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ORIGINAL REPORT

Epacadostat Plus Pembrolizumab in Patients With Advanced Solid Tumors: Phase I Results From a Multicenter, Open-Label Phase I/II Trial (ECHO-202/KEYNOTE-037)

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ABSTRACT

Purpose

Tumors may evade immunosurveillance through upregulation of the indoleamine 2,3-dioxygenase 1 (IDO1) enzyme. Epacadostat is a potent and highly selective IDO1 enzyme inhibitor. The open-label phase I/II ECHO-202/KEYNOTE-037 trial evaluated epacadostat plus pembrolizumab, a programmed death protein 1 inhibitor, in patients with advanced solid tumors. Phase I results on maximum tolerated dose, safety, tolerability, preliminary antitumor activity, and pharmacokinetics are reported.

Patients and Methods

Patients received escalating doses of oral epacadostat (25, 50, 100, or 300 mg) twice per day plus intravenous pembrolizumab 2 mg/kg or 200 mg every 3 weeks. During the safety expansion, patients received epacadostat (50, 100, or 300 mg) twice per day plus pembrolizumab 200 mg every 3 weeks.

Results

Sixty-two patients were enrolled and received one or more doses of study treatment. The maximum tolerated dose of epacadostat in combination with pembrolizumab was not reached. Fifty-two patients (84%) experienced treatment-related adverse events (TRAEs), with fatigue (36%), rash (36%), arthralgia (24%), pruritus (23%), and nausea (21%) occurring in ≥ 20%. Grade 3/4 TRAEs were reported in 24% of patients. Seven patients (11%) discontinued study treatment because of TRAEs. No TRAEs led to death. Epacadostat 100 mg twice per day plus pembrolizumab 200 mg every 3 weeks was recommended for phase II evaluation. Objective responses (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) occurred in 12 (55%) of 22 patients with melanoma and in patients with non–small-cell lung cancer, renal cell carcinoma, endometrial adenocarcinoma, urothelial carcinoma, and squamous cell carcinoma of the head and neck. The pharmacokinetics of epacadostat and pembrolizumab and antidrug antibody rate were comparable to historical controls for monotherapies.

Conclusion

Epacadostat in combination with pembrolizumab generally was well tolerated and had encouraging antitumor activity in multiple advanced solid tumors.

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INTRODUCTION

Immunotherapies, such as immune checkpoint inhibitors (ICIs) that target programmed death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), have resulted in meaningful advances in cancer treatment.[1] However, interest exists in developing combination immunotherapies that target various immune evasion pathways to improve patient response rates and survival. Nivolumab (a PD-1 inhibitor) plus ipilimumab (a CTLA-4 inhibitor) provides improved response rates compared with monotherapy but is associated with high grade 3/4 treatment-related adverse events (TRAEs; 33% to 55%) and immune-related adverse events (AEs; 40% to 45%).[2-5] Other combination immunotherapies, including epacadostat—a potent and

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highly selective oral inhibitor of the indoleamine 2,3-dioxygenase 1 (IDO1) enzyme—plus ICIs, also have been under clinical investigation.

The intracellular IDO1 enzyme catalyzes the first and rate-limiting step in the degradation of tryptophan to kynurenine.[6,7] Induced by interferon-γ, prostaglandin E2, tumor necrosis factor-α, transforming growth factor-β, and other proinflammatory signals, IDO1 primarily is expressed by tumor, endothelial, and dendritic cells and macrophages within the tumor microenvironment (TME).[8,9] IDO1-mediated depletion of cellular tryptophan and production of downstream metabolites may result in cell cycle arrest, anergy, and apoptosis of effector T cells and activation of immunosuppressive cells (eg, regulatory T cells,[6] myeloid-derived suppressor cells,[10] tumor-associated macrophages[11]), thereby contributing to immunosuppression within the TME. Furthermore, IDO1 upregulation may be associated with poor prognosis in patients with advanced cancers.[12,13] Therefore, IDO1 may represent a potential therapeutic target in various cancers, especially in combination with other immunotherapies, including ICIs.

Epacadostat decreases tryptophan metabolism by inhibiting IDO1, which results in enhanced proliferation of effector T cells and natural killer cells, decreased apoptosis and increased activation of $CD86^{high}$ dendritic cells, and reduced expansion of regulatory T cells.[14] These changes shift the TME away from an immunosuppressive state toward one that supports productive immune responses.[14] In preclinical models, epacadostat plus an ICI suppressed tumor growth more effectively than single-agent treatment, primarily through reactivation of antitumor immunity.[15] Phase I and II clinical studies have shown that single-agent epacadostat is well tolerated in patients with advanced cancers,[16,17] and doses ≥ 100 mg twice per day provide optimal inhibition of IDO1 activity and normalization of kynurenine levels.[16] Favorable objective response rate, disease control rate, and progression-free survival were observed in immunotherapy-naive patients with melanoma treated with epacadostat plus ipilimumab.[18] In addition to these encouraging safety and efficacy findings, interferon-γ–induced expression of IDO1 and PD-L1 in the TME[19] supports the investigation of epacadostat plus PD-1/PD-L1 inhibitors, such as pembrolizumab.

