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ORIGINAL ARTICLE

Phase 1/2 study of epacadostat in combination with durvalumab in patients with metastatic solid tumors

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Abstract

BACKGROUND: Targeting programmed cell death protein 1 (PD-1) and indoleamine 2,3-dioxygenase (IDO1) pathways is an appealing option for cancer treatment.

METHODS: The open-label, phase 1/2 ECHO-203 study evaluated the safety, tolerability, and efficacy of the IDO1 inhibitor epacadostat in combination with durvalumab, a human anti–PD-L1 monoclonal antibody in adult patients with advanced solid tumors.

RESULTS: The most common treatment-related adverse events were fatigue (30.7%), nausea (21.0%), decreased appetite (13.1%), pruritus (12.5%), maculopapular rash (10.8%), and diarrhea (10.2%). Objective response rate (ORR) in the overall phase 2 population was 12.0%. Higher ORR was observed in immune

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See editorial on pages 11–4, this issue.

checkpoint inhibitor (CPI)-naïve patients (16.1%) compared with patients who had received previous CPI (4.1%). Epacadostat pharmacodynamics were evaluated by comparing baseline kynurenine levels with those on therapy at various time points. Only the 300-mg epacadostat dose showed evidence of kynurenine modulation, albeit unsustained.

CONCLUSIONS: Epacadostat plus durvalumab was generally well tolerated in patients with advanced solid tumors. ORR was low, and evaluation of kynurenine concentration from baseline to cycle 2, day 1, and cycle 5, day 1, suggested >300 mg epacadostat twice daily is needed to ensure sufficient drug effect.

Clinical trial information: A study of epacadostat (INCB024360) in combination with durvalumab (MEDI4736) in subjects with selected advanced solid tumors (ECHO-203) (NCT02318277).

KEYWORDS
durvalumab, epacadostat, kynurenine, neoplasms, PD-1

INTRODUCTION

Indoleamine 2,3-dioxygenase (IDO1), a potential therapeutic target for cancer treatment, catalyzes the first and rate-limiting step of tryptophan degradation in the kynurenine (KYN) pathway.[1] IDO1 is overexpressed by an array of human tumor and dendritic cells.[2] Increased IDO1 expression in tumor cells is associated with reduced overall survival in patients with melanoma, ovarian, colorectal, and pancreatic cancers.[3–8] Epacadostat is a potent and highly selective IDO1 enzyme inhibitor in both tumor and dendritic cells that reduces conversion of tryptophan to KYN.[9]

In a phase 1 study of advanced solid tumors, epacadostat monotherapy was well tolerated, but no objective responses were reported.[10] Preclinical data demonstrated synergy between immune checkpoint inhibitors (CPIs) and IDO1 inhibitors,[11] and IDO1 and CPI programmed death-ligand 1 (PD-L1) are often coexpressed in tumor microenvironments.[12] Furthermore, anti–programmed cell death protein 1 (PD-1) treatment can induce interferon γ production, which can induce IDO1 expression.[13] Thus, targeting PD-1 and IDO pathways is an attractive option for cancer treatment. Durvalumab, a human anti–PD-L1 monoclonal antibody that inhibits binding of PD-L1 to PD-1,[14] is approved to treat unresectable stage III non–small cell lung cancer (NSCLC) and extensive stage small cell lung cancer.[15,16] The phase 1/2 ECHO-203 (NCT02318277) study evaluated safety, tolerability, and efficacy of epacadostat in combination with durvalumab across multiple advanced solid tumor types.

MATERIALS AND METHODS

Study population

ECHO-203 was an open-label, phase 1/2 study of epacadostat plus durvalumab in patients with histologically confirmed advanced melanoma, NSCLC, pancreatic cancer (phase 1 only), squamous cell carcinoma of the head and neck (SCCHN), triple-negative breast cancer (TNBC), gastric or gastroenterologic cancer, or bladder cancer (phase 2 only). Patients were aged ≥18 years with an Eastern Cooperative Oncology Group performance status of 0 or 1 for whom one or more previous treatment regimen for locally advanced or metastatic disease had failed. Patients with metastatic melanoma were required to have a known V600E-activating *BRAF* mutation status. In phase 1, patients who were *BRAF* mutation positive must have received previous treatment with a BRAF inhibitor with or without a MEK inhibitor. Patients with NSCLC who had an *EGFR* mutation or *ALK* fusion gene must have received targeted therapy and might have received a prior anti–PD-1 target agent. Patients with pancreatic cancer were required to have an exocrine pancreatic neoplasm. Patients with SCCHN must have received prior platinum-based therapy. Patients with gastroenterologic cancer were required to have a known HER2/neu status and have progressed after treatment with platinum or fluoropyrimidine and a HER2-targeted agent, if appropriate. Patients were excluded for chronic use of systemic steroids at doses of ≥10 mg/day, untreated central nervous system metastases or carcinomatous meningitis, interstitial lung disease or noninfectious pneumonitis, clinically significant cardiac disease, known HIV infection, pregnancy, or receipt of monoamine oxidase inhibitors within 3 weeks or radiation within 2 weeks before initial study treatment.

