Clinical Cancer Research

Pembrolizumab Plus Pegylated Interferon alfa-2b or Ipilimumab for Advanced Melanoma or Renal Cell Carcinoma: Dose-Finding Results from the Phase Ib KEYNOTE-029 Study

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Abstract

Purpose: Pembrolizumab monotherapy, ipilimumab monotherapy, and pegylated interferon alfa-2b (PEG-IFN) monotherapy are active against melanoma and renal cell carcinoma (RCC). We explored the safety and preliminary antitumor activity of pembrolizumab combined with either ipilimumab or PEG-IFN in patients with advanced melanoma or RCC.

Experimental Design: The phase Ib KEYNOTE-029 study (ClinicalTrials.gov, NCT02089685) included independent pembrolizumab plus reduced-dose ipilimumab and pembrolizumab plus PEG-IFN cohorts. Pembrolizumab 2 mg/kg every 3 weeks (Q3W) plus 4 doses of ipilimumab 1 mg/kg Q3W was tolerable if $\leq$6 of 18 patients experienced a dose-limiting toxicity (DLT). The target DLT rate for pembrolizumab 2 mg/kg Q3W plus PEG-IFN was 30%, with a maximum of 14 patients per dose level. Response was assessed per RECIST v1.1 by central review.

Results: The ipilimumab cohort enrolled 22 patients, including 19 evaluable for DLTs. Six patients experienced $\geq$1 DLT. Grade 3 to 4 treatment-related adverse events occurred in 13 (59%) patients. Responses occurred in 5 of 12 (42%) patients with melanoma and 3 of 10 (30%) patients with RCC. In the PEG-IFN cohort, DLTs occurred in 2 of 14 (14%) patients treated at dose level 1 (PEG-IFN 1 μg/kg/week) and 2 of 3 (67%) patients treated at dose level 2 (PEG-IFN 2 μg/kg/week). Grade 3 to 4 treatment-related adverse events occurred in 10 of 17 (59%) patients. Responses occurred in 1 of 5 (20%) patients with melanoma and 2 of 12 (17%) patients with RCC.

Conclusions: Pembrolizumab 2 mg/kg Q3W plus ipilimumab 1 mg/kg Q3W was tolerable and provided promising antitumor activity in patients with advanced melanoma or RCC. The maximum tolerated dose of pembrolizumab plus PEG-IFN had limited antitumor activity in this population. *Clin Cancer Res; 24(8); 1805–15. ©2018 AACR.*

Introduction

In recent years, the treatment of advanced malignancies has been revolutionized by the advent of immunotherapy with checkpoint inhibitors, which have been shown to prolong survival in several advanced malignancies, including melanoma (1–4) and renal cell carcinoma (RCC; ref. 5). Advanced melanoma was the first malignancy in which the antitumor activity of checkpoint inhibition was confirmed, with the approval of the cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) inhibitor ipilimumab (1, 2) in 2011 and the programmed death 1 (PD-1) inhibitors pembrolizumab (3, 6–11) and nivolumab (4, 12–15) in 2014. In the phase III KEYNOTE-006 study, pembrolizumab significantly improved survival over ipilimumab (3, 11). Subsequently, anti–PD-1 and anti–programmed death ligand 1 (PD-L1) inhibitors have been approved in various countries for treating several advanced malignancies.

Although immune checkpoint inhibitor monotherapy provides a meaningful survival benefit, further improvement may be achieved with combination immunotherapy. One combination of interest is dual PD-1 and CTLA-4 blockade. By combining CTLA-4 and PD-1 inhibition, it is possible to affect both the priming (anti–CTLA-4) and effector (anti–PD-1) phases of T-cell activation (16). In a mouse model of melanoma, combined CTLA-4 and PD-1 inhibition permitted continued survival and proliferation of intratumoral $CD4^+$ and $CD8^+$ effector T cells and resulted in synergistic tumor rejection (17). Similar findings were observed in a mouse colon carcinoma model (18). *In vitro*, treatment of peripheral blood mononuclear cells with combined

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Translational Relevance

The combination of reduced-dose anti–PD-1 and standard-dose ipilimumab showed significant antitumor activity but considerable toxicity in patients with metastatic melanoma or renal cell carcinoma. Much of this toxicity was attributable to the full-dose ipilimumab regimen. In an effort to develop more tolerable yet equally effective combination regimens, we assessed standard-dose pembrolizumab with either reduced-dose ipilimumab or pegylated IFN. The safety profile and antitumor activity observed for pembrolizumab plus reduced-dose ipilimumab prompted the initiation of a large melanoma expansion cohort. The expansion cohort showed similar antitumor activity but substantially less toxicity for standard-dose pembrolizumab plus reduced-dose ipilimumab than the regimen of reduced-dose anti–PD-1 and standard-dose ipilimumab approved for melanoma treatment, perhaps creating an alternative combination regimen for this population. The pembrolizumab plus pegylated IFNα2b regimen showed significant toxicity and appeared to be less active; consequently, it was not pursued further.

CTLA-4 and PD-1 inhibition resulted in a synergistic increase in IL-2 production compared with CTLA-4 or PD-1 inhibition alone (19).

Another promising combination partner for PD-1 inhibitors is the pleiotropic cytokine IFNα. IFNα has antiangiogenic, immunomodulatory, and proapoptotic properties (20) and is currently used as adjuvant therapy for patients with high-risk melanoma (21, 22) and in combination with bevacizumab as first-line therapy for patients with advanced RCC (23, 24). In mouse colorectal cancer models, treatment with IFNα increased PD-1 expression on tumor-infiltrating lymphocytes (25), and combined IFNα and anti–PD-1 therapy increased tumor infiltration of $CD4^+$ and $CD8^+$ T cells (26) and suppressed tumor growth to a significantly greater degree than IFNα alone (25, 26).

Although anti–PD-1 and anti–CTLA-4 combination therapy with reduced-dose nivolumab and full-dose ipilimumab significantly improved progression-free survival (PFS) and overall survival (OS) over ipilimumab alone in patients with advanced melanoma, it was accompanied by high rates of treatment-related toxicities of grade 3 to 4 severity or that led to treatment discontinuation (14, 15). Using a safety run-in, we assessed whether combination therapy with full-dose pembrolizumab and reduced-dose ipilimumab would have less toxicity but similar antitumor activity in patients with advanced melanoma or RCC. Using a modified toxicity probability interval design (27), we also aimed to determine the maximum tolerated dose of PEG-IFN given in combination with full-dose pembrolizumab in patients with advanced melanoma or RCC.

