)	5 (15.2)
SD	*n* (%)	10 (30.3)
PD	*n* (%)	18 (54.5)
ORR	Rate (CI 90%)	15.2 (6.2, 29.3)
DOR (PR)[a] (First documented PR to earlier date of PD or last imaging study prior to end of trial)	Median individual DOR	4 PR ongoing at EOS (4.2+, 11+, 18.4+, 18.7, 24.7+ months)

Abbreviation: EOS, end of study.
[a]At completion of therapy and study follow-up, 4 PR patients remained in an ongoing PR without further systemic treatment (end of treatment to end of study: up to 16 months). Duration of SD was up to 14+ months, with 2 patients (20%) >6 months and 8 (80%) >3.5 months.

disease progression in multiple metastatic sites. Two months after starting sotigalimab plus nivolumab, reimaging studies demonstrated a PR and subsequent scans showed resolution of all target lesions. After 15 cycles (11 months) of combination therapy, treatment was stopped, and as of July 2022, the PR was ongoing for 45.9+ months without additional therapy.

Correlative studies

Peripheral blood collected pre-start and 4 hours post-start of the first infusion was analyzed for changes in expression of 92 protein biomarkers. Treatment with sotigalimab plus nivolumab increased levels of immune mediators associated with dendritic cell, NK-cell, and T-cell activation, including TNFα, IL12, CD83, sCD4, IFNγ, and IL15 (Supplementary Fig. S1).

Discussion

In this phase II trial, the combination of sotigalimab and nivolumab was safe and active patients with in metastatic melanoma with confirmed progression on prior anti-PD-1 therapy. The ORR was 15.2%, and several additional patients demonstrated clinically meaningful activity, including substantial disease reduction in an unconfirmed partial responder and two additional patients who maintained SD for >6 months. Clinical responses were durable. As of July 2022, responses were ongoing in 2 patients at 26+ and 45.9+ months and they have remained off systemic therapy for 21+ and 37+ months, respectively. The other 3 PR patients experienced DORs of 18.4, 18.7, and 41.1 months before developing PD, and 1 remains free of disease after stereotactic radiation of several isolated brain metastases.

The selection criteria used for the trial minimized the possibility that responses to sotigalimab and nivolumab could be attributed to pseudoprogression or late response to prior anti-PD-1 treatment. Responses were observed in patients who had received prolonged treatment on prior anti-PD-1, had multiple sites of disease progression, and/or had elevated LDH at baseline. Two of the responses occurred in patients who had received initial treatment with ipilimumab plus nivolumab and developed acquired resistance while on nivolumab maintenance.

Overall, treatment was well-tolerated. This study demonstrated that the combination of the CD40 agonist sotigalimab and nivolumab can be administered for up to one year or longer with a favorable safety profile, a low incidence of significant infusion reactions, and no reported CRS in this study's patient population. The limited infusion reactions presented early in the first few cycles, did not recur beyond the fourth dose, and could be mitigated with enhanced premedication prior to subsequent cycles. AEs related to sotigalimab were temporally related to drug administration, resulting in self-limited fevers, chills, myalgias, and transaminase elevations that resolved without intervention or with simple supportive care measures. Grade 3 events and irAEs were infrequent.

The combination of sotigalimab and nivolumab demonstrated durable clinical benefit in a subset of patients with a favorable safety profile. The level of activity demonstrated in this trial is comparable to the data reported for combinations of relatlimab/nivolumab and somewhat less compared to ipilimumab/nivolumab in similar patient populations. In melanoma patients progressing on single agent anti-PD-1, ORRs for ipilimumab/nivolumab and relatlimab/nivolumab were in the range of 25–30% and 11%, respectively (18–20). Like our study, the other ICI combinations produced mixed responses or prolonged SD in a small additional subset of patients which may also be associated with clinical benefit. It is notable that the activity of ipilimumab/nivolumab and relatlimab/nivolumab after progression on anti-PD-1 alone translated into improved outcomes when the combinations were compared to nivolumab alone in first-line metastatic melanoma (1, 21).

Table 4. DOR for the 5 PR patients at end of study (November 2020) and beyond end of study (July 2022).

	Up to EOS (November 2020)				Beyond EOS (July 2022)		
Subject No.	Duration of sotigalimab treatment (months)	PR to last CT scan or PD on study DOR (months)	Duration off sotigalimab (last sotigalimab to last CT or PD) (months)	Reason for stopping sotigalimab	PR to last CT after study completion DOR (months)	Duration off sotigalimab (last sotigalimab to last CT or PD) (months)	Response
PR1	13.4	11	−0.7	EOS	18.4	NA[a]	PD
PR2	12.2	18.4	14.2	PI decision[b]	41.1	36.9	PD
PR3	11.2	18.7	9.4	PI decision[b]	18.7	9.4	PD
PR4	10.6	24.7	16.1	PI decision[b]	45.9	37.3	Ongoing
PR5	9	4.2	−0.8	End of study	26	21	Ongoing

[a]After the study ended, the patient continued to receive treatment on compassionate use.
[b]Patients were clinically well, with minimal to no evidence of disease.

Treatment-free survival (TFS), defined as time from cessation of ICI to initiation of new therapy or death, is increasingly being examined as a meaningful outcome measure for immunotherapies in addition to conventional outcomes such as OS (22, 23). Although the sample size here is very small, 80% of the responders to sotigalimab plus nivolumab remained in response at end of study without needing further systemic therapy. This is less true with other therapies in the anti-PD-1 resistant setting although prolonged periods off treatment can be seen with TIL (24, 25). Due to early and deep responses, the majority of responders to sotigalimab plus nivolumab were taken off treatment by 1 year or just before at the discretion of the treating investigators. The impact of a longer duration of therapy on TFS here is unknown.

Since the completion of this study, the Society for Immunotherapy of Cancer has published consensus clinical definitions for resistance to PD-1 inhibitors and ICI-based combination therapies (26–29). A limitation to this study is that the response data were not collected on the basis of primary versus acquired resistance to prior PD-1 inhibitor therapy because these guidelines postdated the design of the trial. Newly designed clinical trials studying immunotherapeutic agents in the second-line setting or beyond should differentiate between the resistance patterns of enrolled patients. Adhering to these definitions, which have refined and formalized the concept of resistance to anti-PD-1-based therapies, will allow for greater conformity in clinical trial design and reporting in the future.

Improvements in the overall outcome for patients with metastatic melanoma can be achieved only if combination partners for anti-PD-1 overcome anti-PD-1 resistance. Biomarkers to select patients for different anti-PD-1 combinations are not yet available. On the basis of the activity demonstrated in our trial, studies of sotigalimab and nivolumab in patients with primary resistance to ipilimumab/nivolumab and relatlimab/nivolumab are warranted. Although patients responding to ipilimumab/nivolumab and subsequently progressing on nivolumab maintenance could respond again to reinduction with the combination of ipilimumab and nivolumab, prior toxicity during ipilimumab treatment could preclude rechallenge with the agent. This clinical setting provides an opportunity for study of combinations with improved safety profiles, as demonstrated for sotigalimab and nivolumab in this trial. Finally, addition of sotigalimab to the other ICI combinations should be entertained, although preferably in patients selected before or early during treatment with low probability of response to the standard doublets.

Authors' Disclosures

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Note

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