Study design and treatment

Phase 1 was an open-label dose escalation study to identify the maximum tolerated dose (MTD) or pharmacologically active dose of epacadostat in combination with durvalumab using a 3 + 3 dose-escalation design. Patients received 25 mg of oral epacadostat twice daily in combination with 3 mg/kg of intravenous durvalumab

every 2 weeks on day 1 of a 14-day cycle, or 25, 50, 75, 100, or 300 mg of oral epacadostat twice daily in combination with 10 mg/kg of intravenous durvalumab every 2 weeks on day 1 of a 14-day cycle for up to 12 months. A minimum of three patients were treated in each cohort and observed for a minimum of 42 days before enrolling a subsequent cohort. Epacadostat dosing was escalated if none of three evaluable patients in the previous cohort experienced a dose-limiting toxicity (DLT). If a DLT occurred, the cohort was expanded to include three additional patients for treatment at that dose level. If ≥2 of either three or six enrolled patients experienced a DLT, the prior dose level was considered the MTD. Dose interruption or dose reduction (epacadostat only) was allowed in patients experiencing protocol-defined adverse events (AEs). Hematologic DLT was defined as grade 4 thrombocytopenia; grade ≥3 neutropenia lasting >5 days; grade 4 anemia, febrile neutropenia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, disseminated intravascular coagulation, or idiopathic thrombocytopenic purpura; or grade ≥3 hemolysis. Nonhematologic DLT included any grade ≥3 drug-related or immune-related toxicity or any grade ≥3 aspartate aminotransferase, alanine aminotransferase, or total bilirubin elevation. Additionally, patients who experienced >2-week delay in starting cycle 4 or were unable to receive 75% of epacadostat or three doses of durvalumab during the DLT observation period because of a treatment-related toxicity were classified as DLT even if DLT toxicity criteria were not met.

In phase 2, patients received two dose schedules of epacadostat (100 or 300 mg twice daily) plus durvalumab 10 mg/kg every 2 weeks. Enrollment in the melanoma, TNBC, and gastric cohorts was initiated once epacadostat 100 mg twice daily in combination with durvalumab was determined to be safe. On completion of dose escalation and determining the safety of epacadostat 300 mg twice daily in this combination, further enrollment into these and additional cohorts proceeded with this dose. After 12 months of treatment, patients discontinued both drugs and entered the safety follow-up period. The initial version of the protocol allowed patients to continue treatment for up to an additional 12 months if their physician-investigator determined they were experiencing clinical benefit. This option was removed by amendment during the study. Safety follow-up visits were conducted 42 and 90 days after treatment cessation.

Epacadostat pharmacokinetic (PK) samples were collected in phase 1 on cycle 1, day 1 (C1D1), cycle 1, day 8, and cycle 2, day 1 (C2D1), and in phase 2 on C1D1 and C2D1. Durvalumab PK samples were collected in phase 1 on day 1 of cycles 1, 2, 5, 9, and 13 and every 8 weeks thereafter, at the end of treatment, and at the 90-day safety follow-up visit. For patients in phase 1, immunogenicity sampling occurred at cycles 5, 13, and 25. For patients in phase 2, immunogenicity and soluble PD-L1 sampling occurred at cycles 7, 13, and 25.

This study was conducted in accordance with the provisions of the Declaration of Helsinki, as described in the International Council for Harmonization Guidelines for Good Clinical Practice, and was approved by the institutional review board at each participating institution. All patients provided informed consent before treatment initiation.

End Points

The primary endpoint for phase 1 was to determine the MTD or pharmacologically active dose. The primary endpoint for phase 2 was the objective response rate (ORR) per modified Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1), in which confirmation of progressive disease was required by repeated, consecutive assessment no less than 4 weeks from first documentation. Tumor imaging occurred every 8–12 weeks during treatment and within 7 days after the last dose during treatment discontinuation. Stable disease (SD) was defined as meeting SD criteria at least once after study entry at a minimum interval of 56 (±7) days. Subjects who fail to meet these criteria will have best response of progressive disease (PD) if the next available RECIST evaluation after the initial scan indicates PD or not evaluable if there are no additional RECIST evaluations available. ORR by prior CPI status and PD-L1 status were determined by investigator-reported assessment using RECIST criteria.

Secondary endpoints assessed the safety and tolerability of epacadostat and durvalumab combination therapy, progression-free survival (PFS), durvalumab and epacadostat PK, and the prevalence of anti-durvalumab antibodies.

Safety and tolerability were assessed by frequency and severity of AEs as defined by Common Terminology Criteria for Adverse Events (version 4.03). AEs of special interest (AESI) were assessed using a predefined list associated with durvalumab monotherapy.