The primary objectives of the phase I portion of the ECHO-202/KEYNOTE-037 study were to evaluate the dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), safety, and tolerability of epacadostat plus pembrolizumab in patients with advanced solid tumors. Exploratory end points were preliminary antitumor activity of this combination, epacadostat pharmacokinetics, and pharmacokinetic-based projected pharmacodynamics.

PATIENTS AND METHODS

Patients

Eligible patients were ≥ 18 years old with histologically or cytologically confirmed stage IIIB, stage IV, or recurrent non–small-cell lung cancer (NSCLC), melanoma, renal cell cancer (RCC), endometrial adenocarcinoma (EA), urothelial carcinoma (UC), triple-negative breast cancer (TNBC), or squamous cell carcinoma of the head and neck (SCCHN). All patients progressed on one or more prior lines of therapy or had no available curative treatment, except for patients with melanoma. Additional eligibility criteria were presence of measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)[20]; life expectancy > 12 weeks; Eastern Cooperative Oncology Group performance status ≤ 1; ALT, AST, and alkaline phosphatase levels < 2.5 times the upper limit of normal; and conjugated bilirubin < 2.0 times the upper limit of normal. Exclusion criteria included prior treatment with ICIs (except prior adjuvant CTLA-4 inhibitors for melanoma) or IDO inhibitors at any time, investigational device or treatment within 28 days or five half-lives (whichever was longer) before the first dose of study drug, active autoimmune disease, known history of immunodeficiency, and use of systemic corticosteroids within 7 days before the first dose of study drug.

Study Design and Treatment

In this multicenter, nonrandomized, open-label phase I/II study, phase I included a 3 + 3 + 3 epacadostat dose escalation in combination with pembrolizumab, followed by three safety expansion cohorts of up to nine patients each. During dose escalation, patients received oral epacadostat (25, 50, or 100 mg) twice per day in combination with intravenous pembrolizumab 2 mg/kg every 3 weeks or epacadostat 300 mg twice per day with pembrolizumab 200 mg every 3 weeks. The first safety expansion (epacadostat 50 mg twice per day plus pembrolizumab 200 mg every 3 weeks) enrolled patients with melanoma; the second and third expansions (epacadostat 100 mg twice per day and 300 mg twice per day, respectively, plus pembrolizumab 200 mg every 3 weeks) included patients with other eligible tumors. All patients could continue combination treatment with epacadostat and pembrolizumab for up to 24 months followed by optional epacadostat monotherapy until confirmed radiographic disease progression, intolerable toxicity, or withdrawal of consent.

The study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization guidelines for Good Clinical Practice and was approved by an independent ethics committee or institutional review board at each study site. All patients provided written informed consent before initiation of any study procedures or for any biomarker sample collections.

Assessments

Safety and tolerability assessments were conducted at all scheduled study visits (day 1 of every cycle), at end of treatment, and during follow-up. Laboratory assessments, including liver function tests, were performed weekly for the first 6 weeks. AEs were graded per Common Terminology Criteria for Adverse Events (version 4.0). AEs of special interest were those with an immune-related cause regardless of attribution to study treatment by the investigator.

DLTs were protocol-specified AEs that occurred within the first 6 weeks of treatment, regardless of attribution to study drug. Such AEs could include grade 4 thrombocytopenia or neutropenia lasting > 7 days; nonhematologic grade 4 toxicities; any grade 3/4 AST, ALT, or total bilirubin elevation; any other grade 3 nonhematologic toxicity (except protocol-defined controllable nausea, vomiting, and rash); or grade ≥ 2 episcleritis, uveitis, or iritis. The recommended phase II dose (RP2D) was selected on the basis of tolerability during the safety expansion. Per study protocol, dose escalation was permitted if there were no more than zero, one, or three DLTs in three, six, or nine patients, respectively. If four or more of the first six or nine evaluable patients in a dose cohort experienced a DLT, the next-lower dose of epacadostat was deemed the RP2D.

Tumor response was assessed at baseline, every 9 weeks for the first 18 months of treatment, and every 12 weeks thereafter. Objective response rate (complete response [CR] or partial response [PR]) and duration of response (time from response to disease progression) were determined on the basis of investigator assessment per RECIST v1.1. Immune-related RECIST v1.1 was used to guide treatment; if imaging showed progressive disease, patients could continue study treatment at the investigator's discretion until confirmatory assessment ≥ 4 weeks later.