Materials and Methods

Study design and participants

The dose-finding portion of the international, open-label, multicohort, phase Ib KEYNOTE-029 study enrolled patients from seven academic medical centers in the United States. Eligibility criteria included age ≥18 years; histologically confirmed, advanced or metastatic melanoma treated with any number of prior therapies or RCC of predominantly clear cell histology treated with ≥1 prior therapy; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; ≥1 lesion measurable per RECIST v1.1 (28); no previous therapy with IFNα or an anti–PD-1, anti–PD-L1, anti–PD-L2, anti-CD137, or anti–CTLA-4 antibody; and no active autoimmune disease requiring systemic steroids or immunosuppressive agents, active noninfectious pneumonitis, or uncontrolled thyroid dysfunction or diabetes mellitus. Patients with uveal or ocular melanoma or active brain or leptomeningeal metastases were excluded; patients with previously treated, stable brain metastases were eligible.

The study protocol and all amendments were approved by the Institutional Review Board at each center. The study was conducted in accordance with the protocol and its amendments, Good Clinical Practice Guidelines, and the Declaration of Helsinki. All patients provided written informed consent.

Treatment

When both the pembrolizumab plus ipilimumab safety run-in and pembrolizumab plus PEG-IFN dose-finding cohorts were open for enrolment, patients were randomly assigned 1:1 to a cohort based on an allocation schedule generated by the sponsor. In the pembrolizumab plus ipilimumab cohort, patients received pembrolizumab 2 mg/kg intravenously over 30 minutes once every 3 weeks (Q3W) for up to 2 years plus ipilimumab 1 mg/kg intravenously over 90 minutes Q3W for 4 doses. In the pembrolizumab plus PEG-IFN cohort, patients received pembrolizumab 2 mg/kg Q3W for up to 2 years plus PEG-IFN subcutaneously weekly. The PEG-IFN dose was 1 μg/kg at dose level 1 and 2 μg/kg at dose level 2. Regardless of cohort, treatment was continued until disease progression, intolerable toxicity, patient withdrawal of consent, or investigator decision. Patients who permanently discontinued pembrolizumab because of an adverse event (AE) were required to discontinue all study therapies, whereas patients who permanently discontinued ipilimumab or PEG-IFN because of an AE could resume pembrolizumab after resolution of the AE to grade 0 or 1. Patients who were clinically stable but showed radiographic disease progression could continue treatment until progression was confirmed on repeat imaging performed ≥4 weeks later.

Assessments

Tumor images were obtained at baseline, at week 12, then every 6 weeks until week 30, and every 12 weeks thereafter. Assessment of antitumor activity was based on RECIST v1.1 by both independent central review and investigator review. AEs were collected throughout treatment and for 30 days thereafter (90 days thereafter for serious events) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Attribution to study treatment was determined by the investigator based on their assessment of exposure, time course, likely cause, consistency with known treatment profile, and results of treatment dechallenge and rechallenge. AEs that occurred during combination therapy and were considered to be treatment related were to be attributed to both drugs of the combination unless the investigator felt there were sufficient data to support full attribution of the AE to a single agent. AEs of special interest based on their likely immune etiology

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("immune-mediated AEs") were based on a list of terms specified by the sponsor and considered regardless of attribution to treatment or immune relatedness by the investigator.

Samples for pharmacokinetic assessment of pembrolizumab were collected predose on day 1 of cycle 1, postdose on days 1 and 8 of cycle 1, and predose on day 22 of cycle 1, where 1 cycle is equivalent to 6 weeks of treatment. Additional predose samples were collected on day 1 of cycle 4 and every 3 cycles thereafter until discontinuation of pembrolizumab, as well as 30 days, 3 months, and 6 months after stopping pembrolizumab. The serum concentration of pembrolizumab was quantified with a validated electrochemiluminescence-based immunoassay (lower limit of quantitation, 10 ng/mL). The immunogenicity of pembrolizumab was assessed in samples collected predose on days 1 and 22 of cycle 1, predose on day 1 of cycle 4 and every 3 cycles thereafter during pembrolizumab treatment, and 30 days, 3 months, and 6 months after pembrolizumab discontinuation. Serum antidrug antibodies (ADA) were assessed with a validated bridging electrochemiluminescence assay using a standard three-tiered approach (drug tolerance level, 124 μg/mL).

Outcomes

The primary objectives were to determine the tolerability of pembrolizumab plus ipilimumab and the maximum tolerated dose of pembrolizumab plus PEG-IFN based on the rate of prespecified dose-limiting toxicities (DLT; Supplementary Table S1) during cycle 1 (i.e., the first 6 weeks of treatment) and the safety and tolerability of both combinations based on the incidence of AEs throughout treatment. Secondary objectives included overall response rate (ORR) and duration of response. Protocol-specified exploratory objectives included the pharmacokinetics of pembrolizumab and the incidence of anti-pembrolizumab ADA during combination therapy.

DLTs were assessed in the DLT-evaluable population, defined as patients who completed ≥1 cycle of combination therapy or who discontinued because of a treatment-related AE. Safety and ORR were assessed in all patients who received ≥1 dose of combination therapy. The incidence of ADA was defined as the proportion of patients with treatment-emergent ADA out of the total number of patients who were evaluable for ADA.

Statistical analysis

Planned enrollment in the pembrolizumab plus ipilimumab safety run-in was 18 DLT-evaluable patients. Assuming 18 patients evaluable for DLTs, the combination was to be considered tolerable if ≤6 patients experienced a DLT during cycle 1. For pembrolizumab plus PEG-IFN, an initial cohort of 3 patients was enrolled at dose level 1, with subsequent enrollment and dosing decisions based on a modified toxicity probability interval and a target DLT rate of 30% (27). The number of patients treated at each dose level was dependent on the number of DLTs observed, with a maximum of 14 DLT-evaluable patients treated at each dose level (Supplementary Table S2). A given dose level was considered unacceptably toxic if DLTs were observed in 3 of 3, ≥3 of 4, ≥4 of 5, ≥4 of 6, ≥5 of 7, ≥5 of 8, ≥5 of 9, ≥5 of 10, ≥5 of 11, ≥5 of 12, ≥5 of 13, or ≥5 of 14 evaluable patients. In both cohorts, patients were considered nonevaluable for DLTs and were to be replaced if they were enrolled but not treated, discontinued from the study before completing all safety evaluations for reasons other than treatment-related AEs, or received <90% of the total pembrolizumab infusion or <80% of the total ipilimumab or PEG-IFN infusion during cycle 1 and did not experience a treatment-related AE.