Statistical analysis

Safety analysis included all patients who received at ≥1 dose of epacadostat and durvalumab. Efficacy analysis included all enrolled patients (intent-to-treat population). The PK-evaluable population included patients who had received ≥1 epacadostat dose and provided ≥1 postdose plasma sample. Median PFS was estimated using the nonparametric Kaplan–Meier method. Epacadostat PK was estimated by noncompartmental analysis, population PK modeling, or both. SAS software (version 9.1) (SAS Institute Inc., Cary, NC, USA) was used to generate all tables, graphs, and statistical analyses.

RESULTS

Patient disposition

Thirty-four patients with NSCLC, SCCHN, pancreatic cancer, and melanoma were enrolled in phase 1. Patients received epacadostat plus durvalumab across six dosing cohorts as described in the Materials and Methods (Table 1). At the data cutoff date of August 28, 2019, five patients (14.7%) had completed 12 months of treatment, and all 34 patients had discontinued combination treatment. The reasons for treatment discontinuation were disease progression (n = 23; 67.6%), completion of 12-month treatment (n = 5; 14.7%), AEs (n = 3; 8.8%), physician decision (n = 2; 5.9%), and death (n = 1;

TABLE 1 Patient disposition

Disposition status, No. (%)	Phase 1							Phase 2		
	3 mg/kg Durva	10 mg/kg Durva						10 mg/kg Durva		
	25 mg Epa (n = 6)	25 mg Epa (n = 3)	50 mg Epa (n = 4)	75 mg Epa (n = 4)	100 mg Epa (n = 8)	300 mg Epa (n = 9)	Total (N = 34)	100 mg Epa (n = 49)	300 mg Epa (n = 93)	Total (N = 142)
Patients who completed 12 mo of combination treatment	0	1 (33.3)	1 (25.0)	0	1 (12.5)	2 (22.2)	5 (14.7)	4 (8.2)	8 (8.6)	12 (8.5)
Patients who discontinued combination treatment	6 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	8 (100.0)	9 (100.0)	34 (100.0)	49 (100.0)	93 (100.0)	142 (100.0)
Primary reason for treatment discontinuation	6 (100.0)	1 (33.3)	2 (50.0)	4 (100.0)	4 (50.0)	6 (66.7)	23 (67.6)	41 (83.7)	69 (74.2)	110 (77.5)
Disease progression adverse event	0	1 (33.3)	1 (25.0)	0	1 (12.5)	0	3 (8.8)	1 (2.0)	10 (10.8)	11 (7.7)
Death	0	0	0	0	1 (12.5)	0	1 (2.9)	0	1 (1.1)	1 (0.7)
Consent withdrawn	0	0	0	0	0	0	0	1 (2.0)	2 (2.2)	3 (2.1)
Lost to follow-up	0	0	0	0	0	0	0	0	0	0

Abbreviations: Durva, durvalumab; Epa, epacadostat.

2.9%). One patient was ongoing in the study, and 33 patients had been discontinued. The reasons for study discontinuation were death (n = 24; 70.6%), study termination by the sponsor (n = 4; 11.8%), consent withdrawn (n = 3; 8.8%), and loss to follow-up (n = 2; 5.9%).

In phase 2, 142 patients with NSCLC, SCCHN, TNBC, melanoma, bladder cancer, and gastric cancer were treated with epacadostat 100 mg twice daily (n = 49) and 300 mg twice daily (n = 93) in combination with 10 mg/kg of durvalumab (Table 1). As of August 28, 2019, 12 patients (8.5%) had completed 12 months of treatment, and all 142 patients had discontinued combination treatment. Reasons for combination treatment discontinuation were disease progression (n = 110; 77.5%), completion of 12 months of treatment (n = 12; 8.5%), AEs (n = 11; 7.7%), physician decision (n = 4; 2.8%), death (n = 1; 0.7%), and other (n = 1; 0.7%). All 142 patients had discontinued the study because of death (n = 92; 64.8%), study termination by the sponsor (n = 21; 14.8%), consent withdrawn (n = 20; 14.1%), loss to follow-up (n = 7; 4.9%), physician decision (n = 1; 0.7%), or other (n = 1; 0.7%).

Baseline characteristics

Baseline demographics and disease characteristics for all patients are shown in Table 2. Among patients in phase 1, two patients with NSCLC had an *EGFR* mutation, two had a *KRAS* mutation, and one an *ALK* rearrangement; nine patients had adenocarcinoma and one had squamous NSCLC; one patient had received a prior tyrosine kinase inhibitor. Two patients with SCCHN were positive for human papilloma virus; 1 each had an *EGFR* mutation and a *p53* mutation. Two patients had received a prior CPI (ipilimumab, n = 1; ipilimumab and