Tumor PD-L1 status was determined at baseline by immunohistochemistry using an investigational version of the PD-L1 IHC 22C3

pharmDx assay (Agilent, Carpinteria, CA). PD-L1 positivity was defined as membranous PD-L1 expression in ≥ 1% of tumor cells or inflammatory cells in nests of tumor cells (melanoma score) for patients with melanoma; ≥ 1% of viable tumor cells showing partial or complete membrane staining at any intensity (tumor proportion score) for patients with NSCLC; and ≥ 1% of stained tumor and immune cells relative to total tumor cells (combined positive score) for patients with RCC, EA, UC, TNBC, or SCCHN. IDO1 expression in tumor-infiltrating immune cells was determined by in situ hybridization using RNAscope technology (Advanced Cell Diagnostics, Newark, CA); a histoscore ≥ 5 was used as an arbitrary cutoff for IDO1-positive status.

Blood samples were collected predose and postdose at protocol-defined time points for pharmacokinetic assessments of epacadostat and pembrolizumab. Pharmacokinetic-based projected IDO1 inhibition was determined from the plasma concentration of epacadostat using a three-parameter maximum effect model[21] in which the minimum effect and maximum effect were constrained to be 0% and 100%, respectively, and the IC_{50} was 0.070 μM. The immunogenicity of pembrolizumab also was evaluated.

Statistical Analyses

To determine epacadostat MTD and RP2D when administered in combination with pembrolizumab, planned enrollment was approximately 54 patients (three to nine patients per each of four dose levels, plus nine patients per each safety expansion cohort). Safety and efficacy were evaluated in all patients who received one or more doses of study treatment. Pharmacokinetic analyses included patients who provided predose (on cycle 1, day 1) and one or more postdose blood samples. Descriptive statistics were used to summarize findings where appropriate.

Pharmacokinetic and pharmacokinetic-based projected pharmacodynamic data were analyzed using a model-independent approach (ie, noncompartmental analysis) with commercial software (Phoenix WinNonlin 7.0; Certara, Princeton, NJ). Predose (trough) samples were analyzed with an assigned time point of 0. Actual times after dosing for postdose samples were used for pharmacokinetic analysis where available. Because of limited pharmacokinetic sampling up to 6 to 8 hours postdose, 12-hour postdose concentrations for the visit at steady state (cycle 1, day 8, or cycle 2, day 1) were imputed from the predose concentration on the same day.

Table 1. Patient Demographics and Baseline Characteristics

Variable	Total, No. (%)
No. of patients	62
Median age, years (range)	59 (30-88)
Sex	
Male	35 (56)
Female	27 (44)
Race	
White	56 (90)
Black	3 (5)
Asian	2 (3)
Hawaiian/Pacific Islander	1 (2)
ECOG PS	
0	35 (56)
1	27 (44)
Tumor type*	
Melanoma	22 (35)
Non–small-cell lung cancer	12 (19)
Renal cell cancer	11 (18)
Endometrial adenocarcinoma	7 (11)
Urothelial carcinoma	5 (8)
Triple-negative breast cancer	3 (5)
Squamous cell carcinoma of the head and neck	2 (3)
PD-L1 expression	
Positive	32 (52)
Negative	11 (18)
Unknown†	19 (31)
IDO1 expression‡	
Positive	13 (21)
Negative	9 (15)
Unknown§	40 (65)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IDO1, indoleamine 2,3-dioxygenase 1; PD-L1, programmed death-ligand 1.
*Mismatch repair deficiency status was not collected.
†PD-L1 expression was not evaluable at the time of analysis in 14 patients (23%); tumor samples were not submitted or missing in an additional five patients (8%).
‡IDO1 positivity in tumor-infiltrating immune cells was determined by RNAscope assay (Advanced Cell Diagnostics, Newark, CA) using an arbitrary histoscore threshold of ≥ 5%.
§IDO1 expression was not available at the time of analysis in 27 patients (44%); tumor samples were missing in an additional 13 patients (21%).

RESULTS

Patient Disposition and Baseline Characteristics

Between July 15, 2014, and October 13, 2015, 62 patients were enrolled in the phase I portion of the study. Median age was 59 years (range, 30 to 88 years). Most patients were male (56%) and white (90%) with an Eastern Cooperative Oncology Group performance status of 0 (56%; Table 1). Melanoma (22 patients, including 19 who were treatment-naive for advanced or metastatic disease), NSCLC (12 patients), and RCC (11 patients) were the most frequent tumor types. Thirty-two patients were PD-L1 positive and 11 were PD-L1 negative; 19 had unknown PD-L1 status. Thirteen patients were IDO1 positive and nine were IDO1 negative; 40 had unknown IDO1 status. Among 17 patients evaluable for both PD-L1 and IDO1 expression, eight were IDO1 positive and PD-L1 positive. Four patients were treated with epacadostat 25 mg twice per day, 20 with 50 mg twice per day, 18 with 100 mg twice per day, and 20 with 300 mg twice per day (Fig 1). As of October 29, 2017, 15 (24%) of 62 patients had completed combination treatment (12 patients completed 2 years of therapy and three achieved CR and discontinued after ≥ 6 months of therapy), and 46 (74%) had discontinued combination treatment (Fig 1). Median epacadostat exposure was 193 days, with a median daily dose of 197 mg. Patients received a median of nine pembrolizumab doses. Median follow-up was 19 months (range, 11 to 25 months).