SAS, version 9.3, was used for all statistical analyses.

This study is registered with ClinicalTrials.gov, number NCT02089685.

Role of the funding source

Representatives of the study sponsor (Merck & Co., Inc.) contributed to study design, data analysis, and data interpretation and served as authors of this article. The sponsor maintained the study database. All authors had access to all data used to prepare this article and approved the decision to submit the article for publication.

Results

Pembrolizumab plus ipilimumab safety run-in

From April 2, 2014, to November 18, 2014, 12 patients with melanoma and 10 patients with RCC enrolled in the pembrolizumab plus ipilimumab safety run-in and received ≥1 dose of combination therapy. Median age was 60.5 years, 13 (59%) patients were men, and 9 (41%) patients received ≥1 prior therapy (Table 1). As of June 21, 2017, median follow-up was

Table 1. Baseline characteristics

	Pembrolizumab + ipilimumab ***N* = 22**	**Pembrolizumab + PEG-IFN[a]** ***N* = 17**
Age, years	60.5 (24–75)	61 (37–83)
Men	13 (59)	12 (71)
Tumor type		
Melanoma	12 (55)	5 (29)
Renal cell carcinoma	10 (45)	12 (71)
ECOG performance status 0/1	17 (77)/5 (23)	12 (71)/5 (29)
Elevated LDH concentration	5 (23)	2 (12)
BRAF^{V600} mutant/wild type/unknown	4 (18)/6 (27)/12 (55)	1 (6)/4 (24)/12 (71)
M staging of extent of metastasis		
M1	10 (45)	12 (71)
M1a/M1b/M1c	2 (9)/2 (9)/8 (36)	0/3 (18)/2 (12)
Lines of previous systemic therapy		
0	13 (59)	6 (35)
1/2/≥3	5 (23)/4 (18)/0	3 (18)/5 (29)/3 (18)

NOTE: Data are presented as median (range) or *n* (%).

Abbreviation: LDH, lactate dehydrogenase.

[a]Includes the 14 patients treated at dose level 1 and the 3 patients treated at dose level 2.

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25.1 months (range, 0.8–38.7), and no patients remained on pembrolizumab. The reasons for treatment discontinuation were radiologic disease progression (n = 11, 50%), AEs (n = 6, 27%), clinical progression (n = 3, 14%), and completion of 2 years of pembrolizumab (n = 2, 9%). Eleven (50%) patients received all 4 ipilimumab doses; 5 (23%) patients received 3 ipilimumab doses, 2 (9%) received 2 doses, and 4 (18%) received 1 dose (Fig. 1A). The median number of pembrolizumab doses was 6.5 (range, 1–34), and the median duration of pembrolizumab treatment was 5.1 months (range, 1 day–26.3 months; Fig. 1A).

Three patients were not evaluable for DLTs during cycle 1: 2 patients experienced disease progression and discontinued treatment before completing cycle 1, and 1 patient accidentally received ipilimumab 3 mg/kg instead of 1 mg/kg during cycle 1. Six of 19 patients in the DLT-evaluable population experienced ≥1 DLT (Fig. 1A). All DLTs were of grade 3 severity and had resolved at the time of data cutoff except for one case of grade 4 increased lipase. The grade 4 increased lipase was managed by interruption of both pembrolizumab and ipilimumab; during the treatment interruption and before the lipase elevation resolved, the patient experienced disease progression and discontinued from the study. The only patient who permanently discontinued both pembrolizumab and ipilimumab because of a DLT experienced grade 3 colitis. One patient permanently discontinued ipilimumab but continued pembrolizumab without interruption because of grade 3 Vogt–Koyanagi–Harada syndrome. Another patient experienced grade 3 elevations of both alanine and aspartate aminotransferase managed by temporary pembrolizumab interruption, whereas ipilimumab was permanently discontinued for a non-DLT treatment-related AE (grade 2 thyroiditis) reported on the same day as the aminotransferase elevations. Pembrolizumab and ipilimumab were temporarily interrupted in a second patient who experienced grade 3 elevations of both alanine and aspartate aminotransferase. The final patient who experienced ≥1 DLT experienced grade 3 hyperthyroidism and grade 3 elevation of pancreatic enzymes, both of which were managed by temporary pembrolizumab interruption and ipilimumab dose reduction. Based on the prespecified rate of ≤6 patients with DLTs out of 18 DLT-evaluable patients, the combination of pembrolizumab 2 mg/kg Q3W plus 4 doses of ipilimumab 1 mg/kg Q3W was considered to be safe and tolerable.

Among the 22 patients in the safety population, treatment-related AEs occurred in 19 (86%) patients, most commonly fatigue (n = 7, 32%), diarrhea (n = 6, 27%), and nausea (n = 5, 23%; Table 2; Supplementary Table S3). Treatment-related AEs of grade 3 to 4 severity occurred in 13 (59%) patients; colitis (n = 4, 18%), increased lipase (n = 4, 18%), increased alanine aminotransferase (n = 2, 9%), and increased aspartate aminotransferase (n = 2, 9%) were the only grade 3 to 4 treatment-related AEs that occurred in ≥2 patients (Table 2; Supplementary Table S3). No patients died because of a treatment-related AE. Treatment-related AEs led to discontinuation of ipilimumab only in 4 (18%) patients, ipilimumab and pembrolizumab in 3 (14%) patients, including 1 (5%) patient who discontinued ipilimumab for 1 treatment-related AE and later discontinued pembrolizumab for another, and pembrolizumab alone after completion of ipilimumab in 3 (14%) patients (Fig. 1A).