TABLE 2 Patient demographics and disease characteristics at baseline

Baseline characteristics, No. (%)	Phase 1 Total[a] (N = 34)	Phase 2 100 mg Epa[b] (n = 49)	Phase 2 300 mg Epa[b] (n = 93)	Phase 2 Total (N = 142)
Age, median (range), y	68 (46–84)	60 (31–85)	65 (29–87)	64 (29–87)
Age ≥65 y	22 (64.7)	17 (34.7)	49 (52.7)	66 (46.5)
Male	21 (61.8)	30 (61.2)	68 (73.1)	98 (69.0)
Race				
White	33 (97.1)	41 (83.7)	83 (89.2)	124 (87.3)
Black or African American	1 (2.9)	5 (10.2)	5 (5.4)	10 (7.0)
ECOG PS				
0	6 (17.6)	6 (12.2)	20 (21.5)	26 (18.3)
1	28 (82.4)	43 (87.8)	72 (77.4)	115 (81.0)
≥2	0	0	1 (1.1)	1 (0.7)
Tumor type				
Pancreatic	15 (44.1)	0	0	0
TNBC	0	13 (26.5)	0	13 (9.2)
NSCLC	10 (29.4)	9 (18.4)	28 (30.1)	37 (26.1)
SCCHN	8 (23.5)	7 (14.3)	31 (33.3)	38 (26.8)
Melanoma	1 (2.9)	7 (14.3)	8 (8.6)	15 (10.6)
Gastric	0	9 (18.4)	0	9 (6.3)
Bladder	0	4 (8.2)	26 (28.0)	30 (21.1)
Prior treatments for advanced/metastatic disease				
0	1 (2.9)	8 (16.3)	15 (16.1)	23 (16.2)
1	11 (32.4)	10 (20.4)	27 (29.0)	37 (26.1)
≥2	22 (64.7)	31 (63.3)	51 (54.8)	82 (57.7)
Prior use of checkpoint inhibitors				
Yes	2 (5.9)	9 (18.4)	40 (43.0)	49 (34.5)
No	32 (94.1)	40 (81.6)	53 (57.0)	93 (65.5)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; Epa, epacadostat; NSCLC, non–small cell lung cancer; SCCHN, squamous cell carcinoma of the head and neck; TNBC, triple-negative breast cancer.

[a]Plus durvalumab 3 mg/kg every 2 weeks or 10 mg/kg every 2 weeks.

[b]Plus durvalumab 10 mg/kg every 2 weeks.

nivolumab, n = 1). At initial diagnosis, four patients with SCCHN had a primary oral cavity tumor, two in the larynx, one in the oropharynx, and one in other. Five SCCHN patients had a poorly differentiated tumor, one had an intermediately differentiated tumor, and one had an undifferentiated tumor. Among patients with pancreatic cancer, six had a Whipple procedure (pancreatoduodenectomy), four had a pancreatectomy, and six had a biliary stent.

In phase 2, one patient with NSCLC had an *EGFR* mutation, five had a *KRAS* mutation, and one an *ALK* rearrangement; nine patients had received a prior tyrosine kinase inhibitor. Histologically typed NSCLC samples showed that 26 patients had adenocarcinoma, one had large cell carcinoma, six had squamous NSCLC, two had adenosquamous carcinoma (mixed), and two had other types of NSCLC. Sixteen patients with SCCHN were human papilloma virus positive; three patients had an *EGFR* mutation, and five had a *p53* mutation. At initial diagnosis, nine patients had a primary tumor in the oral cavity, five had a tumor in the larynx, 15 a tumor in the oropharynx, two a tumor in the hypopharynx, and seven a tumor in other. Fifteen patients with SCCHN had poorly differentiated tumors, six had intermediately differentiated tumors, four had well-differentiated tumors, and 13 had undifferentiated tumors. Four patients with melanoma were positive for *BRAF-V600*. Three patients with gastric cancer had tumors that were well or moderately differentiated, and six had tumors that were poorly differentiated or undifferentiated. Histologic classification of gastric cancer samples showed that three patients had indeterminate type, four had other types, and two had unknown types of gastric cancer. No patient was positive for Epstein-Barr virus; one was positive for *Helicobacter pylori*. Of 30 patients with bladder cancer, 28 had transitional cell carcinoma, and two had carcinomas of other type. PD-L1 status was positive in one patient, negative in two, and missing in 27. Of 13 patients with TNBC, five were *BRCA* negative, two were PD-L1 negative, and one was MYC rearrangement positive. Forty-nine patients had received a prior CPI (ipilimumab, n = 8; nivolumab, n = 24; pembrolizumab, n = 16; atezolizumab, n = 10; avelumab, n = 1; enoblituzumab, n = 1).

Safety and tolerability

In phase 1, median duration of exposure to epacadostat was 84.5 days (range, 14-1339). The most common (occurring in ≥5% of patients) treatment-related AEs (TRAEs) were fatigue (32.4%), pruritus (17.6%), nausea (11.8%), and diarrhea (11.8%) (Table 3). Grade ≥3 TRAEs were observed in seven patients (20.6%). The only grade ≥3 or higher TRAEs that occurred in >1 patient were fatigue (n = 3; 8.8%) and rash maculopapular (n = 2; 5.9%). No TRAEs leading to death were reported. One DLT of grade 3 rash requiring systemic steroids was reported in the epacadostat 300 mg twice daily plus durvalumab 10 mg/kg every-2-week cohort. The MTD was not reached, and epacadostat 100 mg twice daily and 300 mg twice daily were further evaluated in phase 2. AESIs included immune-mediated AEs and serotonin syndrome. The most common (occurring in ≥5% of patients) immune-mediated AESIs were pruritus (5.9%) and maculopapular rash (5.9%). No hepatic function abnormalities were reported. Two instances of pneumonitis (grade 2 and grade 1) occurred in one patient and resulted in treatment discontinuation; serotonin syndrome (grade 2) occurred in one patient who recovered but discontinued treatment because of disease progression.

