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OX40 Agonist BMS-986178 Alone or in Combination With Nivolumab and/or Ipilimumab in Patients With Advanced Solid Tumors

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ABSTRACT

Purpose: This phase I/IIa study (NCT02737475) evaluated the safety and activity of BMS-986178, a fully human OX40 agonist IgG1 mAb, ± nivolumab and/or ipilimumab in patients with advanced solid tumors.

Patients and Methods: Patients (with non–small cell lung, renal cell, bladder, other advanced cancers) received BMS-986178 (20–320 mg) ± nivolumab (240–480 mg) and/or ipilimumab (1–3 mg/kg). The primary endpoint was safety. Additional endpoints included immunogenicity, pharmacodynamics, pharmacokinetics, and antitumor activity per RECIST version 1.1.

Results: Twenty patients received BMS-986178 monotherapy, and 145 received combination therapy in various regimens (including two patients receiving nivolumab monotherapy). With a follow-up of 1.1 to 103.6 weeks, the most common (≥5%) treatment-related adverse events (TRAEs) included fatigue, pruritus, rash, pyrexia, diarrhea, and infusion-related reactions. Overall, grade 3–4 TRAEs occurred in one of 20 patients (5%) receiving BMS-986178 monotherapy, six of 79 (8%) receiving BMS-986178 plus nivolumab, zero of two receiving nivolumab monotherapy, six of 41 (15%) receiving BMS-986178 plus ipilimumab, and three of 23 (13%) receiving BMS-986178 plus nivolumab plus ipilimumab. No deaths occurred. No dose-limiting toxicities were observed with monotherapy, and the MTD was not reached in either the monotherapy or the combination escalation cohorts. No objective responses were seen with BMS-986178 alone; objective response rates ranged from 0% to 13% across combination therapy cohorts.

Conclusions: In this study, BMS-986178 ± nivolumab and/or ipilimumab appeared to have a manageable safety profile, but no clear efficacy signal was observed above that expected for nivolumab and/or ipilimumab.

Introduction

Cancer immunotherapy modulates the immune system to promote an antitumor response in patients with cancer and includes various approaches (1). One established approach is the utilization of immune checkpoint inhibition with anti-programmed death protein-1 (anti–PD-1)/anti-programmed death protein ligand 1 (anti–PD-L1) and anti-CTL–associated protein 4 (CTLA-4) mAbs. This approach has demonstrated durable antitumor responses and significant survival benefit in many tumor types, including melanoma, bladder, and renal cell carcinoma (RCC) as well as non–small cell lung cancer (NSCLC; refs. 2–4). For example, combination of the anti–PD-1 inhibitor nivolumab and CTLA-4 inhibitor ipilimumab has led to enhanced antitumor responses and survival compared with either inhibitor alone (5–8). Despite these benefits, many patients exhibit resistance to checkpoint inhibitor therapies (3). Thus, there is a need for novel immuno-oncology strategies that modulate the immunosuppressive tumor microenvironment and enhance antitumor T-cell responses (4, 5).

Activation of costimulatory pathways that stimulate T-cell response and inhibit regulatory T-cell–mediated suppression of effector $CD4^+$ and $CD8^+$ T cells is associated with enhanced antitumor response induced by checkpoint inhibitors in preclinical models (9). The tumor necrosis factor receptor super family (TNFRSF) includes several costimulatory proteins with key roles in T-cell development and survival, immune activation, and antitumor immune responses (9–11). Preclinical data suggest that agonistic antibodies to TNFRSF costimulatory receptors could provide therapeutic benefit and further enhance the antitumor response observed when they are combined with checkpoint inhibitors (12–15). OX40 is a member of the TNFRSF and regulates multiple T-cell functions (4, 16–18). The cell surface expression of OX40 is upregulated following T-cell activation; upon binding the OX40 ligand, it provides costimulatory signals, increasing the activation of $CD4^+$ and $CD8^+$ T effector cells in preclinical studies (4, 16, 17). OX40 may also inhibit regulatory T-cell–mediated suppression and block the generation of regulatory T cells, leading to enhanced T effector cell activity (17). Anti-OX40

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

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Translational Relevance

Immune checkpoint inhibitors have improved the treatment of several cancers, but novel approaches are needed to extend benefits to more patients and to enhance the duration of response. Combination of immune checkpoint inhibitors with OX40.23, a murine ligand-blocking OX40 agonist, demonstrated enhanced efficacy in preclinical models. In this phase I/IIa study, BMS-986178, a fully human IgG1 agonist mAb, with or without nivolumab and/or ipilimumab exhibited an acceptable safety profile in patients with advanced solid tumors. Objective response rates were not higher than those that would have been expected with nivolumab with or without ipilimumab. In summary, the findings of this study in a broad population of patients with advanced cancer did not demonstrate a clear improved efficacy signal for BMS-986178 with or without nivolumab and/or ipilimumab.

monotherapy suppressed tumor growth in several preclinical mouse tumor models and also enhanced antitumor T-cell activity when combined with checkpoint inhibitors, supporting the potential of these combinations to provide more durable responses than checkpoint inhibitor monotherapy (4, 19–21). The role of OX40 activity is being studied in various human cancers, including bladder (22), colorectal (23, 24), RCC (22, 25, 26), and NSCLC (27).

BMS-986178 is a fully human IgG1 agonist mAb that binds with high affinity to the OX40 receptor (28). Preclinical studies with the murine analogue OX40.23 as monotherapy demonstrated antitumor activity that was further enhanced when it was combined with checkpoint inhibitors (29). In the phase I clinical trial, the combination of BMS-986178 and nivolumab or ipilimumab demonstrated linear pharmacokinetics with dose-related increases in exposure (30). BMS-986178 monotherapy increased proinflammatory cytokines, such as IFNγ and the IFNγ-induced cytokines CXCL9 and CXCL10, in patients with advanced solid tumors, with greater effects observed after combination therapy (28). In addition, BMS-986178 treatment increased the proliferation of $CD4^+/CD8^+$ effector memory cells that was enhanced when BMS-986178 was combined with nivolumab (anti–PD-1) or ipilimumab (anti–CTLA-4; ref. 28). Although increases in exposure corresponded with pharmacodynamic effects, as previously reported, the optimal dose of OX40 agonism may not be the highest dose possible. Dose-optimization studies demonstrated that OX40 receptor occupancy (RO) between 20% and 50% both *in vitro* and *in vivo* was associated with maximal enhancement of T-cell effector function by anti-OX40 treatment, whereas a RO >40% led to a profound loss in OX40 receptor expression (28). Here we describe results of a phase I/IIa dose-escalation and -expansion study of BMS-986178 with or without nivolumab and/or ipilimumab in patients with advanced solid tumors (NCT02737475).