Fourteen of 22 (64%) patients in the safety population experienced a total of 18 immune-mediated AEs, including 6 (27%) patients who experienced a total of 6 grade 3 to 4 immune-mediated AEs (Table 3). The most common immune-mediated AEs were colitis and hyperthyroidism (n = 4, 18% each). The only grade 3 to 4 AE that occurred in >1 patient was colitis (n = 4, 18%). Overall, 11 of 18 (61%) immune-mediated AEs resolved, including all 6 grade 3 to 4 events (Table 3). High-dose corticosteroids, defined as a prednisone starting dose ≥40 mg/day or the equivalent, were used to manage the single case of pneumonitis and all four cases of colitis; low-dose corticosteroids (prednisone starting dose <40 mg/day or the equivalent) were used to manage the one case of adrenal insufficiency and the three cases of hypophysitis (Table 3).

Among the 12 patients with melanoma in the efficacy population, ORR per independent central review was 42% [95% confidence interval (CI), 15%–72%], with 1 complete and 4 partial responses. Four patients had stable disease, and 2 patients had progressive disease as their best response. The final patient did not have disease considered to be measurable per RECIST v1.1 by the central reviewers at baseline, and the response was noncomplete response/nonprogressive disease (i.e., disease did not completely resolve, nor did it grow sufficiently to be considered progressive disease). By investigator review, ORR was 33% (95% CI, 10%–65%), with a best overall response of partial response (n = 4). Among the 10 patients with RCC in the efficacy population, ORR was 30% (95% CI, 7%–65%) by both central and investigator review. According to central review, best overall response was complete response in 1 patient, partial response in 2 patients, stable disease in 3 patients, and progressive disease in 2 patients; 2 patients had postbaseline imaging assessments, but the images were not considered evaluable for response. Change from baseline in target lesion size is shown in Fig. 2A. As assessed by central review, median duration of response was not reached in the 5 responders with melanoma (range of response duration, 14.8+ to 27.2+ months) and was 24.0 months (range, 9.3–24.0) in the 3 responders with RCC.

Pembrolizumab plus PEG-IFN dose finding

Between April 15, 2014, and August 17, 2015, 17 patients enrolled in the pembrolizumab plus PEG-IFN cohort and received ≥1 dose of combination therapy. Dose level 1 included 5 patients with melanoma and 9 patients with RCC; dose level 2 included 3 patients with RCC. Across dose levels, median age was 61 years, 12 (71%) patients were men, and 11 (65%) received ≥1 line of prior therapy for advanced disease (Table 1). As of June 19, 2017, median follow-up was 22.2 months (range, 2.5–37.7), and 2 of 14 (14%) patients at dose level 1 and 0 of 3 patients at dose level 2 remained on therapy (Fig. 1B). Reasons for discontinuation were radiologic disease progression (n = 10, 59%), AEs (n = 2, 12%), and withdrawal of consent (n = 2, 12%); 1 patient treated at dose level 2 completed 2 years of pembrolizumab. Across dose levels, median duration of treatment was 6.2 months (range, 0.7–24.2) for pembrolizumab and 3.2 months (range, 0.3–20.0) for PEG-IFN; the median number of doses administered was 10 (range, 2–34) and 15 (range, 2–88), respectively (Fig. 1B).

All 17 patients enrolled in the pembrolizumab plus PEG-IFN cohort were evaluable for DLTs during cycle 1. Per the dose-finding rules (Supplementary Table S2), 3 patients were treated at dose level 1 (pembrolizumab 2 mg/kg Q3W plus PEG-IFN 1 μg/kg/week) and evaluated for DLTs before additional patients were enrolled. No DLTs were observed during cycle 1 among these first 3 patients, and the next 3 patients were enrolled at dose level 2 (pembrolizumab 2 mg/kg Q3W plus PEG-IFN 2 μg/kg/week).

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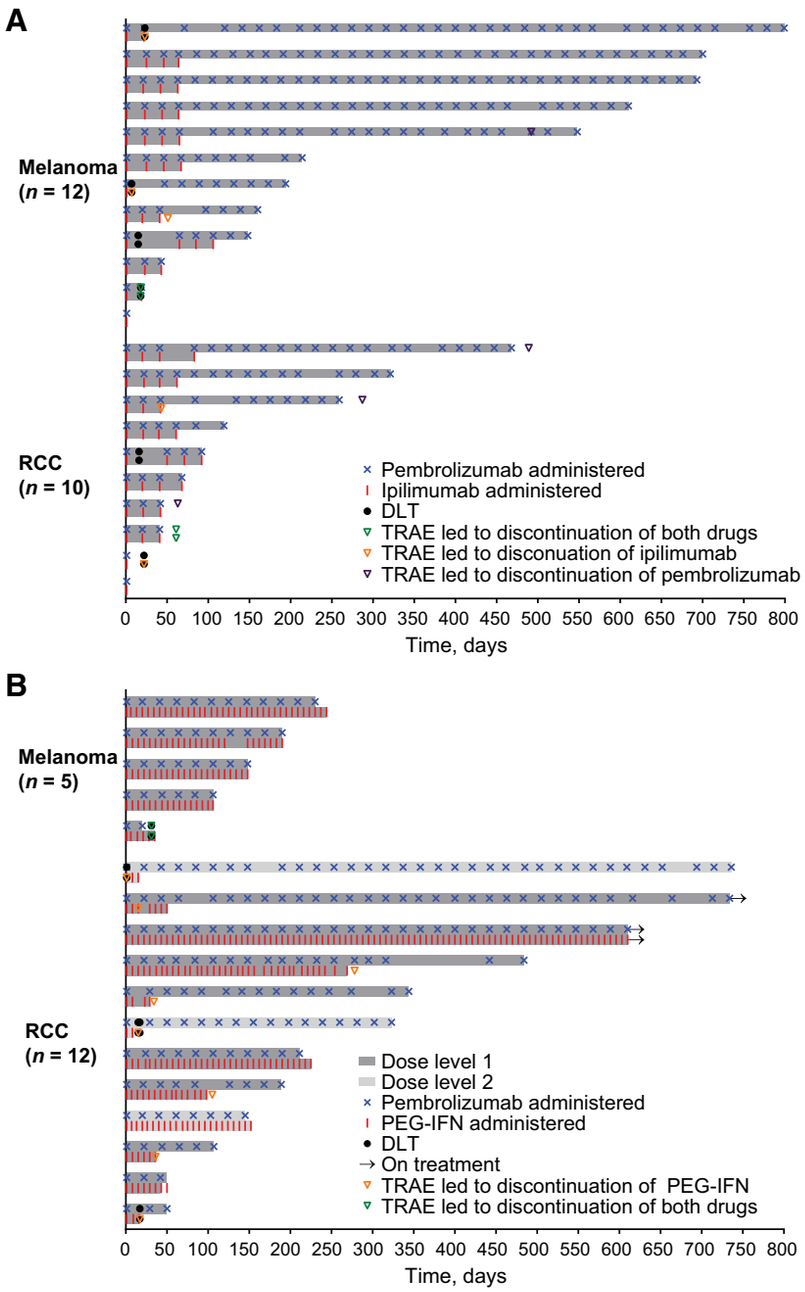

Figure 1.