In phase 2, median duration of exposure to epacadostat was 62.0 days (range, 5–839). The most common (occurring in ≥5% of patients) TRAEs were fatigue (30.3%), nausea (23.2%), decreased appetite (14.1%), maculopapular rash (12.0%), and pruritus (11.3%) (Table 3). Grade ≥3 TRAEs were observed in 26 patients (18.3%). No TRAEs leading to death were reported. The most common (occurring in ≥5% of patients) immune-mediated AESIs were maculopapular rash (7.7%) and pruritus (5.6%); no other AESIs were reported in phase 2.

Efficacy

In the overall population, 17 patients (12.0%) had objective responses per RECIST (95% CI, 7.1–18.5); three patients (2.1%) had a complete response (CR), and 14 patients (9.9%) had a partial response (PR). A higher ORR was observed in the CPI-naïve population than in the CPI-experienced population. ORR in CPI-naïve patients (n = 93) was 16.1% (95% CI, 9.3–25.2) (Table 4); three patients (3.2%) had a CR and 12 patients (12.9%) had a PR. Among CPI-naïve patients, those with melanoma had the best ORR (n = 5; 80.0%; 95% CI, 28.4–99.5) in comparison with patients with other tumor types, including two CRs and two PRs. ORR in CPI-experienced patients (n = 49) was 4.1% (95% CI, 0.5–14.0); no patient had a CR, and two patients (4.1%) had a PR. One patient with NSCLC previously received pembrolizumab for approximately 6 months with a best response of stable disease before disease progression. The other patient had melanoma and previously received nivolumab for approximately 2 months with a best response of progressive disease. Treatment in the current trial for the NSCLC and melanoma patients began 4 months and 1 month after discontinuing prior anti–PD-1 treatment, respectively. Both PRs with previous CPI treatment received epacadostat 300 mg twice daily and durvalumab 10 mg/kg every 2 weeks in the current study. No responses were observed in patients with gastric cancer (0%; 95% CI, 0.0–33.6) in either category. Treatment responses by dose in CPI-naïve individual patients enrolled in phase 2 are presented in Figure 1. There was no clear relationship between doses of epacadostat (100 mg twice daily vs 300 mg twice daily) and tumor responses. Median PFS was 1.9 months (range, 1.8–3.6) in CPI-naïve patients and 2.0 months (95% CI, 1.9–2.7) in all phase 2 patients.

Pharmacokinetics

Epacadostat exposure was generally consistent with previous reports. Peak exposures (C_{max}±SD) of 100 mg epacadostat twice daily and 300 mg epacadostat twice daily doses were 960 ± 499 nM and

TABLE 3 Treatment-related adverse events occurring in ≥5% of patients in phase 1 and phase 2

	Phase 1		Phase 2					
	Total (N = 34)		100 mg Epa[a] (n = 49)		300 mg Epa[a] (n = 93)		Total (N = 142)	
Adverse event, No. (%)	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Total	27 (79.4)	7 (20.6)	35 (71.4)	3 (6.1)	79 (84.9)	23 (24.7)	114 (80.3)	26 (18.3)
Fatigue	11 (32.4)	3 (8.8)	12 (24.5)	0	31 (33.3)	4 (4.3)	43 (30.3)	4 (2.8)
Nausea	4 (11.8)	0	11 (22.4)	0	22 (23.7)	1 (1.1)	33 (23.2)	1 (0.7)
Decreased appetite	3 (8.8)	0	5 (10.2)	0	15 (16.1)	0	20 (14.1)	0
Maculopapular rash	2 (5.9)	2 (5.9)	8 (16.3)	1 (2.0)	9 (9.7)	5 (5.4)	17 (12.0)	6 (4.2)
Pruritus	6 (17.6)	0	3 (6.1)	0	13 (14.0)	0	16 (11.3)	0
Diarrhea	4 (11.8)	0	4 (8.2)	0	10 (10.8)	0	14 (9.9)	0
Vomiting	0	0	3 (6.1)	1 (2.0)	10 (10.8)	1 (1.1)	13 (9.2)	2 (1.4)
Increased AST	1 (2.9)	0	2 (4.1)	0	9 (9.7)	2 (2.2)	11 (7.7)	2 (1.4)
Rash	1 (2.9)	0	2 (4.1)	0	9 (9.7)	0	11 (7.7)	0
Increased ALP	1 (2.9)	0	0	0	9 (9.7)	2 (2.2)	9 (6.3)	2 (1.4)
Chills	1 (2.9)	0	4 (8.2)	0	5 (5.4)	0	9 (6.3)	0
Headache	1 (2.9)	0	2 (4.1)	0	7 (7.5)	0	9 (6.3)	0
Pyrexia	2 (5.9)	0	6 (12.2)	0	2 (2.2)	0	8 (5.6)	0
Increased ALT	0	0	1 (2.0)	0	7 (7.5)	2 (2.2)	8 (5.6)	2 (1.4)
Dizziness	2 (5.9)	0	2 (4.1)	0	3 (3.2)	1 (1.1)	5 (3.5)	1 (0.7)
Tumor flare	3 (8.8)	0	1 (2.0)	0	3 (3.2)	0	4 (2.8)	0
Constipation	2 (5.9)	0	1 (2.0)	0	3 (3.2)	2 (2.2)	4 (2.8)	2 (1.4)
Dyspnea	2 (5.9)	1 (2.9)	3 (6.1)	0	1 (1.1)	0	4 (2.8)	0
Influenza-like illness	2 (5.9)	0	0	0	4 (4.3)	0	4 (2.8)	0
Anxiety	2 (5.9)	0	0	0	0	0	0	0
Bone pain	2 (5.9)	0	2 (4.1)	0	1 (1.1)	0	3 (2.1)	0
Dry mouth	2 (5.9)	0	0	0	3 (3.2)	0	3 (2.1)	0
Hyponatremia	2 (5.9)	0	1 (2.0)	0	1 (1.1)	1 (1.1)	2 (1.4)	1 (0.7)
Decreased weight	2 (5.9)	0	0	0	2 (2.2)	0	2 (1.4)	0
Cough	2 (5.9)	0	0	0	1 (1.1)	0	1 (0.7)	0