Patients and Methods

Study design and treatment

NCT02737475 (CA012004) is an open-label phase I/IIa study investigating the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of BMS-986178 as monotherapy and in combination with nivolumab and/or ipilimumab in patients with advanced

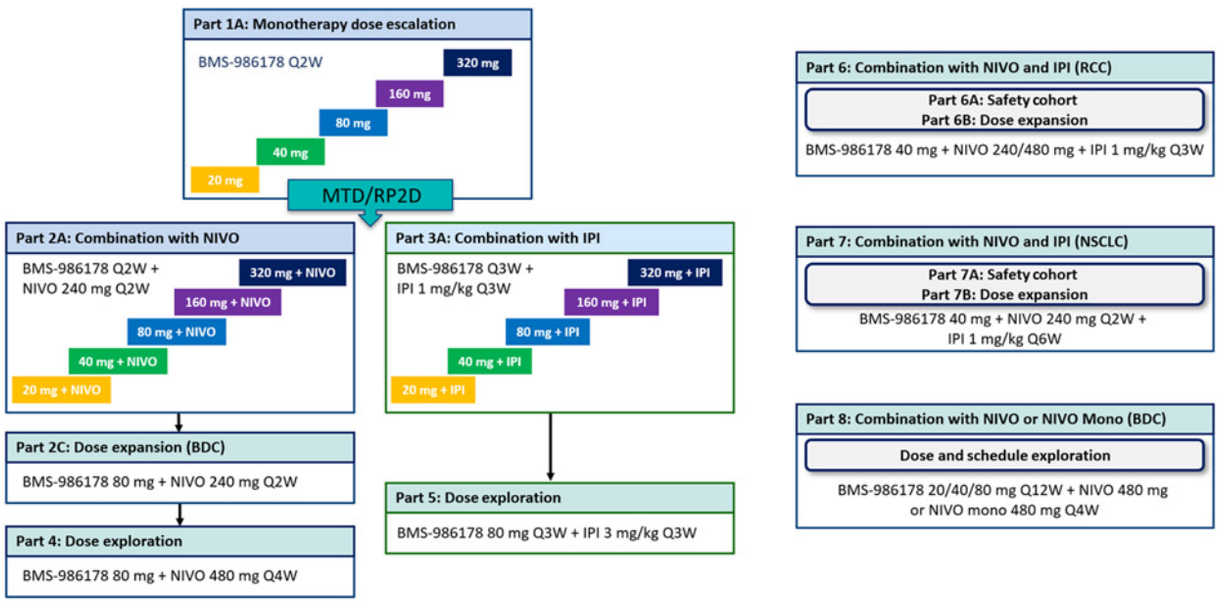

Figure 1.

Study design for evaluation of BMS-986178 and nivolumab and/or ipilimumab in patients with advanced solid tumors. Dose-escalation cohorts were treated with 20, 40, 80, 160, or 320 mg of BMS-986178 Q2W (monotherapy; part 1A); BMS-986178 Q2W plus NIVO 240 mg Q2W (combination; part 2A); BMS-986178 Q3W plus IPI 1 mg/kg Q3W (combination; part 3A). In the dose-expansion cohorts, patients with bladder cancer were treated with BMS-986178 80 mg plus NIVO 240 mg Q2W, patients with renal cell carcinoma were treated with BMS-986178 40 mg plus NIVO 240/480 mg and IPI 1 mg/kg Q3W, and patients with NSCLC were treated with BMS-986178 40 mg plus NIVO 240 mg Q2W and IPI 1 mg/kg Q6W. In the dose-exploration cohorts, patients were treated with BMS-986178 80 mg plus NIVO 480 mg Q4W or BMS-986178 80 mg Q3W plus IPI 3 mg/kg Q3W (parts 4 and 5, respectively) and BMS-986178 20/40/80 mg Q12W plus NIVO 480 mg Q4W or NIVO monotherapy 480 mg Q4W (part 8). Note: For parts 3A, 5, and 6, IPI was administered through cycle 4 only. IPI, ipilimumab; NIVO, nivolumab; Q2W, every 2 weeks, Q3W, every 3 weeks, Q4W, every 4 weeks; Q6W, every 6 weeks; Q12W, every 12 weeks.

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solid tumors across 28 sites in Canada, France, Israel, Italy, the Netherlands, Spain, and the United States. This multicohort study is composed of dose-escalation/exploration and dose-expansion phases that evaluated BMS-986178 alone or in combination with nivolumab and/or ipilimumab. Each cohort proceeded in a phased approach based on study-emergent safety, pharmacokinetic, and pharmacodynamic data. During the dose-escalation phase, patients with advanced solid tumors who were refractory to or intolerant of the established therapy known to provide clinical benefit for their disease in the advanced, recurrent, or metastatic setting were treated with 20, 40, 80, 160, or 320 mg of BMS-986178 intravenously every 2 weeks (monotherapy; part 1A), BMS-986178 (monotherapy escalation doses) plus nivolumab 240 mg i.v. every 2 weeks (part 2A), or BMS-986178 (monotherapy escalation doses) plus ipilimumab 1 mg/kg i.v. every 3 weeks (part 3A; **Fig. 1**).

The rationale for selection of these doses has been described previously and was based on pharmacokinetic and pharmacodynamic modeling of the relationship between RO, pharmacodynamic modulation, and efficacy (28–31). On the basis of preclinical data, available RO data from the every 2 weeks cohort receiving monotherapy, and C_{min} (minimum plasma concentration after dosing) data at day 14 (trough sample), a mathematical model was developed to predict RO at various dosing regimens (e.g., every 4 weeks, every 6 weeks, and every 12 weeks), taking into account interpatient variability in both pharmacokinetics and pharmacodynamics (RO), to maximize the potentiation of T-cell responses (28, 31).

Combination treatments in parts 2A and 3A were initiated after completion of ≥3 dose cohorts in part 1A. Dose-escalation decisions were based on dose-limiting toxicities (DLTs) using a Bayesian logistic regression model (for BMS-986178 monotherapy) or a Bayesian copula logistic regression model (for BMS-986178 in combination with nivolumab and/or ipilimumab) along with pharmacokinetic, pharmacodynamic, immunogenicity, and safety data. The observation period to detect a DLT was 28 days for both monotherapy and combination therapy dose-escalation parts. Dose-escalation recommendations were made after DLT information became available for each dosing cohort of patients. The sample size for each dose-escalation cohort depended on observed toxicity and posterior inference. Approximately 90 patients were expected to be treated during the dose-escalation phase [BMS-986178 monotherapy (part 1A), $n = 30$; BMS-986178 in combination with nivolumab (part 2A), $n = 30$; BMS-986178 in combination with ipilimumab (part 3A), $n = 30$].

In the dose-expansion phase, patients with advanced bladder cancer received BMS-986178 80 mg plus nivolumab 240 mg every 2 weeks (part 2C), patients with RCC received BMS-986178 40 mg plus nivolumab 240 mg plus ipilimumab 1 mg/kg every 3 weeks for four cycles followed by maintenance BMS-986178 and nivolumab 480 mg every 4 weeks (part 6B), and patients with NSCLC received BMS-986178 40 mg plus nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (part 7B; **Fig. 1**). These doses were determined following initiation of parts 1A, 2A, and 3A and evaluation of safety after initial dose escalation. The dose-expansion cohorts evaluating the combination of BMS-986178 plus nivolumab and ipilimumab were preceded by safety lead-in cohorts (parts 6A and 7A).

The estimated sample size for the dose-expansion phase was guided by a Simon two-stage design, which was based on target response rate [target objective response rate (ORR)] and the ability to identify a signal. The total sample size for each expansion cohort was calculated to provide reasonable false-positive and false-negative rates based on assumptions of true (target) and historical ORRs for each indication (sample size determinations are described in the online Supplement). Decisions regarding continuing or not continuing enrollment in a specific arm were based on a combination of model guidance, clinical judgment on the totality of data, and the discretion of the sponsor and investigators.