Treatment exposure. **A,** Pembrolizumab plus ipilimumab. **B,** Pembrolizumab plus pegylated IFNα2b. In both plots, the length of the bar is equivalent to the time to the last dose of study treatment and the symbols for the DLTs and treatment-related AEs that led to treatment discontinuation are equivalent to the time of onset of the AE. TRAE, treatment-related adverse event.

Two of these patients experienced DLTs (Fig. 1B). One patient experienced grade 3 aspartate aminotransferase elevation, whereas a second experienced grade 4 depression and grade 4 suicide attempt. All events resolved after discontinuation of PEG-IFN alone and without interruption of pembrolizumab. Based on the dose-finding rules (Supplementary Table S2), subsequent patients were enrolled at dose level 1. Enrollment at dose level 1 was able to continue until the maximum numbers of 14 patients were enrolled at this dose level. Overall, 2 patients at dose level 1 experienced a DLT. One patient experienced grade 3 depression that resolved after discontinuation of PEG-IFN and temporary interruption of pembrolizumab. A second patient experienced grade 2 third nerve disorder that resolved after discontinuation of pembrolizumab and PEG-IFN (Fig. 1B). Based on the dose-finding rules, pembrolizumab 2 mg/kg Q3W plus PEG-IFN 1 μg/kg/week was considered the maximum tolerated dose.

All 17 patients enrolled were included in the safety population and experienced ≥1 treatment-related AE, including 8 of 14 (57%) at dose level 1 and 2 of 3 (67%) at dose level 2 who experienced ≥1 grade 3 to 4 toxicity. Across dose levels, the most common treatment-related AEs of any grade were fatigue ($n = 11$, 65%), pyrexia ($n = 7$, 41%), and chills, diarrhea, and nausea ($n = 6$, 35% each); the only grade 3 to 4 toxicity that occurred in >1 patient was depression ($n = 2$, 12%; Table 2; Supplementary Table S4). No patients died because of a treatment-related AE. Treatment-related AEs led to PEG-IFN discontinuation in 6 of 14

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Table 2. Treatment-related adverse events of any grade observed in ≥3 patients in either cohort

	Pembrolizumab + ipilimumab		Pembrolizumab + PEG-IFN	
	N = 22		*N* = 17	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Blood and lymphatic system disorders				
Anemia	1 (5)	0	5 (29)	1 (6)
Endocrine disorders				
Hypophysitis	3 (14)	0	0	0
Hypothyroidism	3 (14)	0	1 (6)	0
Gastrointestinal disorders				
Abdominal pain	3 (14)	0	2 (12)	0
Colitis	4 (18)	4 (18)	0	0
Diarrhea	6 (27)	1 (5)	6 (35)	0
Nausea	5 (23)	0	6 (35)	0
General disorders and administration site conditions				
Chills	0	0	6 (35)	0
Fatigue	7 (32)	0	11 (65)	1 (6)
Influenza-like illness	0	0	4 (24)	0
Pyrexia	2 (9)	0	7 (41)	0
Investigations				
Alanine aminotransferase increased	4 (18)	2 (9)	5 (29)	0
Aspartate aminotransferase increased	4 (18)	2 (9)	3 (18)	1 (6)
Blood creatinine increased	0	0	3 (18)	0
Lipase increased	4 (18)	4 (18)	1 (6)	0
Lymphocyte count decreased	0	0	3 (18)	0
Neutrophil count decreased	0	0	5 (29)	1 (6)
Platelet count decreased	0	0	3 (18)	0
White blood cell count decreased	0	0	5 (29)	0
Metabolism and nutrition disorders				
Decreased appetite	1 (5)	0	3 (18)	0
Nervous system disorders				
Dysgeusia	0	0	3 (18)	0
Psychiatric disorders				
Depression	0	0	3 (18)	2 (12)
Respiratory, thoracic, and mediastinal disorders				
Cough	1 (5)	0	3 (18)	0
Skin and subcutaneous tissue disorders				
Pruritus	2 (9)	0	4 (24)	0
Rash	4 (18)	0	4 (24)	0
Vitiligo	3 (14)	0	0	0

NOTE: Relationship to study treatment was determined by the investigator. Data are presented as *n* (%) and listed by System Organ Class.

(43%) patients at dose level 1 and 2 of 3 (67%) patients at dose level 2 (Fig. 1B); 1 (7%) patient at dose level 1 discontinued both pembrolizumab and PEG-IFN because of treatment-related AEs. Four of 17 (24%) patients experienced a total of 8 immune-mediated AEs. Pneumonitis and hyperthyroidism were reported in 2 (12%) patients each, with hepatitis, hypothyroidism, myositis, and thyroiditis all reported in 1 (6%) patient each (Table 3). The only grade 3 to 4 immune-mediated AE was hepatitis. Five of 8 (62%) immune-mediated AEs resolved, including the single grade 3 to 4 event (Table 3).

All patients were included in the efficacy population. By both central and investigator review, 1 of 5 patients with melanoma experienced partial response, for an ORR of 20% (<1%–72%); at the time this patient withdrew from the study because of international relocation, the response was ongoing (duration, 5.5 months). Best overall response in the remaining patients with melanoma was stable disease and progressive disease in 2 patients each. By both central and investigator review, 2 of 12 patients with RCC, both treated at dose level 1, experienced partial response, for an ORR of 17% (2%–48%); the response ended after 1.7 months in 1 patient and was ongoing at 13.9 months in the second. No patients treated at dose level 2 experienced tumor response. Best overall response per central review in the remaining patients with RCC was stable disease in 4 patients and progressive disease in 6 patients. Change from baseline in target lesion size is shown in Fig. 2B.