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Epa, epacadostat.

[a]Plus durvalumab 10 mg/kg every 2 weeks.

2500 ± 1190 nM, respectively. The areas under the concentration-time curves (AUC±SD) for 100 mg epacadostat twice daily and 300 mg epacadostat twice daily doses were 4130 ± 1960 h/nM and 12,200 ± 5950 h/nM, respectively. Both 100 mg epacadostat twice daily and 300 mg epacadostat twice daily doses exhibited similar half-lives ($t_{1/2}$±SD, 4.10 h ± 1.69 h and 4.09 h ± 1.99 h, respectively), which were also consistent with historical data.

Patients with pancreatic cancer had lower peak exposures (C_{max}). When dose-normalized to 100 mg twice daily, patients who had a Whipple procedure demonstrated a lower AUC and C_{max} (n = 5; 31.7 ± 22.2 h/nM/mg and 5.76 ± 6.43 nM/mg, respectively) in comparison to those who did not have a Whipple procedure (n = 101; 41.2 ± 20.2 h/nM/mg and 8.78 ± 4.39 nM/mg, respectively), suggesting a slight difficulty in absorbing epacadostat. These exposures are similar to those reported for epacadostat 50 mg twice daily.[13]

Pharmacodynamics

The PD activity of epacadostat is demonstrated by the dose-dependent decrease of KYN in plasma. Dose-dependent PD change of plasma KYN (in microns) is shown in Figure 2. The 25-mg group showed no decrease in KYN from cycle 1 to cycle 2. In fact, six of eight participants from this group demonstrated a slight increase in KYN level. This is presumably from the increased IDO1 activity from

TABLE 4 Best ORR by RECIST in CPI-naïve patients

	NSCLC (N = 20)	SCCHN (N = 27)	Melanoma (N = 5)	Bladder cancer (N = 19)	Gastric cancer (N = 9)	TNBC (N = 13)	Total (N = 93)
ORR, % (95% CI)	15.0 (3.2–37.9)	14.8 (4.2–33.7)	80.0 (28.4–99.5)	15.8 (3.4–39.6)	0 (0.0–33.6)	7.7 (0.2–36.0)	16.1 (9.3–25.2)
CR, No. (%)	0	0	2 (40.0)	1 (5.3)	0	0	3 (3.2)
PR, No. (%)	3 (15.0)	4 (14.8)	2 (40.0)	2 (10.5)	0	1 (7.7)	12 (12.9)
SD, No. (%)	7 (35.0)	11 (40.7)	0	0	0	3 (23.1)	21 (22.6)
PD, No. (%)	7 (35.0)	7 (25.9)	1 (20.0)	8 (42.1)	6 (66.7)	7 (53.8)	36 (38.7)
NE, No. (%)	0	0	0	0	0	1 (7.7)	1 (1.1)
Missing, No. (%)	3 (15.0)	5 (18.5)	0	8 (42.1)	3 (33.3)	1 (7.7)	20 (21.5)

Abbreviations: CPI, checkpoint inhibitor; CR, complete response; NE, not evaluable; NSCLC, non–small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SCCHN, squamous cell carcinoma of head and neck cancer; SD, stable disease; TNBC, triple negative breast cancer.