Safety

During dose escalation, eight of 53 patients experienced DLTs. At 50 mg twice per day (18 patients), grade 3 arthralgia and grade 3 rash occurred in one patient each. At 100 mg twice per day (15 patients), a grade 3 AST increased/grade 2 ALT increased and grade 2 nervous system disorder occurred in one patient each. At 300 mg twice per day (16 patients), a grade 3 rash occurred in two patients; grade 2 brain edema and grade 1 skin erythema (recurrent grade 2 rash that required a dose reduction) occurred in one patient each. All DLTs resolved with dose modification, drug discontinuation, and/or concomitant medications, except in the one patient with brain edema who died as a result of disease progression before resolution of this event. MTD of epacadostat in combination with pembrolizumab was not reached.

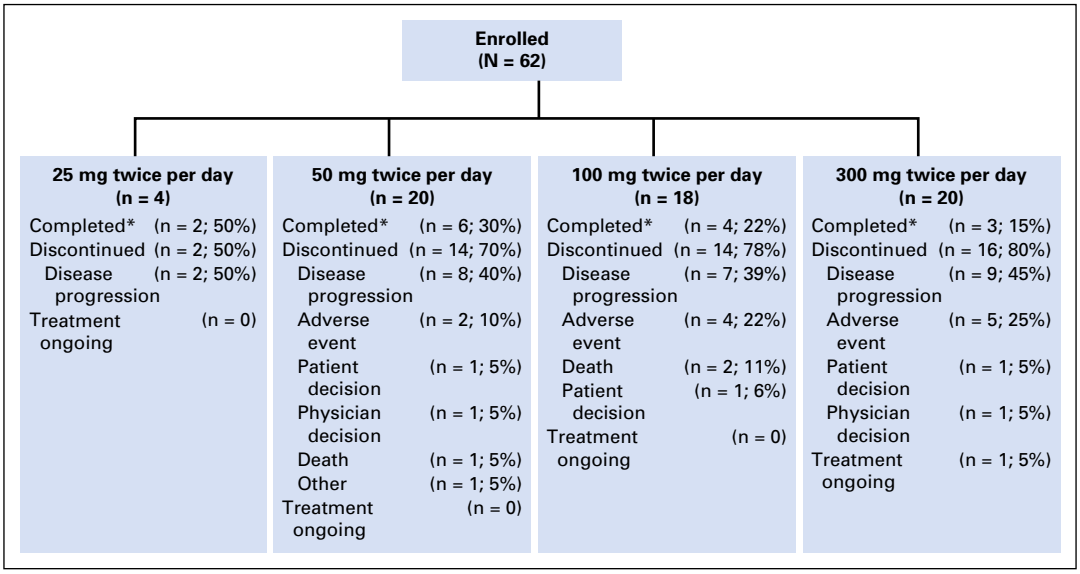

Fig 1. CONSORT diagram of the study design and patient disposition. (*) Patients who completed treatment either received 2 years of combination therapy or received ≥ 6 months of combination treatment and achieved a complete response with two or more doses of pembrolizumab administered beyond the date of initial complete response. Three patients with melanoma met the latter criteria for early stopping of treatment (50 mg twice per day, two patients; 100 mg twice per day, one patient).

TRAEs of any grade and grade 3/4 occurred in 84% and 24% of patients, respectively (Table 2). TRAEs reported in ≥ 20% of patients were fatigue (36%), rash (36%), arthralgia (24%), pruritus (23%), and nausea (21%). Grade 3/4 TRAEs that occurred in more than one patient were rash (five patients), lipase increased (five patients), and amylase increased (two patients). TRAEs led to dose interruption and reduction in 32% and 19% of patients, respectively. Seven patients (11%) discontinued treatment because of TRAEs (grade 3 arthralgia, grade 3 AST increased, grade 3 lipase increased, grade 3 aseptic meningitis, grade 2 brain edema, grade 2