Pharmacokinetics and immunogenicity

All patients in the pembrolizumab plus ipilimumab ($N = 22$) and pembrolizumab plus PEG-IFN ($N = 17$) cohorts provided ≥1 sample evaluable for pharmacokinetic analysis. The observed pembrolizumab concentrations in these two cohorts were comparable with those predicted by a model of pembrolizumab monotherapy pharmacokinetics that was developed using a dataset of 2,993 patients with advanced melanoma and non–small cell lung cancer (NSCLC) treated with pembrolizumab 2 mg/kg Q3W, 10 mg/kg Q3W, 10 mg/kg Q2W, or 200 mg Q3W (29). Observed pembrolizumab serum concentrations in patients treated with pembrolizumab plus ipilimumab fell within the 90% prediction interval for pembrolizumab monotherapy after the first dose and at steady state (i.e., beyond 16 weeks of treatment; Fig. 3A). In patients treated with pembrolizumab plus PEG-IFN, the observed pembrolizumab serum concentrations appeared to be slightly elevated compared with the model predictions after the first dose (Fig. 3B), but were consistent at steady state (Fig. 3C). All observed concentrations fell within the 90% prediction interval after both the first dose and at steady state.

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Table 3. Immune-mediated adverse events

	Any grade	Grade 3–4	Resolved	Required high-dose corticosteroids[a]	Required low-dose corticosteroids[a]
Pembrolizumab + ipilimumab, $N = 22$					
Colitis	4 (18)	4 (18)	4 (100)	4 (100)	0
Hyperthyroidism	4 (18)	1 (5)	3 (75)	0	0
Hypophysitis	3 (14)	0	0	0	3 (100)
Hypothyroidism	3 (14)	0	1 (33)	0	0
Adrenal insufficiency	1 (5)	0	0	0	1 (100)
Pneumonitis	1 (5)	1 (5)	1 (100)	1 (100)	0
Thyroiditis	1 (5)	0	1 (100)	0	0
Uveitis	1 (5)	0	1 (100)	0	0
Pembrolizumab + PEG-IFN, $N = 17$					
Hyperthyroidism	2 (12)	0	2 (100)	0	0
Pneumonitis	2 (12)	0	0	1 (50)	0
Hepatitis	1 (6)	1 (6)	1 (100)	1 (100)	0
Hypothyroidism	1 (6)	0	1 (100)	0	0
Myositis	1 (6)	0	1 (100)	0	0
Thyroiditis	1 (6)	0	0	0	0

NOTE: Events were based on a list of terms specified at the time of analysis and were included regardless of whether they were considered to be immune related or attributed to study treatment by the investigator. Data are presented as *n* (%), where the denominator for the any-grade and grade 3–4 columns is the total population and the denominator for resolved, required high-dose corticosteroids, and required low-dose corticosteroids is the total number of episodes of that event (equivalent to the total number of patients with each event as no patient experienced recurrence of the same event).

[a]Refers to the starting dose, where high dose is defined as ≥40 mg/day prednisone or equivalent and low dose is defined as <40 mg/day prednisone or equivalent.

Thirty-five patients were evaluable for treatment-emergent anti-pembrolizumab ADA, including 18 patients treated with pembrolizumab plus ipilimumab ($n = 11$ melanoma, $n = 7$ RCC) and all 17 patients treated with pembrolizumab plus PEG-IFN. In the pembrolizumab plus ipilimumab cohort, 1 patient with melanoma tested positive for treatment-emergent anti-pembrolizumab ADA. The ADA titer was <1 and was detected on day 229, 37 days after treatment discontinuation because of disease progression following a best overall response of stable disease. Two patients with RCC who received pembrolizumab plus PEG-IFN tested positive for treatment-emergent anti-pembrolizumab ADA. The first patient tested positive on day 252 with an ADA titer of 5; this patient had a best overall response of stable disease per both central and investigator review but experienced disease progression on day 294. The second patient tested positive on day 140 with an ADA titer of 125; upon retesting on day 273, the ADA results were negative. Per central review, the best overall response in this patient was progressive disease at day 85. Per investigator review, the patient had stable disease at day 85, and treatment was continued until progression was observed on day 294.

Discussion

In this population of patients with advanced melanoma or previously treated RCC, we identified the combination of

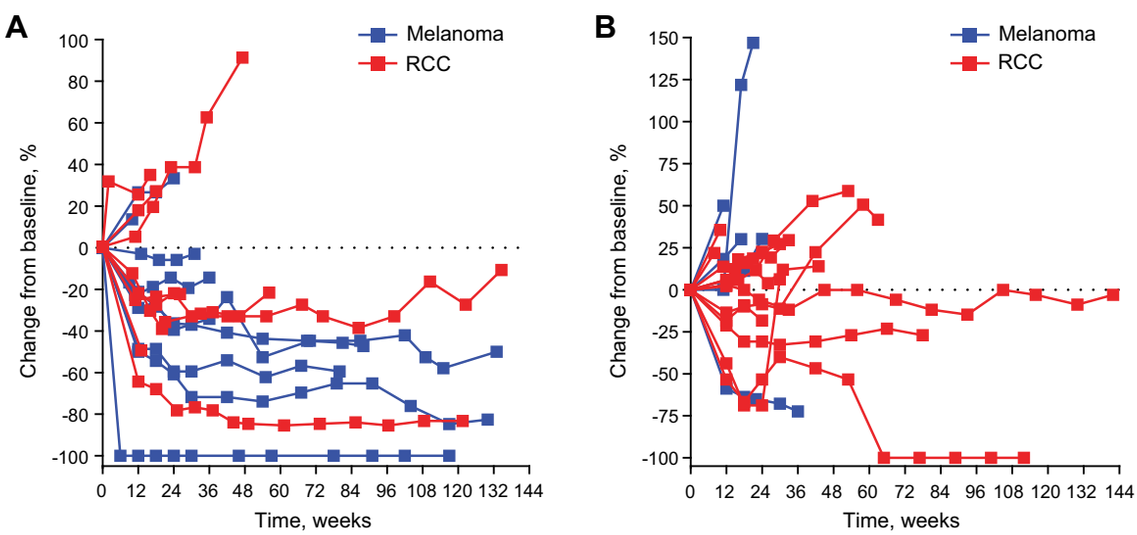

Figure 2.