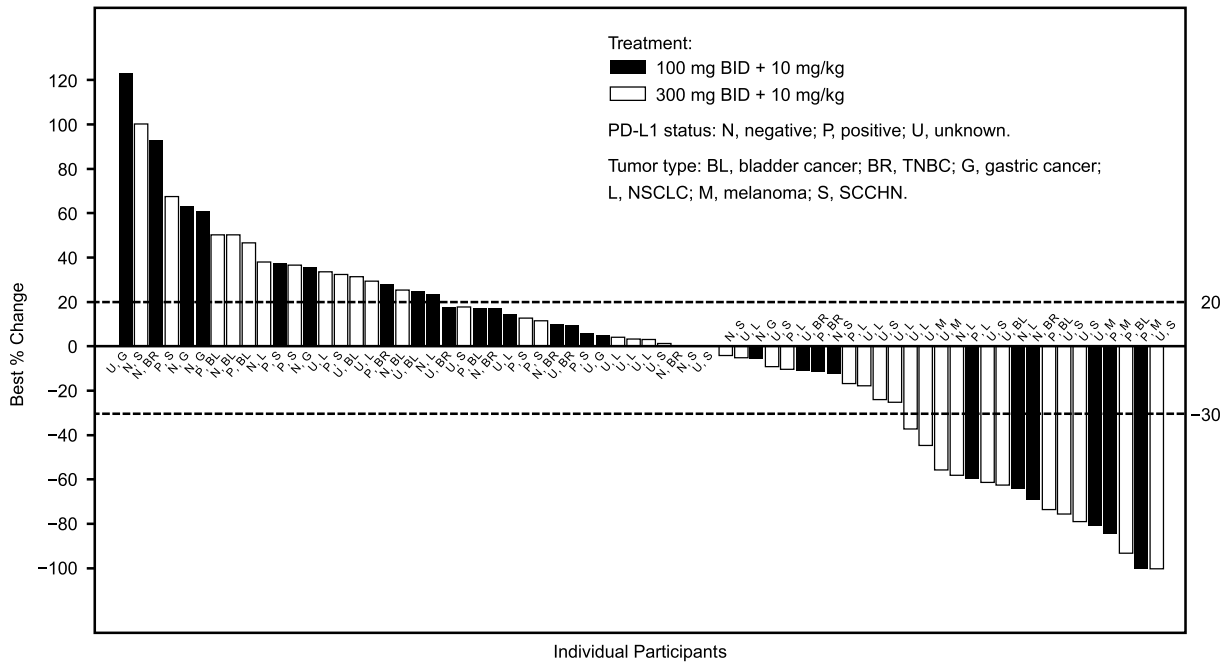

FIGURE 1 Change in target lesion from baseline (best response) in CPI-naïve patients enrolled in phase 2 of the study. BID indicates twice daily; CPI, checkpoint inhibitor; NSCLC, non–small cell lung cancer; PD-L1, programmed death ligand-1; SCCHN, squamous cell carcinoma of the head and neck; TNBC, triple-negative breast cancer.

anti–PD-L1 (durvalumab) therapy. By paired *t* test, the 300-mg group was the only dose group with a significant decrease in KYN between C1D1 and C2D1.

To further evaluate the PD effect of epacadostat 300 mg BID, we compared plasma KYN concentration at steady state on C2D1 with the pretreatment level on C1D1 in patients with potentially immune responsive tumor types (SCCHN and NSCLC). Notably, there was a lack of consistent KYN reduction at C2D1 in responders treated with epacadostat 300 mg twice daily in CPI-naïve patients (data on file). Further analysis revealed a rebound effect in mean KYN concentration at cycle 5, day 1, in patients with SCCHN and melanoma.

DISCUSSION

As a key regulator of immune escape,[17] IDO1 continues to be a valid target for cancer treatment. Previous studies have shown IDO1 is often overexpressed in cancer patients, and IDO1 overexpression is correlated with higher mortality. Additionally, studies with 1-methyl-tryptophan demonstrate IDO1 inhibition can significantly increase chemotherapy efficacy without increased toxicity.[17] Together, these results suggest IDO1 inhibitors are promising agents to study for the treatment of advanced solid tumors in combination with chemotherapeutics or immunotherapies.