Table 2. Summary of Treatment-Related AEs

	Epacadostat Treatment Group, No. (%)									
	25 mg Twice Per Day* (n = 4)		50 mg Twice Per Day* (n = 20)		100 mg Twice Per Day* (n = 18)		300 mg Twice Per Day* (n = 20)		Total (N = 62)	
Event	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Treatment-related AEs	4 (100)	1 (25)	14 (70)	2 (10)	16 (89)	5 (28)	18 (90)	7 (35)	52 (84)	15 (24)
Fatigue	3 (75)	0	7 (35)	0	6 (33)	0	6 (30)	1 (5)	22 (36)	1 (2)
Rash†	2 (50)	0	9 (45)	1 (5)	0	0	11 (55)	4 (20)	22 (36)	5 (8)
Arthralgia	2 (50)	0	4 (20)	1 (5)	4 (22)	0	5 (25)	0	15 (24)	1 (2)
Pruritus‡	2 (50)	0	5 (25)	0	0	0	7 (35)	0	14 (23)	0
Nausea	3 (75)	0	3 (15)	0	3 (17)	0	4 (20)	0	13 (21)	0
Diarrhea	2 (50)	0	3 (15)	0	3 (17)	0	3 (15)	0	11 (18)	0
Pyrexia	0	0	1 (5)	0	1 (6)	0	5 (25)	0	7 (11)	0
AST increased	0	0	2 (10)	0	4 (22)	1 (6)	0	0	6 (10)	1 (2)
Dizziness	0	0	4 (20)	0	1 (6)	0	1 (5)	0	6 (10)	0
Vomiting	0	0	1 (5)	0	3 (17)	0	2 (10)	0	6 (10)	0
Chills	0	0	2 (10)	0	2 (11)	0	1 (5)	0	5 (8)	0
Cough	0	0	2 (10)	0	1 (6)	0	2 (10)	0	5 (8)	0
Lipase increased	0	0	0	0	3 (17)	3 (17)	2 (10)	2 (10)	5 (8)	5 (8)
Myalgia	0	0	1 (5)	0	2 (11)	0	2 (10)	0	5 (8)	0
ALT increased	0	0	1 (5)	0	3 (17)	0	0	0	4 (7)	0
Back pain	0	0	0	0	1 (6)	0	3 (15)	0	4 (7)	0
Constipation	2 (50)	0	1 (5)	0	0	0	1 (5)	0	4 (7)	0
Decreased appetite	0	0	0	0	0	0	4 (20)	0	4 (7)	0
Musculoskeletal pain	0	0	2 (10)	1 (5)	1 (6)	0	0	0	3 (5)	1 (2)

NOTE. Treatment-related AEs are listed by preferred term for events that occurred in ≥ 5% of the total study population. Grade 3/4 treatment-related AEs not listed in the table were amylase increased (n = 2), stomatitis (n = 1), and aseptic meningitis (n = 1).
Abbreviation: AE, adverse event.
*Combined with pembrolizumab 2 mg/kg every 3 weeks or 200 mg every 3 weeks.
†Rash includes the following Medical Dictionary for Regulatory Activities–preferred terms: rash, rash maculopapular, rash generalized, rash pruritic, erythema, erythema multiforme, rash erythematous, palmar-plantar erythrodysesthesia syndrome, rash follicular, rash pustular, and skin exfoliation.
‡Pruritus includes the following Medical Dictionary for Regulatory Activities–preferred terms: pruritus and pruritus generalized.

Table 3. Pharmacokinetic Assessments of Epacadostat

Parameter	Epacadostat*, Mean ± SD (geometric mean)			
	25 mg Twice Per Day	50 mg Twice Per Day	100 mg Twice Per Day	300 mg Twice Per Day
Cycle 1, day 1, No. of patients	3	20	18	19
C_{max}, μM	0.23 ± 0.15 (0.20)	0.54 ± 0.22 (0.50)	0.80 ± 0.38 (0.72)	2.3 ± 1.2 (2.0)
t_{max}, hours†	2.0 (1.0-3.2)	2.0 (0.45-4.0)	2.0 (0.83-4.4)	2.0 (0.53-6.0)
AUC_{last}, hours · μM	0.71 ± 0.35 (0.65)	1.4 ± 0.62 (1.3)	2.4 ± 0.82 (2.3)	7.2 ± 2.9 (6.7)
Cycle 1, day 8, No. of patients	3	19	16	19
C_{max}, μM	0.27 ± 0.16 (0.24)	0.50 ± 0.24 (0.45)	0.92 ± 0.42 (0.81)	2.7 ± 1.2 (2.5)
t_{max}, hours†	1.0 (1.0-2.0)	2.0 (0.85-4.0)	2.0 (1.0-4.0)	2.0 (0.50-4.1)
$t_{1/2}$, hours	5.2, 5.5‡	3.5 ± 1.4 (3.3)	3.9 ± 1.6 (3.6)	4.0 ± 1.4 (3.8)
$AUC_{0-\tau}$, hours · μM	1.2 ± 0.17 (1.2)	2.1 ± 1.1 (1.8)	3.7 ± 1.4 (3.4)	12 ± 5.8 (11)