Longitudinal change from baseline in target lesion size. **A,** Pembrolizumab plus ipilimumab. **B,** Pembrolizumab plus pegylated IFNα2b. In both plots, response was assessed according to RECIST v1.1 by investigator review. Only patients who had at least one evaluable postbaseline tumor assessment were included in the analysis ($n = 18$ for pembrolizumab plus ipilimumab, $n = 17$ for pembrolizumab plus pegylated IFNα2b).

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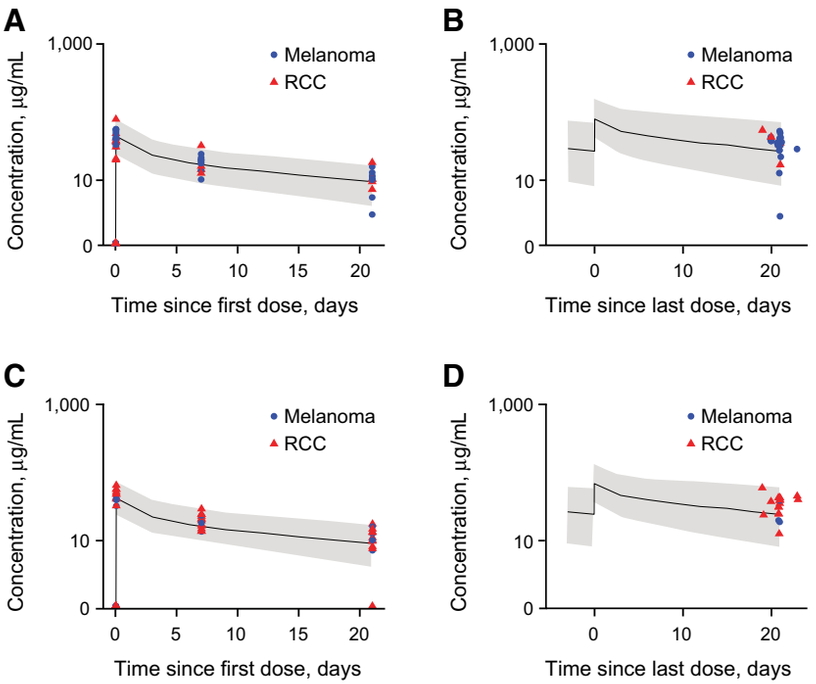

Figure 3.
Serum pembrolizumab concentration. **A,** Concentration after one dose in patients receiving concomitant ipilimumab. **B,** Concentration at steady state in patients receiving concomitant ipilimumab. **C,** Concentration after one dose in patients receiving concomitant pegylated IFNα2b. **D,** Concentration at steady state in patients receiving concomitant pegylated IFNα2b. In all plots, the predicted median (black line) and 90% prediction interval (gray shading) were generated from a model that described the pharmacokinetics of pembrolizumab monotherapy. Data from patients with melanoma are shown as blue circles, and data from patients with renal cell carcinoma are shown as red triangles.

standard-dose pembrolizumab (i.e., 2 mg/kg Q3W) plus 4 doses of reduced-dose ipilimumab (i.e., 1 mg/kg Q3W) as tolerable based on the observed DLT rate. We also identified the combination of standard-dose pembrolizumab plus PEG-IFN 1 μg/kg/week as the maximum tolerated dose. Although evidence of antitumor activity was observed for pembrolizumab plus ipilimumab in both melanoma and RCC, antitumor activity appeared to be limited for pembrolizumab plus PEG-IFN. Given the DLT rate during cycle 1, treatment-related AE rate throughout treatment, and preliminary antitumor activity observed for each combination, the protocol-specified melanoma expansion cohort for the ipilimumab combination was initiated, whereas development of the PEG-IFN combination was discontinued.

In the pembrolizumab plus ipilimumab cohort, there were no treatment-related deaths or new safety signals observed over those expected with pembrolizumab or ipilimumab monotherapy. The rate of grade 3 to 4 treatment-related AEs was 59%, which is higher than the incidence observed with pembrolizumab or ipilimumab monotherapy (1–3, 6, 8–11, 14, 15, 30). Among patients treated with monotherapy, ipilimumab is associated with a higher rate of treatment-related AEs than PD-1 inhibitors (3, 14, 15). This is likely because ipilimumab functions largely at the antigen-presenting phase of the immune response, leading to more broad-based immune activation, whereas PD-1 inhibitors function to restore immunity, largely in the tumor microenvironment (31). Thus, it is not surprising that the incidence of treatment-related AEs is greater in patients treated with anti–PD-1 and ipilimumab combination therapy than with either anti–PD-1 therapy or ipilimumab alone. The higher incidence of treatment-related AEs with combination anti–PD-1/anti–PD-L1 and anti–CTLA-4 therapies has also been observed for combinations of nivolumab and ipilimumab in patients with melanoma (14, 15), RCC (32), and NSCLC (33, 34) and durvalumab and tremelimumab in NSCLC (35). Colitis was the only grade 3 to 4 treatment-related AE reported in ≥1 patient in this study that was not a laboratory abnormality; furthermore, all 6 grade 3 to 4 immune-related AEs resolved. The treatment-related AE profile proved to be similar in the pembrolizumab plus ipilimumab expansion cohort, in which the grade 3 to 4 treatment-related AE rate was 45% (36). The lower event rate in the expansion cohort may be a reflection of the larger population size ($N = 153$ vs. 22), the less heavily pretreated population (87% vs. 59% with no previous treatment for advanced disease), or the restriction of the expansion cohort to patients with melanoma while the safety run-in cohort included 10 of 22 (45%) patients with RCC.

Examination of the treatment-related AE profile for pembrolizumab plus PEG-IFN revealed a high incidence of general conditions such as fatigue (65%) and pyrexia (41%) and laboratory abnormalities such as increased alanine aminotransferase (29%). Notably, many of the DLTs observed were psychiatric disorders associated with PEG-IFN: depression in 2 patients and suicide attempt in 1 patient.