In additional dose-exploration cohorts, patients were treated with BMS-986178 80 mg every 2 weeks plus nivolumab 480 mg every 4 weeks (part 4), BMS-986178 80 mg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks (part 5), or BMS-986178 20/40/80 mg every 12 weeks plus nivolumab 480 mg every 4 weeks or nivolumab monotherapy 480 mg every 4 weeks (part 8). The 12-week interval was derived on the basis of the population pharmacokinetic model described above (28).

A minimum of six patients (up to 12) were treated in the different dose-exploration cohorts. A sample size of six to 12 patients per dose level and schedule provided 90% probability of observing ≥1 occurrence of a specific adverse event (AE) that would occur with a 32% or 17% incidence in the population, respectively. It was assumed that this number of patients would provide an accurate estimate (within 20% of the true value) of the ratio of on-treatment to baseline pharmacodynamic biomarker values.

Patients were treated with BMS-986178 alone or in combination with nivolumab and/or ipilimumab for 24 weeks (parts 1–7) or 24 months (part 8) or until meeting protocol-specified discontinuation criteria, followed by a safety follow-up of 100 days. For part 8 and any patients in part 2, 4, 6, or 7 who were approved for additional cycles up to 2 years of treatment, patients were monitored for 2 years from the first study dose to evaluate tumor response and survival. In all study sections, patients were treated until clinical deterioration, progressive disease, unacceptable toxicity, or completion of 24 weeks of treatment. Treatment beyond progression was allowed if patients were continuing to experience clinical benefit as assessed by the investigator, tolerating treatment, and meeting other protocol-specified criteria. Patients completing approximately 24 weeks of treatment with ongoing disease control [complete response, partial response (PR), or stable disease (SD)] and without any significant toxicity were eligible for retreatment.

The study protocols were approved by the institutional review board or independent ethics committee of each participating institution. The studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice as defined by the International Council for Harmonization. All patients provided written informed consent prior to enrollment.

Patient eligibility

Eligible patients were aged ≥18 years, had confirmed advanced solid tumors (metastatic, recurrent, refractory, and/or unresectable) and ≥1 lesion with measurable disease per RECIST version 1.1, and had progressed on or been intolerant of ≥1 standard treatment regimen in the advanced or metastatic setting (parts 1A, 2A, 2E, 3A, 4, 5, 6A, 7A). However, in patients with bladder cancer (parts 2C, 8) or cervical cancer (part 2D), patients must have been offered and/or received or refused ≥1 prior platinum-based therapy. In part 6A, patients with RCC must have progressed on or been intolerant of ≥1 standard treatment regimen in the advanced/metastatic setting. In part 6B, no prior therapy was allowed for patients with RCC, with the exception of 1 prior adjuvant or neoadjuvant therapy for completely resectable disease that did not include an agent targeting VEGF or VEGFRs. In part 7B, no prior systemic therapy was allowed for patients with stage IV or recurrent NSCLC and if recurrence occurred ≥6 months after the last dose. Other key eligibility criteria included Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were required

to provide pretreatment and on-treatment tumor biopsies (core needle, excisional, or incisional). Prior immune checkpoint inhibitor therapy was permitted following a washout period >4 weeks after the last treatment. Specific eligibility criteria for dose-expansion and -exploration cohorts are described in the Supplementary Materials.

Patients were excluded if they had metastases in the central nervous system or it was the only site of disease, carcinomatous meningitis, autoimmune disease, interstitial lung disease that was symptomatic and required systemic treatment with either corticosteroids (prednisone equivalents >10 mg daily) or other immunosuppressive medications within 14 days of study drug administration, uncontrolled or significant cardiovascular disease, or history of chronic hepatitis.

Patients were also excluded if they had been treated previously with T-cell costimulation agents; had a history of life-threatening toxicity related to prior immune therapy; had evidence of active infection, positive HIV test history, or known AIDS; or had any major surgery within 4 weeks of study drug administration.

Study objectives and assessments

The primary objective of this trial was to determine the safety, tolerability, DLTs, and MTD/recommended phase II dose of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab in patients with advanced solid tumors. AEs were assessed according to the NCI Common Terminology Criteria for Adverse Events version 4.03 during treatment and for ≥100 days after the last dose of study treatment. Secondary objectives included antitumor activity, immunogenicity, pharmacokinetics, and pharmacodynamics. Exploratory endpoints included the change from baseline in biomarker measurements of peripheral blood and/or tumor tissue. Disease status was assessed by investigators using CT scans and/or MRI at baseline and every 8 weeks (±1 week), followed by every 12 weeks during the response follow-up phases per RECIST v1.1 (32) until discontinuation of treatment or withdrawal from the study.

Serum samples for pharmacokinetics and immunogenicity assessments were collected from all patients receiving BMS-986178 alone or in combination with nivolumab and/or ipilimumab. Pharmacokinetics was characterized by noncompartmental analysis. Immunogenicity analyses for antidrug antibodies (anti-BMS-986178 and/or anti-nivolumab and/or anti-ipilimumab) were performed using validated immunoassays. An assay to measure total soluble OX40 in patient serum was developed and validated (fit for purpose) using the Meso Scale Discovery platform. IHC for biomarkers, including FoxP3 (clone 23A/E7), CD8 (clone C8/144B), PD-L1 (clone 28-8), and OX40 (clone ACT35), was performed by Mosaic Laboratories on 4-mm-thick formalin-fixed, paraffin-embedded sections of tumor biopsy tissue using a BOND RX platform (Leica Biosystems). PD-L1 expression was assessed in both tumor and immune cell peripheral blood compartments. Mandatory biopsies were obtained at screening (all parts). On-treatment biopsies were collected at cycle 2 day 1 (parts 1 and 2), cycle 1 day 15 (parts 3, 5, and 6), cycle 1 day 15 (parts 4 and 7), and cycle 1 days 15 and 78 (part 8); however, on-treatment biopsies were not mandatory during dose escalation for monotherapy.

Results

Patient baseline characteristics

From June 2016 to September 2018, a total of 165 patients with advanced tumors were treated with BMS-986178 with or without nivolumab and/or ipilimumab (**Table 1**; **Fig. 1**). Ninety-eight patients were treated in the dose-escalation cohorts (BMS-986178 monotherapy, $n = 20$; BMS-986178 plus nivolumab, $n = 43$; BMS-986178 plus ipilimumab, $n = 35$). Sixty-seven patients were treated in the dose-expansion, safety, and dose-exploration cohorts [BMS-986178 plus nivolumab, $n = 18$ (bladder cancer); BMS-986178 plus nivolumab, $n = 12$ (advanced tumors); BMS-986178 plus ipilimumab, $n = 6$ (advanced tumors); BMS-986178 plus nivolumab and ipilimumab, $n = 8$ (RCC); BMS-986178 plus nivolumab and ipilimumab, $n = 15$ (NSCLC); and BMS-986178 plus nivolumab or nivolumab monotherapy, $n = 8$ (bladder cancer)].

Across all cohorts, the median age ranged from 55 to 69 years. The majority of patients were male (60%) and predominantly white (93%). Most patients had received prior therapy; 38% had received ≥3 prior lines of therapy. Twenty-four percent of patients had received prior anti–PD-1/anti–PD-L1 and 7% had received prior anti–CTLA-4 therapy (**Table 1**). At the time of database lock (March 8, 2019), the duration of follow-up for response in evaluable patients ranged from 1.14 to 103.57 weeks.

