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.
highly selective oral inhibitor of the indoleamine 2,3-dioxygenase 1 (IDO1) enzyme—which 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).6,9 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 macrophages11), 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 CD86high dendritic cells, and reduced expansion of regulatory T cells.14 These changes shift the TME away from an immunosuppressive state toward one that supports protective 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.16 In addition to these encouraging safety and efficacy findings, interferon-γ–induced expression of IDO1 and PD-L1 in the TME19 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. 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 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 epidermolysis, 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
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.

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%).
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

| Event                      | 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) |
|----------------------------|------------------------------|-------------------------------|--------------------------------|--------------------------------|---------------|
| Treatment-related AEs      | 4 (100)                      | 14 (70)                       | 18 (90)                        | 52 (84)                        | 15 (24)       |
| Fatigue                   | 3 (75)                       | 7 (35)                        | 6 (30)                         | 6 (30)                         | 22 (36)       |
| Rash†                     | 2 (50)                       | 9 (45)                        | 11 (60)                        | 22 (36)                        | 5 (8)         |
| Arthralgia                | 2 (50)                       | 4 (20)                        | 5 (25)                         | 16 (25)                        | 2 (3)         |
| Pruritus‡                 | 2 (50)                       | 5 (25)                        | 7 (35)                         | 14 (23)                        | 0             |
| Nausea                    | 3 (75)                       | 3 (15)                        | 4 (20)                         | 13 (21)                        | 0             |
| Diarrhea                  | 2 (50)                       | 3 (15)                        | 3 (15)                         | 11 (18)                        | 0             |
| Pyrexia                   | 0                            | 1 (5)                         | 1 (5)                          | 7 (11)                         | 0             |
| AST increased             | 0                            | 2 (10)                        | 4 (22)                         | 6 (10)                         | 1 (2)         |
| Dizziness                 | 0                            | 4 (20)                        | 1 (5)                          | 6 (10)                         | 0             |
| Vomiting                  | 0                            | 1 (5)                         | 2 (10)                         | 6 (10)                         | 0             |
| Nausea                    | 0                            | 2 (10)                        | 1 (5)                          | 5 (8)                          | 0             |
| Cough                     | 0                            | 2 (10)                        | 2 (10)                         | 5 (8)                          | 0             |
| Lipase increased          | 0                            | 0                             | 3 (17)                         | 5 (8)                          | 0             |
| Myalgia                   | 0                            | 1 (5)                         | 2 (10)                         | 5 (8)                          | 0             |
| ALT increased             | 0                            | 1 (5)                         | 3 (17)                         | 4 (7)                          | 0             |
| Back pain                 | 0                            | 0                             | 3 (15)                         | 4 (7)                          | 0             |
| Constipation              | 2 (50)                       | 1 (5)                         | 1 (5)                          | 4 (7)                          | 0             |
| Decreased appetite        | 0                            | 0                             | 0                              | 4 (7)                          | 0             |
| Musculoskeletal pain      | 0                            | 0                             | 0                              | 3 (6)                          | 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.
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 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. 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). 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%), 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.](jco.org)

| Table 3. Pharmacokinetic Assessments of Epacadostat |
|-----------------------------------------------|
| Parameter | 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<sub>max</sub>, 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<sub>max</sub>, 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<sub>last</sub>, 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<sub>max</sub>, 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<sub>max</sub>, hours† | 1.0 (1.0-2.0) | 2.0 (0.85-4.0) | 2.0 (1.0-4.0) | 2.0 (0.50-4.0) |
| t<sub>1/2</sub>, hours | 5.2, 5.5‡ | 3.5 ± 1.4 (3.3) | 3.9 ± 1.6 (3.6) | 4.0 ± 1.4 (3.8) |
| AUC<sub>0-∞</sub>, hours | 1.2 ± 0.17 (1.2) | 2.1 ± 1.1 (1.8) | 3.7 ± 1.4 (3.4) | 12 ± 5.8 (11) |

Abbreviations: AUC<sub>0-∞</sub>, area under the steady-state concentration versus time curve over one dosing interval; AUC<sub>last</sub>, area under the concentration versus time curve from time zero to the time of the last measurable concentration; C<sub>max</sub>, maximum observed plasma concentration; SD, standard deviation; t<sub>1/2</sub>, terminal elimination half-life; t<sub>max</sub>, 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.
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 $\geq 100$ 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 $\geq 1\%$), 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 $\geq 1\%$), 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 $\geq 50\%$ time-averaged IDO1 inhibition; the majority of
patients treated with 100 mg twice per day achieved a minimum IDO1 inhibition of $\geq 50\%$. 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 $\geq 45\%$ 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 $\geq 100$ 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-naïve and previously treated (cytotoxic 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.