Abbreviations: $AUC_{0-\tau}$, area under the steady-state concentration versus time curve over one dosing interval; AUC_{last}, area under the concentration versus time curve from time zero to the time of the last measurable concentration; C_{max}, maximum observed plasma concentration; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; t_{max}, time of observed maximum observed plasma concentration.
*Combined with pembrolizumab 2 mg/kg every 3 weeks or 200 mg every 3 weeks.
†Median (range).
‡One of the three patients was excluded because of pathologic plasma epacadostat concentration-time profile at cycle 1, day 8; individual values for the remaining two patients are listed.

colitis, and grade 3 fatigue [one patient each]). The grade 3 aseptic meningitis subsequently resolved after hospitalization and treatment (including empirical antibiotic treatment and oral dexamethasone). No TRAEs led to death. AEs of special interest occurred in 10 patients (16%): severe skin reactions (five patients [all grade ≥ 3 rash]), hypothyroidism (three patients), colitis (one patient), and pneumonitis (one patient).

Pharmacokinetics, Pharmacodynamics, and Immunogenicity

Pharmacokinetic parameters of epacadostat at days 1 and 8 of cycle 1 are listed in Table 3. Epacadostat plasma exposures (area under the concentration *v* time curve and maximum observed plasma concentration) increased in an approximately dose-proportional manner, with time of observed a maximum observed plasma concentration at approximately 2 hours. Serum concentrations of pembrolizumab 2 mg/kg and 200 mg every 3 weeks during cycle 1 and at steady state were similar to each other and consistent with simulated concentration-time profiles for similar doses from a population pharmacokinetic model of pembrolizumab monotherapy using data from approximately 3,000 patients.[22]

Pharmacokinetic-based projected IDO1 inhibition at steady state is plotted in Figure 2 for individual patients grouped by epacadostat dose. Most patients (> 90%) were projected to have achieved ≥ 50% time-averaged IDO1 inhibition (level of pharmacodynamic activity associated with inhibition of tumor growth seen in nonclinical models).[23] PD-L1 expression did not seem to have any clear effects on pharmacokinetic-predicted pharmacodynamics.

The treatment-emergent antipembrolizumab antibody rate in the 54 evaluable patients treated with pembrolizumab plus epacadostat was 3.7%. This rate seemed to be similar to that observed in a pembrolizumab monotherapy reference data set (2.1%),[24] although the small number of patients evaluated in this study makes it difficult to draw conclusions about the effects of epacadostat on pembrolizumab immunogenicity.

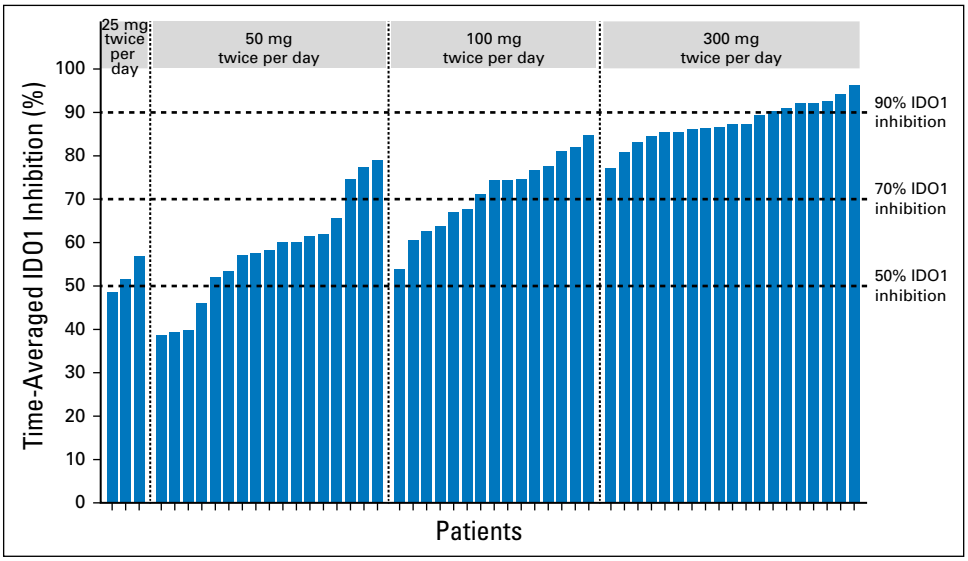

Fig 2. Pharmacokinetic-predicted time–averaged inhibition of indoleamine 2,3-dioxygenase 1 (IDO1) inhibition for individual patients by epacadostat dose.