Safety

In the dose-escalation cohorts (parts 1A, 2A, 3A), no DLTs were observed. Treatment-related AEs (TRAEs) were reported in five of 20 patients (25%) in the BMS 986178 monotherapy cohort, and one of 20 (5%) had a grade 3–4 TRAE. In the BMS 986178 plus nivolumab cohort, 21 of 43 patients (49%) had a TRAE, with two of 43 (5%) having grade 3 or 4 TRAEs. In the BMS 986178 plus ipilimumab cohort, 18 of 35 patients (51%) had a TRAE, with four of 35 (11%) having grade 3 or 4 TRAEs (**Table 2**). Serious TRAEs, as reported by the investigators, occurred in 5% ($n = 1$; grade 2 pneumonitis), 2.3% ($n = 1$; grade 3 pneumonitis), and 5.7% ($n = 2$; grade 3 infusion-related reaction and grade 3 diarrhea) of patients, respectively, in parts 1A, 2A, and 3A. TRAEs leading to discontinuation were reported in two patients in the BMS-986187 plus nivolumab cohort (grade 3 pneumonitis and duodenitis) and two patients in the BMS 986178 plus ipilimumab cohort (grade 2 and 3 infusion-related reactions). An MTD was not reached in the monotherapy or combination dose-escalation cohorts.

In the dose-expansion phase (parts 2C, 6, 7), TRAEs were reported in 12 of 18 patients (67%) with bladder cancer in the BMS 986178 plus nivolumab cohort, with two of 18 having grade 3–4 TRAEs (11%). In patients with RCC treated with BMS 986178 plus nivolumab and/or ipilimumab (part 6), TRAEs were reported in five of eight patients (63%); no grade 3–4 TRAEs were reported. In patients with NSCLC (part 7) treated with BMS 986178 plus nivolumab and ipilimumab, TRAEs were reported in 12 of 15 patients (80%), with three of 15 (20%) having grade 3–4 TRAEs. Serious TRAEs were reported in one patient with RCC (grade 2 diarrhea) and one patient with NSCLC (grade 2 facial paralysis).

In the dose-exploration cohorts (parts 4, 5, 8), TRAEs were reported in nine of 18 patients (50%) in the BMS 986178 plus nivolumab cohort, with two of 18 (11%) having grade 3 or 4 TRAEs (parts 4 and 8). In the BMS 986178 plus ipilimumab group (part 5), three of six patients (50%) had a TRAE, with two of six (33%) having grade 3–4 TRAEs. One TRAE was noted in the nivolumab monotherapy cohort (part 8). Serious TRAEs were reported in 17% of patients in parts 4 and 8 BMS-986178 plus nivolumab (n = 3/18; grade 3 duodenitis, grade 2 exacerbation of preexisting psoriatic arthropathy, grade 3 infusion-related reaction). Serious TRAEs were reported in 17% of patients in part 5 ($n = 1/6$; grade 3 adrenal insufficiency). TRAEs leading to discontinuation were reported in one patient treated with BMS986178 plus nivolumab (grade 3 duodenitis).

Overall, grade 3–4 TRAEs occurred in one of 20 patients (5%) receiving BMS-986178 monotherapy, six of 79 (8%) receiving BMS-986178 plus nivolumab, zero of two receiving nivolumab monotherapy, six of 41 (15%) receiving BMS-986178 plus ipilimumab, and three

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Table 1. Baseline demographics and prior therapy in patients treated with BMS-986178 and nivolumab and/or ipilimumab.

	Monotherapy	Combination therapy		Dose expansion	Dose exploration		Safety/dose expansion		Dose/schedule exploration
	Part 1A	Part 2A	Part 3A	Part 2C	Part 4	Part 5	Part 6A/6B	Part 7A/7B	Part 8
	BMS-986178 Q2W ($n = 20$)	BMS-986178 + NIVO Q2W ($n = 43$)	BMS-986178 + IPI Q3W ($n = 35$)	BMS-986178 80 mg + NIVO 240 mg Q2W (BDC) ($n = 18$)	BMS-986178 80 mg + NIVO 480 mg Q4W ($n = 12$)	BMS-986178 80 mg + IPI 3 mg/kg Q3W ($n = 6$)	BMS-986178 40 mg + NIVO 240 mg + IPI 1 mg/kg Q3W (RCC) ($n = 8$)	BMS-986178 40 mg Q2W + NIVO 240/ 480 mg Q2W + IPI 1 mg/kg Q6W (NSCLC) ($n = 15$)	BMS-986178 20/40/80 mg Q12W + NIVO 480 mg Q4W and NIVO Mono Q4W (BDC)[a] ($n = 8$)
Median age (range), years	61 (24–80)	60 (32–82)	55 (24–79)	66 (50–80)	58 (38–70)	59 (27–73)	57.5 (25–71)	67 (56–84)	69 (60–79)
Sex, *n* (%)									
Male	13 (65)	23 (53.5)	14 (40)	17 (94.4)	4 (33.3)	3 (50)	6 (75)	13 (86.7)	6 (75)
Race, *n* (%)									
White	16 (80)	42 (97.7)	32 (91.4)	18 (100)	11 (91.7)	6 (100)	8 (100)	13 (86.7)	8 (100)
Black	2 (10)	0	0	0	1 (8.3)	0	0	1 (6.7)	0
Asian	1 (5.0)	1 (2.3)	1 (2.9)	0	0	0	0	1 (6.7)	0
American Indian or Alaska Native	0	0	1 (2.9)	0	0	0	0	0	0
Other	1 (5.0)	0	1 (2.9)	0	0	0	0	0	0
No. of prior therapies, *n* (%)									
0	0	2 (4.7)	1 (2.9)	0	0	0	1 (12.5)	7 (46.7)	2 (25.0)
1	8 (40.0)	7 (16.3)	16 (45.7)	11 (61.1)	5 (41.7)	1 (16.7)	4 (50.0)	8 (53.3)	4 (50.0)
2	3 (15.0)	9 (20.9)	5 (14.3)	2 (11.1)	2 (16.7)	2 (33.3)	2 (25.0)	0	1 (12.5)
≥3	9 (45.0)	25 (58.1)	13 (37.1)	5 (27.8)	5 (41.7)	3 (50.0)	1 (12.5)	0	1 (12.5)
Prior anti–PD-1/ PD-L1, *n* (%)	7 (35.0)	14 (32.6)	9 (25.7)	3 (16.7)	2 (16.7)	2 (33.3)	0	1 (6.7)	1 (12.5)
Prior anti–CTLA-4, *n* (%)	4 (20.0)	4 (9.3)	0	2 (11.1)	0	1 (16.7)	0	0	0

Note: All patients had Eastern Cooperative Oncology Group performance status of 0 or 1. For parts 3A, 5, and 6, ipilimumab was administered through cycle 4 only.
Abbreviations: BDC, bladder cancer; IPI, ipilimumab; Mono, monotherapy; NIVO, nivolumab; Q6W, every 6 weeks; Q12W, every 12 weeks.
[a]Two of eight patients in part 8 were treated with nivolumab monotherapy.

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Table 2. TRAEs in patients treated with BMS-986178 and nivolumab and/or ipilimumab.