**REFERENCES**

1. Abri-Rodriguez G, Ribas A: SnapShot: Immune checkpoint inhibitors. Cancer Cell 31:848-848e1, 2017
2. Hodi FS, O’Day SJ, McDermott DF, et al: Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363:711-723, 2010
3. Larkin J, Chiarion-Sileni V, Gonzalez R, et al: Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 373:23-34, 2015
4. Hodi FS, Chesney J, Pavlick AC, et al: Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol 17:1558-1568, 2016
5. Hellmann MD, Rizvi NA, Goldman JW, et al: Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): Results of an open-label, phase 1, multicohort study. Lancet Oncol 18:31-41, 2017
6. Munn DH, Mellor AL: Indoleamine 2,3-dioxygenase and tumor-induced tolerance. J Clin Invest 117:1147-1154, 2007
7. Prendergast GC, Mondal A, Dey S, et al: Inflammatory reprogramming with IDO1 inhibitors: Turning immunologically unresponsive ‘cold’ tumors ‘hot’. Trends Cancer 4:38-88, 2018
8. Thèate I, van Baren N, Pilotté L, et al: Extensive profiling of the expression of the indoleamine 2,3-dioxygenase 1 protein in normal and tumoral human tissues. Cancer Immunol Res 3:161-172, 2015
9. Zhao Q, Kuang DM, Wu Y, et al: Activated CD8+ T cells foster immune privilege by regulating IDO expression in tumor-associated macrophages. J Immunol 188:1117-1124, 2012

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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

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10. Holmgaard RB, Zamarin D, Li Y, et al: Tumor-expressed IDO recruits and activates MDSCs in a Treg-dependent manner. Cell Reports 13:412-424, 2015

11. Wang XF, Wang HS, Wang H, et al: The role of indoleamine 2,3-dioxygenase (IDO) in immune tolerance: Focus on macrophage polarization of TH-1 cells. Cell Immunol 289:42-48, 2014

12. Ino K, Yoshida N, Kajiyama H, et al: Indoleamine 2,3-dioxygenase is a novel prognostic indicator for tumor angiogenesis. Br J Cancer 95:1555-1561, 2006

13. Okamoto A, Nikaio T, Ochiai K, et al: Indoleamine 2,3-dioxygenase serves as a marker of poor prognosis in gene expression profiles of serous ovarian cancer cells. Clin Cancer Res 11:6030-6039, 2005

14. Liu X, Shin N, Koblish HK, et al: Selective inhibition of IDO1 effectively regulates mediators of antitumor immunity. Blood 116:3520-3530, 2010

15. Spranger S, Koblish HK, Horton B, et al: Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of CD8(+) T cells directly within the tumor microenvironment. J Immunother Cancer 2:3, 2014

16. Beatty GL, O’Dwyer PJ, Clark J, et al: First-in-human phase I study of the oral inhibitor of indoleamine 2,3-dioxygenase-1 epacadostat (INCB024360) in patients with advanced solid malignancies. Clin Cancer Res 23:3269-3276, 2017

17. Kristeleit R, Davidenko I, Shrininkin V, et al: A randomised, open-label, phase 2 study of the IDO1 inhibitor epacadostat (INCB024360) versus tamoxifen as therapy for biochemically recurrent (CA-125 relapse)-only epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer. Gynecol Oncol 146:484-490, 2017

18. Gibney GT, Hamid O, Lutzky J, et al: Updated results from a phase 1/2 study of epacadostat (INCB024360) in combination with ipilimumab in patients with metastatic melanoma. Eur J Cancer 51: S106-S107, 2015

19. Spranger S, Spaapen RM, Zha Y, et al: Up-regulation of PD-L1, IDO, and T(regs) in the melanoma tumor microenvironment is driven by CD8(+) T cells. Sci Transl Med 5:200ra116, 2013

20. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45:228-247, 2009

21. Shi JG, Bowman KJ, Chen X, et al: Population pharmacokinetic and pharmacodynamic modeling of epacadostat in patients with advanced solid malignancies. J Clin Pharmacol 57:720-729, 2017

22. Li H, Yu J, Liu C, et al: Time dependent pharmacokinetics of pembrolizumab in patients with solid tumor and its correlation with best overall response. J Pharmacokinet Pharmacodyn 44:403-414, 2017

23. Koblish HK, Hansbury MJ, Bowman KJ, et al: Hydroxyamide inhibitors of indoleamine-2,3-dioxygenase potently suppress systemic tryptophan catabolism and the growth of IDO-expressing tumors. Mol Cancer Ther 9:489-498, 2010

24. Keytruda (pembrolizumab) [full prescribing information], Whitehouse Station, NJ, Merck & Co, 2017

25. Long GV, Atkinson V, Cebon JS, et al: Pembrolizumab versus ipilimumab in combination with reduced-dose ipilimumab for patients with advanced melanoma (KEYNOTE-029): An open-label, phase 1b trial. Lancet Oncol 18:1202-1210, 2017

26. Robert C, Schachter J, Long GV, et al: Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 372:2521-2532, 2015

27. Reck M, Rodríguez-Abreu D, Robinson AG, et al: Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375:1823-1833, 2016

28. Motzer RJ, Escudier B, McDermott DF, et al: Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 373:1803-1813, 2015

29. Long GV, Dummer R, Hani O, et al: Epacadostat plus pembrolizumab versus pembrolizumab alone in patients with unsegregable or metastatic melanoma: Results of the phase 3 ECHO-301/KEYNOTE-252 study. J Clin Oncol 36, (suppl; abstr 108), 2018

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