

Epacadostat Plus Pembrolizumab and Chemotherapy for Advanced Solid Tumors: Results from the Phase I/II ECHO-207/KEYNOTE-723 Study

John D. Powderly^{1,*}, Samuel J. Klempner², Aung Naing³, Johanna Bendell⁴, Ignacio Garrido-Laguna⁵, Daniel V.T. Catenacci⁶, Matthew H. Taylor⁷, James J. Lee⁸, Fred Zheng⁹, Feng Zhou⁹, Xiaohua Gong⁹, Hema Gowda⁹, Gregory L. Beatty^{10,‡,*}

¹Cancer Research Clinic, Carolina BioOncology Institute, Huntersville, NC, USA

²Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

³Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

⁴Drug Development Unit, Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA

⁵Division of Oncology, University of Utah School of Medicine, Huntsman Cancer Institute, Salt Lake City, UT, USA

⁶Department of Medicine, University of Chicago, Chicago, IL, USA

⁷Division of Hematology and Oncology, Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA

⁸Cancer Therapeutics Program, UPMC Hillman Cancer Center, Pittsburgh, PA, USA

⁹Incyte Corporation, Wilmington, DE, USA

¹⁰Department of Medicine, Abramson Cancer Center and Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

*Corresponding author: Gregory L. Beatty, MD, PhD, Abramson Cancer Center of the University of Pennsylvania, Perelman Center for Advanced Medicine, South Pavilion Room 8-107, 3400 Civic Center Boulevard, Philadelphia, PA 19104-5156, USA. Tel: +1 215 746 7764; Email: gregory.beatty@penmedicine.upenn.edu; or, John D. Powderly, MD, Carolina BioOncology Institute, 9801 West Kincey Avenue, Suite 145, Huntersville, NC 28078, USA. Tel: +1 704 947 6599; Email: jpowderly@carolinabiooncology.org

‡Principal Investigator: Gregory L. Beatty

Abstract

Background: Epacadostat, an oral, selective inhibitor of IDO1, has shown activity when administered with pembrolizumab. We evaluated the addition of chemotherapy to epacadostat and pembrolizumab in patients with advanced or metastatic solid tumors. One proposed mechanism of resistance to PD-1 checkpoint inhibition is through immunosuppression mediated by Lkynurenine. IDO1, indoleamine-2,3-dioxygenase 1 is the rate-limiting enzyme catalyzing the conversion of L-tryptophan to Lkynurenine. If IDO1 is a mechanism of tumor escape from checkpoint inhibition, then addition of an IDO1 inhibitor with a PD-1 checkpoint inhibitor could enable tumor response to immunotherapy.

Methods: Patients received one of 7 tumor-appropriate chemotherapy regimens. Pembrolizumab 200 mg was infused intravenously every 3 weeks. Epacadostat 100 mg was administered orally twice daily. The primary objectives of phase I were determining safety/tolerability and defining the maximum tolerated or pharmacologically active dose of epacadostat. Phase II of the study was designed to enroll efficacy-expansion cohorts and to assess changes in the tumor and tumor microenvironment via mandatory-biopsy cohorts.

Results: A total of 70 patients were enrolled. Twelve patients were enrolled in the phase II mandatory-biopsy cohorts. Due to early study closure, efficacy expansion did not enroll. Grades 3 and 4 treatment-emergent adverse events (TEAEs) occurred in 78.6% of patients. Neutropenia and disease progression were the only grades 3 and 4 TEAEs reported in ≥10.0% of patients. One treatment-related death was reported. The ORR was 31.4% across all treatment groups.

Conclusion: The combination of epacadostat 100 mg bid with pembrolizumab and chemotherapy had an acceptable safety profile. This regimen showed antitumor activity across multiple types of advanced or metastatic solid tumors (ClinicalTrials.gov Identifier: NCT03085914).

Key words: epacadostat; pembrolizumab; solid tumors; chemotherapy; cancer.

Lessons Learned

- Epacadostat safely combines with the PD-1 inhibitor pembrolizumab and tumor-appropriate chemotherapy in solid tumors, and together, combination therapy produces tumor responses in some patients.
- Further investigation with higher doses of epacadostat to assess optimal IDO1 inhibition in combination with a PD-1 inhibitor and chemotherapy are warranted.

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Discussion

This study investigated the addition of epacadostat 100 mg BID to a pembrolizumab and tumor-appropriate chemotherapy regimen in patients with advanced solid tumors (Fig. 1). The combinations were generally well tolerated, and no new safety concerns were identified. The proportion of patients experiencing AEs leading to dose reduction of epacadostat (4.3%) or to discontinuation of epacadostat or pembrolizumab (15.7%) was low. The overall ORR was 31.4%. However, in the absence of a control arm, assessing the contribution of epacadostat to responses is not possible. PD-L1 status was not a requirement for enrollment, and data were unavailable to correlate with treatment responses. Overall, the study population was highly heterogeneous, but does provide early data on the activity of epacadostat-based combination therapy in several tumor types. Pharmacokinetic data showed that plasma exposure to epacadostat administered in combination with pembrolizumab and chemotherapy were comparable to epacadostat monotherapy.

The current study was closed to accrual after considering the results of the ECHO-301/KEYNOTE-252 phase III study, which did not show significant improvements in PFS or OS with epacadostat 100 mg BID plus pembrolizumab versus placebo plus pembrolizumab in patients with advanced melanoma.¹ Early termination prevented analysis of biological

correlates of response. In addition, given the small number of patients with any given tumor type, we could not conclusively assess responses by tumor histology, and the optimal chemotherapy agent(s) to combine with epacadostat remains unknown. Also, >30% of patients had tumor types historically associated with poor responsiveness to checkpoint inhibition (eg, PDAC, CRC, cholangiocarcinoma, gastroesophageal cancer).