	Monotherapy	Combination therapy		Dose expansion	Dose exploration		Safety/dose expansion		Dose/schedule exploration	
	Part 1A	Part 2A	Part 3A	Part 2C	Part 4	Part 5	Part 6A/6B	Part 7A/7B	Part 8	
	BMS-986178 Q2W ($n = 20$)	BMS-986178 + NIVO Q2W ($n = 43$)	BMS-986178 + IPI Q3W ($n = 35$)	BMS-986178 80 mg + NIVO 240 mg Q2W (BDC) ($n = 18$)	BMS-986178 80 mg + NIVO 480 mg Q4W ($n = 12$)	BMS-986178 80 mg + IPI 3 mg/kg Q3W ($n = 6$)	BMS-986178 40 mg + NIVO 240 mg + IPI 1 mg/kg Q3W (RCC) ($n = 8$)	BMS-986178 40 mg Q2W + NIVO 240/480 mg Q2W + IPI 1 mg/kg Q6W (NSCLC) ($n = 15$)	BMS-986178 20/40/80 mg Q12W + NIVO 480 mg Q4W (BDC) ($n = 6$)	NIVO 480 mg Q4W Mono (BDC) ($n = 2$)
Any TRAEs, *n* (%)	5 (25)	21 (48.8)	18 (51.4)	**12 (66.7)**	**6 (50.0)**	**3 (50.0)**	**5 (62.5)**	**12 (80.0)**	**3 (50)**	**1 (50)**
Grade 1 or 2 TRAEs in ≥5% of patients in any cohort, *n* (%)[a]										
Diarrhea	1 (5.0)	2 (4.7)	1 (2.9)	1 (5.6)	1 (8.3)	0	3 (37.5)	2 (13.3)	0	0
Fatigue	1 (5.0)	5 (11.6)	3 (8.6)	5 (27.8)	2 (16.7)	3 (50.0)	3 (37.5)	3 (20.0)	0	0
Infusion-related reaction	0	1 (2.3)	5 (14.3)	0	1 (8.3)	0	0	3 (20.0)	0	0
Pruritus	0	1 (2.3)	3 (8.6)	2 (11.1)	2 (16.7)	1 (16.7)	1 (12.5)	1 (6.7)	2 (33.3)	0
Pyrexia	1 (5.0)	6 (13.9)	1 (2.9)	2 (11.1)	0	0	1 (12.5)	0	1 (16.7)	0
Rash	0	1 (2.3)	4 (11.4)	0	1 (8.3)	1 (16.7)	1 (12.5)	4 (26.7)	1 (16.7)	0
Any grade 3 or 4 TRAEs, *n* (%)[a]										
Adrenal insufficiency	0	0	0	0	0	1 (16.7)	0	0	0	0
Alkaline phosphatase increased	0	1 (2.3)	0	0	0	0	0	0	0	0
Asthenia	0	0	1 (2.9)	0	0	0	0	1 (6.7)	0	0
Decreased appetite	0	0	1 (2.9)	0	0	0	0	0	0	0
Diarrhea	0	0	1 (2.9)	0	0	0	0	0	0	0
Duodenitis	0	0	0	0	1 (8.3)	0	0	0	0	0
Fatigue	1 (5.0)	0	0	0	0	0	0	0	0	0
Infusion-related reaction	0	0	1 (2.9)	0	0	0	0	0	1 (16.7)	0
Lipase increased	0	0	0	1 (5.6)	0	0	0	1 (6.7)	0	0
Lymphocyte count decreased	0	0	0	1 (5.6)	0	0	0	0	0	0
Pneumonitis	0	1 (2.3)	0	0	0	0	0	0	0	0
Pruritus	0	0	0	0	0	1 (16.7)	0	1 (6.7)	0	0
Pyrexia	0	0	0	0	0	0	0	0	0	0
Rash	0	0	1 (2.9)	0	0	0	0	0	0	0

(Continued on the following page)

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Table 2. TRAEs in patients treated with BMS-986178 and nivolumab and/or ipilimumab. (Cont'd)

	Monotherapy	Combination therapy		Dose expansion	Dose exploration		Safety/dose expansion		Dose/schedule exploration	
	Part 1A	Part 2A	Part 3A	Part 2C	Part 4	Part 5	Part 6A/6B	Part 7A/7B	Part 8	
	BMS-986178 Q2W ($n = 20$)	BMS-986178 + NIVO Q2W ($n = 43$)	BMS-986178 + IPI Q3W ($n = 35$)	BMS-986178 80 mg + NIVO 240 mg Q2W (BDC) ($n = 18$)	BMS-986178 80 mg + NIVO 480 mg Q4W ($n = 12$)	BMS-986178 80 mg + IPI 3 mg/kg Q3W ($n = 6$)	BMS-986178 40 mg + NIVO 240 mg + IPI 1 mg/kg Q3W (RCC) ($n = 8$)	BMS-986178 40 mg Q2W + NIVO 240/480 mg Q2W + IPI 1 mg/kg Q6W (NSCLC) ($n = 15$)	BMS-986178 20/40/80 mg Q12W + NIVO 480 mg Q4W (BDC) ($n = 6$)	NIVO 480 mg Q4W Mono (BDC) ($n = 2$)
Serious TRAEs, *n* (%)										
Adrenal insufficiency	0	0	0	0	0	1 (16.7)	0	0	0	0
Diarrhea	0	0	1 (2.9)	0	0	0	1 (12.5)	0	0	0
Duodenitis	0	0	0	0	1 (8.3)	0	0	0	0	0
Facial paralysis	0	0	0	0	0	0	0	1 (6.7)	0	0
Infusion-related reaction	0	0	1 (2.9)	0	0	0	0	0	1 (16.7)	0
Pneumonitis	1 (5.0)	1 (2.3)	0	0	0	0	0	0	0	0
Psoriatic arthropathy exacerbated	0	0	0	0	1 (8.3)	0	0	0	0	0

Note: For parts 3A, 5, and 6, ipilimumab was administered through cycle 4 only.

Abbreviations: BDC, bladder cancer; IPI, ipilimumab; Mono, monotherapy; NIVO, nivolumab; Q6W, every 6 weeks.

[a]A patient could have >1 TRAE.

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of 23 (13%) receiving BMS-986178 plus nivolumab and ipilimumab (**Table 2**). No treatment-related deaths were reported.

Immunogenicity

Evaluation of the development of BMS-986178 antidrug antibodies (ADAs) during dose escalation in patients receiving monotherapy (part 1A) or BMS-986178 in combination with nivolumab (part 2A) or ipilimumab (part 3A) are shown in Supplementary Table S1. In patients treated with BMS-986178 monotherapy, one of 12 evaluated patients (8%) had developed BMS-986178 ADAs and 92% did not. In patients receiving combination therapy, eight of 30 (27%) treated with BMS-986178 plus nivolumab developed ADAs to BMS-986178 and 11 of 26 (42%) treated with BMS-986178 plus ipilimumab developed ADAs to BMS-986178. Two of 34 patients (6%) developed ADAs to nivolumab in part 2A and two of 29 (7%) developed ADAs to ipilimumab in part 3A. No apparent association was observed between BMS-986178 ADAs and doses over the range of 20 to 320 mg in patients treated with BMS-986178 monotherapy.

Dose-related drug exposure

BMS-986178 exposure measured as area under the concentration versus time curve during cycle 1 was largely linear within the evaluated dose range of 20 to 320 mg for both BMS-986178 alone and in combination with nivolumab or ipilimumab (Supplementary Fig. S1A). Normalized area under the concentration versus time curve for free soluble OX40 increased with increasing BMS-986178 doses and plateaued at 160 mg (Supplementary Fig. S1B). This observed time- and dose-dependent modulation of soluble OX40 confirmed target engagement.