Antitumor Activity

Antitumor activity was observed at all epacadostat doses and in several tumor types (Fig 3). Per investigator assessment by RECIST v1.1, eight of 62 patients achieved CR as best response (treatment-naive melanoma [5 patients] and previously treated for advanced/metastatic melanoma, EA, or UC [one patient each]), and 17 patients achieved PR (treatment-naive melanoma [six patients], NSCLC [five patients], RCC and UC [two patients each], and EA and SCCHN [one patient each]). Of 25 patients who achieved an objective response, 14 received epacadostat doses ≥ 100 mg twice a day. Seventeen of 25 responses were ongoing at data cutoff.

Among the 12 responders with melanoma, eight had stage M1c disease at baseline, three were *BRAF* mutation positive, six were PD-L1 positive (melanoma score ≥ 1%), one was PD-L1 negative, four were IDO1 positive, and one was IDO1 negative. Responses were ongoing in 10 of 12 patients. By immune-related RECIST criteria, one additional patient achieved PR.

Among the five responders with NSCLC, three had adenocarcinoma histology, one was *EGFR* mutation positive, two were *KRAS* mutation positive, three were PD-L1 positive (tumor proportion score ≥ 1%), one was PD-L1 negative, and one was IDO1 negative. Responses were ongoing in four of five patients.

Among the two responders with RCC, each had intermediate and favorable Memorial Sloan Kettering Cancer Center risk, and one was PD-L1 positive. Both responses were maintained for approximately 15 months.

Thirteen patients across all doses experienced stable disease as best response. These included four with melanoma, two with NSCLC, five with RCC, one with TNBC, and one with SCCHN.

For the purpose of RP2D evaluation, antitumor activities were observed at all dose levels, and no dose exceeded the MTD. Epacadostat 100 mg twice per day seemed to be better tolerated than 300 mg twice per day, with lower rates of grade 3/4 TRAEs (28% *v* 35%), treatment-related dose interruptions (22% *v* 45%) and reductions (11% *v* 35%), and AEs of special interest (6% *v* 30%). Furthermore, all patients treated with epacadostat 100 mg twice per day or 300 mg twice per day were projected to have achieved ≥ 50% time-averaged IDO1 inhibition; the majority of