In the pembrolizumab plus ipilimumab safety run-in, ORR as assessed per RECIST v1.1 by independent central review was 42% in patients with melanoma and 30% in patients with RCC. In the phase III CheckMate 067 and CheckMate 214 studies of nivolumab plus ipilimumab for treatment-naïve melanoma and RCC, ORR was 58% (14, 15) and 39% (37), respectively. Of note, ORR in the melanoma expansion cohort ($N = 153$) was 61% (36), which is similar to the ORR observed for nivolumab plus ipilimumab in CheckMate 067 (14, 15). The lower ORR observed for pembrolizumab plus ipilimumab in the safety run-in was likely due to the small number of patients enrolled and the fact that these patients were more heavily pretreated compared with those enrolled in the KEYNOTE-029 single-arm melanoma expansion cohort (36) and the randomized, phase III CheckMate 067 study (14, 15). Although the small sample size precluded assessment of survival in the safety run-in, data from the expansion cohort suggest there may be a

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survival benefit for patients treated with standard-dose pembrolizumab combined with reduced-dose ipilimumab. Over a median follow-up of 17.0 months, neither median PFS nor OS was reached in the expansion cohort, with 12-month estimates of 69% for PFS and 89% for OS compared with estimates of approximately 50% and 72%, respectively, for nivolumab plus ipilimumab combination therapy in CheckMate 067 (15). With regard to RCC, there was no expansion cohort in KEYNOTE-029 for this population, and no single-agent data exist for comparison. However, the ongoing KEYNOTE-427 study (ClinicalTrials.gov identifier, NCT02853344) is evaluating the efficacy and safety of pembrolizumab monotherapy in patients with treatment-naïve advanced RCC.

The antitumor activity observed for the PEG-IFN combination was less than what would be expected for pembrolizumab monotherapy. Given the preclinical synergism observed for PD-1 inhibition combined with IFNα (25, 26) and the lack of DLTs and 43% ORR (RECIST v1.1, investigator review) observed in a previously reported dose-finding study of pembrolizumab 2 mg/kg Q3W plus PEG-IFN at doses of 1, 2, or 3 μg/kg/week for patients with advanced melanoma ($N = 24$; ref. 38), the observed ORR of 18% in our dose-finding study was likely due to the fact that the vast majority of patients had RCC, which might be less responsive to pembrolizumab and/or PEG-IFN than melanoma.

There was no clinically meaningful impact on pembrolizumab serum concentrations when pembrolizumab was coadministered with ipilimumab or PEG-IFN. These observations were as expected given that biologic therapies are metabolized by catabolic pathways similar to those used for endogenous proteins. These pathways are present ubiquitously throughout the body, limiting the susceptibility to pharmacokinetic-based drug interactions between two biological therapies. A similar lack of a clinically significant change in pharmacokinetics has been demonstrated for several concomitantly administered biological therapies (39, 40), including nivolumab plus ipilimumab (41). Anti-pembrolizumab ADA were observed in both the pembrolizumab plus ipilimumab (incidence 6%) and pembrolizumab plus PEG-IFN (incidence 12%) cohorts. In an analysis of 1,087 patients with advanced melanoma or NSCLC treated with pembrolizumab monotherapy, the incidence of treatment-emergent ADA was 1.7% (42). Although the incidence of anti-pembrolizumab ADA appeared higher with combination therapy in this trial versus monotherapy in the pooled analysis, it is not possible to draw any conclusions regarding whether coadministration of ipilimumab or PEG-IFN increases the rate of anti-pembrolizumab ADA because of the small number of patients evaluable for ADA in this study ($n = 18$ for pembrolizumab plus ipilimumab, $n = 17$ for pembrolizumab plus PEG-IFN). Of note, in an immunogenicity analysis that included patients treated with pembrolizumab plus ipilimumab in the KEYNOTE-029 safety run-in and the expansion cohort, the incidence of treatment-emergent ADA was only 1.2% (2 of 162 evaluable patients; ref. 43). The small sample size also precludes assessment of whether ADA is correlated with clinical outcome or toxicity in patients treated with pembrolizumab and ipilimumab or PEG-IFN.

The development of immune checkpoint inhibitor–based combination therapies is a key area of research in oncology (31). Several ongoing studies in multiple tumor types are examining various doses and schedules of anti–PD-1 and anti–CTLA-4 combination therapy. This includes a new cohort of the KEYNOTE-029 study, in which patients with previously untreated advanced melanoma are randomized to receive pembrolizumab 200 mg Q3W for 2 years plus ipilimumab 50 mg Q6W for 4 doses or pembrolizumab 200 mg Q3W for 2 years plus ipilimumab 100 mg Q12W for 4 doses. In an effort to improve efficacy and reduce toxicity, additional immunotherapy combinations are being evaluated. These include, but are not limited to, combinations of immune checkpoint inhibitors with immune-stimulatory agents (e.g., cytokines or agonist antibodies), inhibitors of other immune checkpoints (e.g., LAG-3, TIM-3, TIGIT) or other immune modulators (e.g., IDO, VEGF, HDACs) in the tumor microenvironment, intralesional immune stimulants (e.g., oncolytic viruses, TLR agonists, STING), and tumor-specific cancer vaccines (31).

Overall, standard-dose pembrolizumab plus reduced-dose ipilimumab has a manageable safety profile and promising antitumor activity in patients with advanced melanoma or RCC, supporting further development of this regimen. The poor tolerability profile and minimal antitumor activity observed for standard-dose pembrolizumab plus PEG-IFN in patients with advanced melanoma or RCC preclude further study of this combination.

Disclosure of Potential Conflicts of Interest

M.B. Atkins is a consultant/advisory board member for Bristol-Myers Squibb, Merck, AstraZeneca, Roche, and Pfizer. F.S. Hodi reports receiving commercial research grants from Bristol-Myers Squibb, and is a consultant/advisory board member for Merck, Bristol-Myers Squibb, Genentech, EMD Serono, Celldex, and Amgen. D.F. McDermott is a consultant/advisory board member for Merck, Bristol-Myers Squibb, and Roche. W.-J. Hwu reports receiving commercial research grants from Merck, Bristol-Myers Squibb, MedImmune, and GlaxoSmithKline, and is a consultant/advisory board member for Merck. N. A. Dawson reports receiving speakers bureau honoraria from Merck. S. Bhatia is a consultant/advisory board member for EMD Serono and Genentech. T.K. Choueiri reports receiving commercial research grants from Bristol-Myers Squibb, Merck, and Pfizer, and is a consultant/advisory board member for Bristol-Myers Squibb, Merck, Pfizer, Exelixis, Novartis, Ipsen, and Eisai. A. Ribas is a consultant/advisory board member for Merck. No potential conflicts of interest were disclosed by the other authors.

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