Antitumor activity

No antitumor responses were observed with BMS-986178 monotherapy. The ORR was 12% (5 PRs) with BMS-986178 plus nivolumab every 2 weeks [part 2A; cervical cancer ($n = 1$), RCC ($n = 1$), endometrial cancer ($n = 1$), breast cancer ($n = 2$)]. The ORR was 6% (one complete response) with BMS-986178 plus nivolumab every 2 weeks (part 2C; bladder cancer; **Table 3**). In the dose-expansion cohorts with BMS-986178 plus nivolumab and ipilimumab, the ORR was 13% (one PR) and 13% (two PRs) in patients with RCC (part 6) and NSCLC (part 7), respectively. Overall, seven of 20 patients in the BMS-986178 monotherapy cohort and 50 in the combination therapy cohorts (including nivolumab monotherapy) had SD as their best response (**Table 3**). Among 39 patients who had received prior immuno-oncology therapy, one had a PR and 13 had SD.

Biomarkers

The pharmacodynamic effect of treatment on proliferating ($Ki67^+$) $CD8^+$ cells and regulatory $FoxP3^+$ T cells was interrogated by IHC analysis of paired tumor biopsy samples. Because of the protocol design, limited on-treatment tumor samples were collected in the BMS-986178 monotherapy cohort. A trend toward increased frequency of $Ki67^+CD8^+$ cells and decreased percentage of $FoxP3^+$ T cells was observed in tumor tissue following treatment with BMS-986178 with nivolumab; however, this trend was not apparent in patients treated with BMS-986178 combined with ipilimumab or nivolumab and ipilimumab (**Fig. 2**). No consistent changes in tumor PD-L1 expression were observed during treatment with BMS-986178 and nivolumab and/or ipilimumab (Supplementary Fig. S2). At screening, 82% of tumor samples (97/118) tested had low levels (<1%) of OX40 expression (**Fig. 3A**). No significant changes in the percentage of OX40 expression were noted over the course of the study (**Fig. 3B**).

Discussion

This phase I/IIa dose-escalation and -expansion study evaluated the safety and preliminary antitumor activity of the OX40 agonist antibody BMS-986178 with or without nivolumab and/or ipilimumab in patients with advanced solid tumors. Overall, BMS-986178 monotherapy exhibited a tolerable safety profile, with no DLTs observed and no discontinuations due to toxicity of the study treatment. The safety of BMS-986178 demonstrated in this trial was similar to previous reports on safety from other anti-OX40 therapy clinical trials, which reported lymphopenia, fatigue, rash, infusion-related reactions, pyrexia, and pneumonitis (13, 25, 33–35). In the dose-escalation cohorts, any-grade TRAEs were reported in 25% of patients receiving monotherapy and approximately 50% of patients receiving combination therapy. However, no new safety signals were observed with checkpoint inhibitors compared with monotherapy, and no MTD was reached with either combination therapy regimen.

In an earlier report from this study, although there was some evidence that BMS-986178 monotherapy induced cytokines in peripheral blood (28), BMS-986178 did not appear to increase consistent changes in tumor total $CD8^+$ T cells, proliferating $CD8^+$ T cells, or regulatory T-cell density or provide any substantial clinical benefit in a broad population of patients with advanced solid tumors. Multiple doses, schedules, combination partners, and tumor-specific cohorts for more homogeneous patient populations were also investigated; however, no responders to monotherapy were observed. These findings suggest that the responses observed in the combination treatment groups in this study were not greater than what may have been expected with nivolumab and/or ipilimumab.

No apparent association between the BMS-986178 dose and percentage of ADAs was observed with monotherapy in this patient population. Although the percentage of ADAs appeared to be higher in the combination groups than in the monotherapy group, pharmacokinetic analysis demonstrated a linear area under the curve increase that was proportional to the dose and seemed to be comparable between monotherapy and combination therapy. Therefore, we had no expectation of an impact of ADAs on pharmacokinetics. The possible impact of ADAs on efficacy in the combination therapy group has not been assessed due to the small sample size.

Preliminary antitumor activity has been investigated with other OX40 agonists with or without PD-L1 inhibitors, with similar results (13, 25, 34, 35). In a phase I trial, monotherapy with MEDI0562, a humanized IgG4 OX40 mAb, resulted in limited PRs in two of 50 response-evaluable patients (squamous cell carcinoma of the larynx and bladder cancer; ref. 34). In another phase I trial, monotherapy with PF-8600, a fully human agonist IgG2 mAb that targets OX40, resulted in a PR only in one of 25 patients with advanced malignancies (25). In a preliminary report, combination of the OX40 agonist MOXR0916 and the PD-L1 inhibitor atezolizumab in a phase Ib trial in patients with advanced solid tumors demonstrated efficacy similar to that of atezolizumab monotherapy (35).

Although preclinical data demonstrated that antitumor activity with OX40 monotherapy was further enhanced with anti–PD-1 therapy, such activity was not reflected in this clinical study. Potential explanations include unknown optimal dosing considerations, limited translation of preclinical activity in the clinic, and lack of OX40 expression at screening/baseline [82% of tumor samples (97/118) exhibited low levels (<1%) of OX40 expression in this study; **Fig. 3A**]. In addition, no significant changes in the percentage of OX40 expression were noted over the course of the study (**Fig. 3B**). Another factor may have been that the patient cohorts in this study were heterogeneous, and most had multiple prior lines of treatment

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Table 3. Response in patients treated with BMS-986178 and nivolumab and/or ipilimumab.

	Monotherapy	Combination therapy		Dose expansion	Dose exploration		Safety/dose expansion		Dose/schedule exploration	
	Part 1A	Part 2A	Part 3A	Part 2C	Part 4	Part 5	Part 6A/6B	Part 7A/7B	Part 8	
	BMS-986178 Q2W ($n = 20$)	BMS-986178 + NIVO Q2W ($n = 43$)	BMS-986178 + IPI 1 mg/kg Q3W ($n = 34$)[a]	BMS-986178 80 mg + NIVO 240 mg Q2W (BDC) ($n = 18$)	BMS-986178 80 mg + NIVO 480 mg Q4W ($n = 12$)	BMS-986178 80 mg + IPI 3 mg/kg Q3W ($n = 6$)	BMS-986178 40 mg+ NIVO 240 mg + IPI 1 mg/kg Q3W (RCC) ($n = 8$)	BMS-986178 40 mg Q2W + NIVO 240 mg Q2W + IPI 1 mg/kg Q6W (NSCLC) ($n = 15$)	BMS-986178 20/40/ 80 mg Q12W + NIVO 480 mg Q4W ($n = 6$)	NIVO 480 mg Q4W Mono-therapy ($n = 2$)
ORR, *n* (%)	0	5 (12)	0	1 (6)	0	0	1 (13)	2 (13)	0	0
Best overall response, *n* (%)										
Complete response	0	0	0	1 (6)	0	0	0	0	0	0
Partial response	0	5 (12)	0	0	0	0	1 (13)	2 (13)	0	0
Stable disease	7 (35)	12 (28)	7 (21)	9 (50)	6 (50)	2 (33)	3 (38)	9 (60)	0	2 (100)
Progressive disease	11 (55)	21 (49)	20 (59)	8 (44)	3 (25)	4 (67)	3 (38)	3 (20)	6 (100)	0
Unable to determine	2 (10)	5 (12)	7 (21)	0	3 (25)	0	1 (13)	1 (7)	0	0
Disease control rate, *n* (%)	7 (35)	17 (40)	7 (21)	10 (56)	6 (50)	2 (33)	4 (50)	11 (73)	0	2 (100)

Note: For parts 3A, 5, and 6, ipilimumab was administered through cycle 4 only. Investigators were unable to determine the response if a patient was never treated, had the wrong cancer diagnosis, died prior to disease assessment, discontinued early due to toxicity, had relapse/progressive disease, or for other unspecified reason.