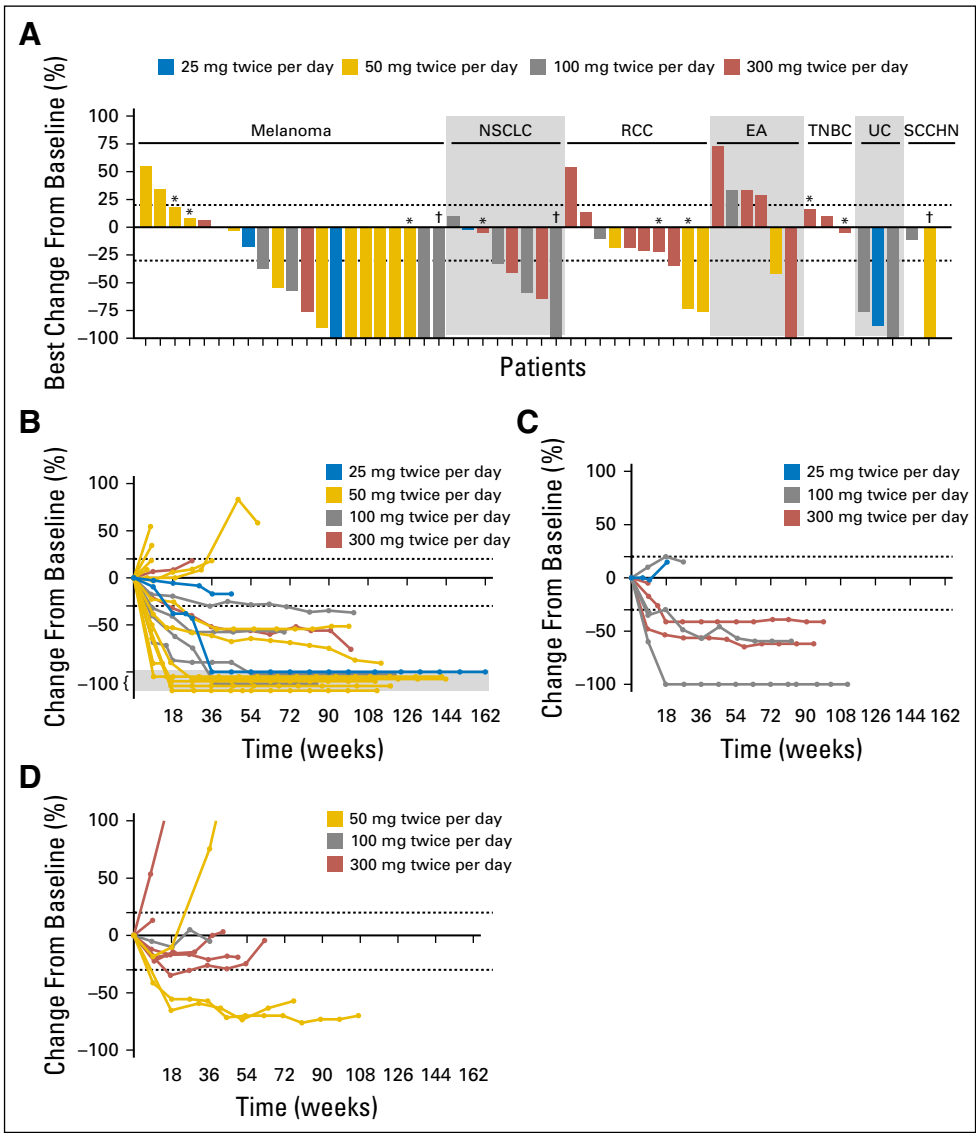

Fig 3. Change from baseline in target lesions. (A) Best percentage change from baseline in target lesions by tumor type in all patients. (B) to (D) Percentage change from baseline in target lesions over time in patients with (B) melanoma, (C) non–small-cell lung cancer (NSCLC), and (D) renal cell cancer (RCC). EA, endometrial adenocarcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; SCCHN, squamous cell carcinoma of the head and neck; TNBC, triple-negative breast cancer; UC, urothelial carcinoma. (*) Progressive disease per RECIST version 1.1. (†) Partial response per RECIST version 1.1.

patients treated with 100 mg twice per day achieved a minimum IDO1 inhibition of ≥ 50%. On the basis of these considerations, epacadostat 100 mg twice per day plus pembrolizumab 200 mg every 3 weeks was selected for additional investigation in phase II.

DISCUSSION

Phase I results of this trial show that epacadostat plus pembrolizumab generally is well tolerated in patients with various advanced solid tumors; the safety profile is similar to previous experience with pembrolizumab monotherapy. No new safety signals were detected for either epacadostat or pembrolizumab. TRAEs were primarily grade 1/2 and manageable with dose modifications or concomitant medications. Seven patients (11%) discontinued because of TRAEs. No epacadostat MTD was determined, and no patients died as a result of TRAEs. The safety profile observed with epacadostat plus pembrolizumab compares favorably with studies of other combination immunotherapies, such as nivolumab plus ipilimumab or pembrolizumab plus low-dose ipilimumab in advanced cancers. Nivolumab plus ipilimumab has been associated with higher rates of toxicities in patients with advanced melanoma, including grade 3/4 TRAEs in ≥ 45% and drug discontinuations in approximately one third.[3,4,25] The preliminary findings reported here suggest that dual inhibition of the IDO1 enzyme and PD-1 is feasible with minimal additive toxicity.[26-28]

Analyses of the pharmacokinetic parameters were comparable to previous reports of epacadostat and pembrolizumab monotherapies,[16] which suggests that the combination does not affect the pharmacokinetics of either individual agent in patients with solid tumors. Kynurenine inhibition over time was not directly measured in this study, so the pharmacodynamics were projected on the basis of the phase I patient pharmacokinetic data to yield time-averaged IDO1 inhibition. All patients who received epacadostat ≥ 100 mg twice per day achieved average concentrations at steady state that exceeded the IC_{50} associated with optimal target inhibition on the basis of preclinical models.

Although not powered to evaluate efficacy, the phase I portion of this study showed that epacadostat plus pembrolizumab had encouraging and durable antitumor activity. Objective responses were observed in patients with treatment-naive and previously treated (cytokine or interferon therapy) melanoma, NSCLC, RCC, UC, EA, and SCCHN. Responses were observed in both PD-L1–positive and –negative patients; however, correlative analyses of biomarkers, including PD-L1 and IDO1, with treatment response were not feasible in this study because of insufficient patient numbers. Across various tumor types, patients achieved durable response, with the majority of responses (17 [68%] of 25) ongoing at data cutoff. The preliminary favorable toxicity profile, pharmacokinetics, and pharmacokinetic-predicted pharmacodynamics along with encouraging clinical activity of epacadostat plus pembrolizumab reported here support additional phase II investigation of the combination, with epacadostat 100 mg twice per day selected as the RP2D.

At the time of this publication, it has been announced that the pivotal phase III ECHO-301/KEYNOTE-252 study (ClinicalTrials.gov identifier: NCT02752074) that was evaluating epacadostat plus pembrolizumab in patients with unresectable or metastatic melanoma did not meet the primary end point of improving progression-free survival in the overall population compared with pembrolizumab monotherapy.[29] Future results from ECHO-301/KEYNOTE-252, including analyses of an extensive biomarker panel and other pharmacodynamic analyses, will contribute to the understanding of the role of IDO1 inhibition, and epacadostat in combination with PD-1 inhibitors, in cancer therapy.

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Disclosures provided by the authors are available with this article at jco.org.

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