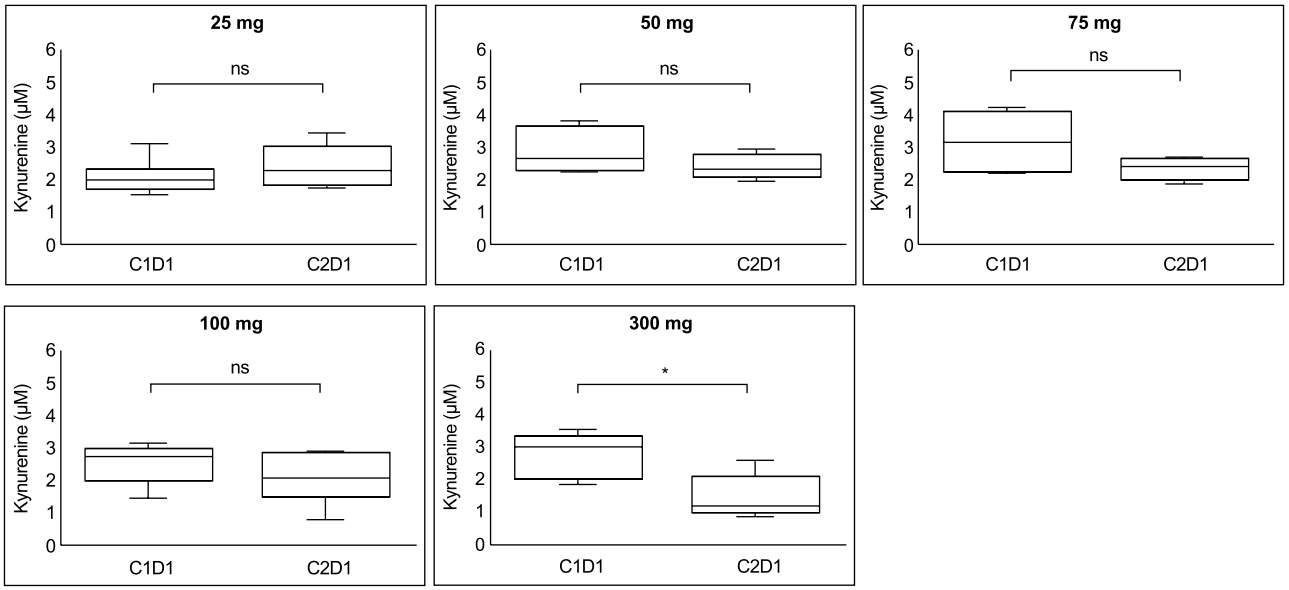

FIGURE 2 Dose-dependent pharmacodynamic change of kynurenine. Kynurenine level at trough on C1D1 and C2D1 are shown in box graphs. Significance of difference from C1D1 to C2D1 was calculated using paired *t* test. Median levels are indicated. C1D1 indicates cycle 1 day 1; C2D1, cycle 2 day 1; ns, not significant. $^{*}p < .05$.

In this phase 1/2 study in patients with advanced solid tumors, we show that epacadostat plus durvalumab was generally well tolerated, and epacadostat's safety profile was consistent with previous reports of durvalumab monotherapy.[18] Epacadostat exposure was generally consistent with previous reports, except in patients with pancreatic cancer, in whom lower peak exposures were observed (potentially because of Whipple procedures). After the phase 3 study of epacadostat in combination with pembrolizumab (ECHO-301/KEYNOTE-252) failed to meet its primary endpoint, enrollment in the current study was stopped.[19] However, dose exposure differed between the studies; ECHO-301 provided patients with epacadostat 100 mg twice daily, whereas in phase 2 of this study, patients received two dose schedules of epacadostat (100 or 300 mg twice daily). Our pharmacokinetic and pharmacodynamic data suggest that even 300 mg epacadostat twice daily was insufficient to induce sustained target inhibition. Thus, the limited clinical activity observed in this study and in previously reported randomized phase 3 trials may be due to inadequate epacadostat exposure. Consistent with this hypothesis, a retrospective pooled analysis of several studies in combination with PD-1 inhibition has shown epacadostat doses of ≥600 mg twice daily may be required to suppress kynurenine production to levels reported in healthy individuals.[20]

Thus, the modest response rate observed is unsurprising. Overall ORR per RECIST criteria was 12.0%. Although ORR was higher among CPI-naïve patients (16.1%) and highest among CPI-naïve patients with melanoma (80.0%), the nominal response rates appear similar to what might be expected with PD-L1 monotherapy,[21,22] although sample sizes in disease-specific cohorts were limited. No baseline disease characteristics predictive of response were identified. Data interpretations in the current study are limited by several factors including small patient numbers, uncertainty of the correlation between plasma KYN and intratumoral KYN, correlation of changes in plasma KYN, and other predictors of response to CPI therapy.

In summary, epacadostat with durvalumab was well tolerated, but epacadostat exposure in this and other recent studies may have been subtherapeutic. Future studies should evaluate higher doses of epacadostat and potential predictive biomarkers, including baseline expression of intratumoral IDO1 expression, to identify patients with tumors likely to respond to epacadostat combination therapies.

AUTHOR CONTRIBUTIONS

Aung Naing: Conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript, and accountability for all aspects of the work. **Alain P. Algazi:** Collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript, and accountability for all aspects of the work. **Gerald S. Falchook:** Collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript, and accountability for all aspects of the work. **Benjamin C. Creelan:** Collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript, and accountability for all aspects of the work. **John Powderly:** Collection and assembly of data, manuscript writing, final approval of manuscript, and accountability for all aspects of the work. **Seth Rosen:** Collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript, and accountability for all aspects of the work. **Minal Barve:** Collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript, and accountability for all aspects of the work. **Niharika B. Mettu:** Collection and assembly of data, data analysis and interpretation,

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CONFLICT OF INTEREST

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