Abbreviations: BDC, bladder cancer; IPI, ipilimumab; NIVO, nivolumab; Q6W, every 6 weeks.

[a]One patient in the BMS-986178 320 mg dose group of this cohort did not have any postbaseline tumor lesions and was not included in the analysis.

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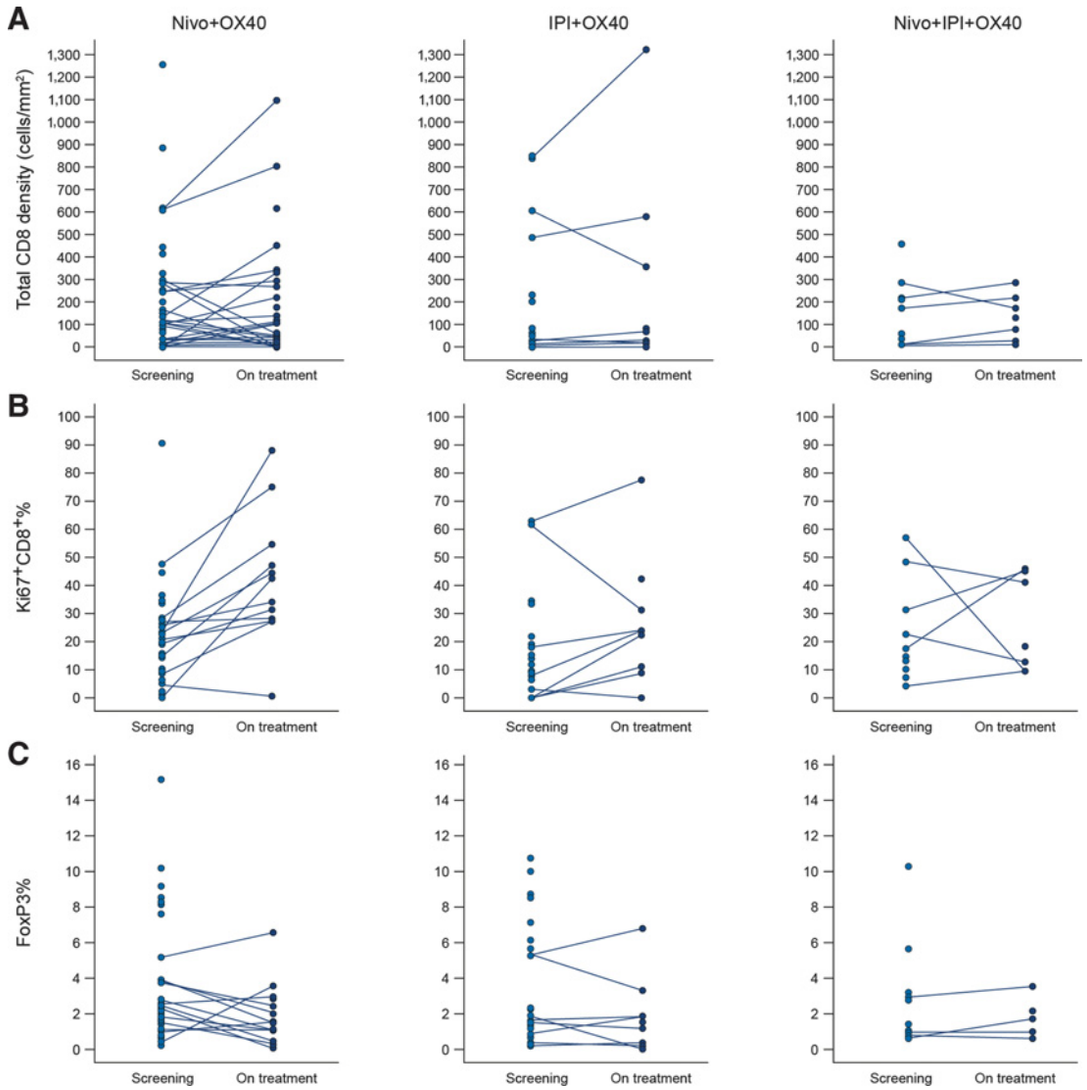

Figure 2.

Pharmacodynamics of BMS-986178 in combination with nivolumab and/or ipilimumab. Total $CD8^+$ T cells (**A**), percentage of proliferating $Ki67^+CD8^+$ T cells (**B**), and FoxP3 regulatory T cells (**C**) were analyzed by IHC in patients treated with BMS-986178 plus nivolumab ($n = 62$), BMS-986178 plus ipilimumab ($n = 37$), and BMS-986178 plus nivolumab and ipilimumab ($n = 15$). Plots show individual patient values at screening vs on treatment. A trend toward increased frequency of $Ki67^+CD8^+$ cells and decreased percentage of $FoxP3^+$ T cells was observed in tumor tissue after treatment with BMS-986178 with nivolumab and/or ipilimumab; however, this trend was not apparent in patients treated with BMS-986178 plus ipilimumab. IPI, ipilimumab; NIVO, nivolumab.

and recurrent refractory disease, which may have negatively influenced efficacy responses.

Optimal dosing of agonist antibodies, including those directed at T-cell agonists, is still under investigation. Antagonists are dosed to the MTD, leading to complete and sustained occupation of receptors or ligands, which may be required for maximal activity (36). However, the optimal dosing regimen for agonists may be lower or more intermittent in nature. In our previous report, OX40 RO >40% led to a profound loss in OX40 receptor expression in mice and humans treated every 2 weeks as well as decreased pharmacodynamic modulation (28). The previous report was based in part on RO measured in some of the patients enrolled earlier in the current study, which showed a high degree of RO even at the lowest dose (20 mg every 2 weeks; ref. 28). Pharmacokinetic–pharmacodynamic modeling indicated that lower doses administered at dosing intervals of up to 12 weeks would result in a trough RO between 20% and 50%; part 8 of the study was included to evaluate a longer interval of BMS-986178 dosing, but no additional efficacy signals were observed in that cohort.

Furthermore, the optimal sequencing of checkpoint inhibitors and T-cell agonists is unclear. It has been reported that concomitant exposure to PD-1 blockade and an OX40 agonist antibody could be detrimental (37). In a mouse model of PD-1–refractory breast cancer, concomitant PD-1 blockade reduced the therapeutic effect of anti-OX40 administered alone and was associated with increased serum cytokines and peripheral T-cell apoptosis (37). Anti-OX40 antibody followed several days later by anti–PD-1 resulted in increased

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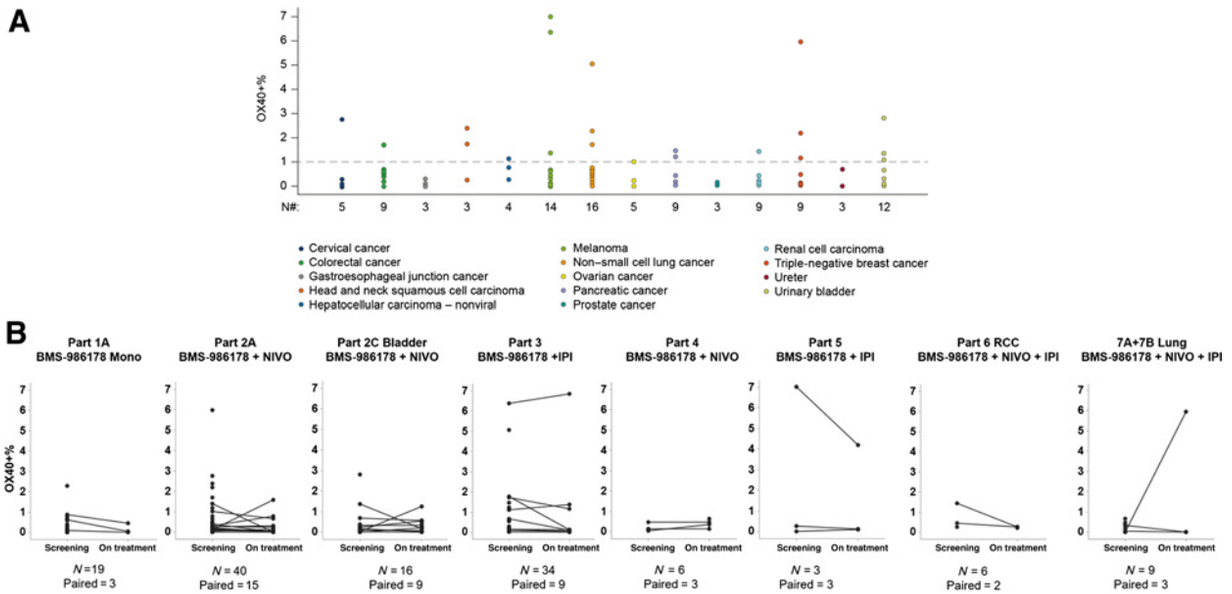

Figure 3.

OX40 expression in various tumor types at baseline (**A**) and pretreatment and posttreatment per cohort in patients with paired samples (**B**). In **A**, the plot shows the percentage of OX40 expression assessed by IHC in biopsy samples from individual patients with various tumor types. Tumor type is depicted by color. The number of tumors sampled is shown below the *x*-axis; some symbols may overlap. In **B**, the plot shows the percentage of OX40 expression before and after treatment by cohort. The number of tumors sampled is shown below the *x*-axis; some symbols may overlap. OX40 expression values were not obtained in all patients at all time points.

antitumor effects. In the mouse model, anti-OX40 antibodies administered alone appeared to stimulate tumor-specific T cells to a state in which checkpoints inhibited the antitumor response. Delaying administration of anti–PD-1 optimized the antitumor immune response. Conversely, others have reported that OX40 agonist antibodies increase the antitumor effectiveness of PD-1 blockade in mice when administered concomitantly (19, 38). The possibility that the sequence of administration may impact the response remains, but our concomitant treatment of BMS-986178 with nivolumab did not appear to result in loss of anti–PD-1 efficacy (28).

Despite preclinical activity being observed with OX40 agonists (and other T-cell agonists)—including monotherapy activity (10, 39)—these findings have not been replicated in the clinic. Although traditional xenograft and syngeneic models have been used for cytotoxic and targeted therapies, there may be limitations to these models for immunotherapy (40–42). Reasons may include but are not limited to (i) species differences in the immune system, (ii) a lack of genetic, antigenic, and environmental variability in the immune systems of animal models that does not recapitulate the reality of humans, and (iii) the complexity of the tumor microenvironment; the naturally occurring development of human tumors over time, including immunosurveillance, is likely a different hurdle for immunotherapy to overcome compared with that of a controlled injection of tumor cells that causes a de novo immune response at the same time that the immunotherapy is being investigated in animal models. Thus, a great need exists for improved preclinical models to allow for a more efficient and accurate assessment of novel agents to be prioritized for evaluation in the clinic.

Strategies to increase OX40 receptor expression and activated T cells include vaccines, toll-like receptor (TLR) agents, oncolytic viruses, and radiation (43, 44) and are being tested in combination in multiple clinical trials. For example, combinations of ABBV-927 (CD40 agonist) and ABBV-368 (OX40 agonist) with or without ABBV-181 (PD-1 inhibitor; NCT03893955), GSK3174998 (OX40 agonist) with pembrolizumab (anti–PD-1; NCT03447314), and BMS-986178 with SD-101 (TLR 9 agonist; NCT03831295) are currently being evaluated.

In summary, this study demonstrated that agonism of the OX40 costimulatory receptor with BMS-986178 plus checkpoint inhibitor blockade was safe in patients with advanced malignancies but yielded no clear efficacy signal.

Authors' Disclosures

M. Gutierrez reports other from Bristol Myers Squibb during the conduct of the study and personal fees from Merck, Bristol Myers Squibb, COTA, Guardant 360, Esanex, Foundation One, and Eli Lilly outside the submitted work. V. Moreno reports personal fees from Bristol Myers Squibb, Janssen, and Bayer outside the submitted work. A.J. Olszanski reports other from Bristol Myers Squibb during the conduct of the study and personal fees from Merck, Bristol Myers Squibb, Pfizer, Array, EMD Serono, Iovance, Novartis, and Alkermes outside the submitted work. A. Spreafico reports other from Bristol-Myers Squibb, Merck, Novartis, Roche, Alkermes, Surface Oncology, Symphogen, AstraZeneca/Medimmune, Janssen Oncology/Johnson & Johnson, GSK, and Bayer outside the submitted work. M. Ong reports personal fees from Bristol Myers Squibb, Merck, and EMD-Serono and grants and personal fees from AstraZeneca outside the submitted work. Q.S. Chu reports grants and personal fees from AstraZeneca; personal fees from Bristol Myers Squibb, Eli Lilly, Boeringher Ingelheim, Merck, Novartis, Pfizer, and Roche; other from Merck KgaA outside the submitted work. R.D. Carvajal reports personal fees and other from Bristol Myers Squibb during the conduct of the study; personal fees from Castle Biosciences, TriSalus, PureTech Health, Pierre Fabre; personal fees and other from Regeneron, Sanofi Genzyme, Merck, InxMed, and Immunocore; other from Plexxikon, Novartis, Mirati, Astellis, Amgen outside the submitted work; and is a scientific advisory board member at Rgenix, Aura Biosciences, and Chimeron. J. Trigo reports grants from AstraZeneca, Bristol Myers Squibb, Roche, and MSD outside the submitted work. M. Provencio reports grants and nonfinancial support from Bristol Myers Squibb

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Authors' Contributions

M. Gutierrez: Writing-review and editing. **V. Moreno:** Writing-review and editing. **K.M. Heinhuis:** Writing-review and editing. **A.J. Olszanski:** Writing-review and editing. **A. Spreafico:** Writing-review and editing. **M. Ong:** Writing-review and editing. **Q. Chu:** Writing-review and editing. **R.D. Carvajal:** Writing-review and editing. **J. Trigo:** Writing-review and editing. **M. Ochoa de Olza:** Writing-review and editing. **M. Provencio:** Writing-review and editing. **F.Y. De Vos:** Writing-review and editing. **F. De Braud:** Writing-review and editing. **S. Leong:** Writing-review and editing. **D. Lathers:** Writing-review and editing. **R. Wang:** Writing-review and editing. **P. Ravindran:** Writing-review and editing. **Y. Feng:** Writing-review and editing. **P. Aanur:** Writing-review and editing. **I. Melero:** Writing-review and editing.

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