Epacadostat 100 mg BID was predicted to achieve IC90 inhibition of IDO1 in peripheral blood, but the effect in tumor tissue remains unclear. Epacadostat dosing may have been insufficient to achieve optimal intratumoral IDO1 inhibition.² In a retrospective analysis, pembrolizumab increased production of plasma kynurenine levels and required epacadostat 600 mg BID for suppression of plasma kynurenine production.³ Future pharmacodynamic/biomarker studies with higher epacadostat dosing should provide further insights, especially given the anticipated importance of sustained suppression of intratumoral kynurenine. It will also be important to consider inhibition of parallel pathways of tryptophan metabolism, such as tryptophan 2,3-dioxygenase 2.

Taken together, despite a relatively small sample size (N = 70), short duration of follow-up, and limited numbers of each tumor histology, this study shows that epacadostat can be administered in combination with pembrolizumab plus chemotherapy and that this combination may have clinical activity across multiple types of advanced solid tumors.

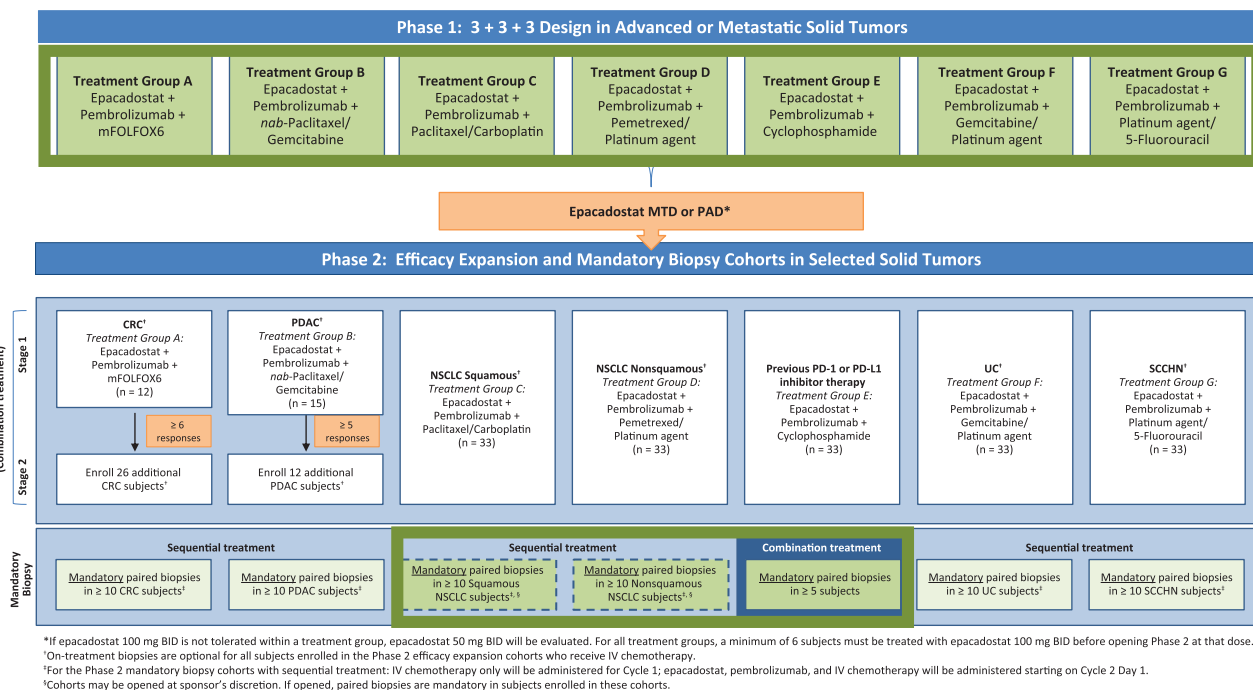


Figure 1. Original study design with final groups enrolled highlighted in green.

TRIAL INFORMATION	
Disease	Solid tumors
Stage of disease/treatment	Metastatic/advanced
Prior therapy	No designated number of regimens
Type of study	3 + 3
Primary endpoint	Safety, tolerability, maximum tolerated dose
Secondary endpoints	Investigator-assessed objective response rate
Investigator's analysis	Inconclusive due to early study termination

Additional Details of Endpoints or Study Design

Patients

Study participants were adults (aged ≥ 18 years) with advanced or metastatic solid tumors. Eligible patients had ≥ 1 lesion that was measurable per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and an Eastern Cooperative Oncology Group performance status score of 0-1. Patients enrolled in the phase I portion of the study had confirmed locally advanced or metastatic solid tumors and had either experienced disease progression during prior treatment with ≥ 1 standard therapy or refused or were intolerant to the standard-of-care for their tumor. Patients enrolled in the phase II portion of the study had either (1) confirmed advanced or metastatic CRC, pancreatic ductal adenocarcinoma (PDAC), non-squamous or squamous non-small cell lung cancer (NSCLC), urothelial carcinoma (UC), or squamous cell carcinoma of the head and neck (SCCHN) that was not previously treated in the advanced/metastatic setting or (2) any confirmed advanced or metastatic solid tumor that had progressed during prior treatment with a PD-1/PD-L1 inhibitor. Key exclusion criteria included abnormal laboratory measurements (eg, absolute neutrophil count $< 1.5 \times 10^9/L$; platelet count $< 100 \times 10^9/L$; hemoglobin < 9 g/dL; aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase ≥ 2.5 times the upper limit of normal), radiotherapy within 14 days of starting study treatment, symptomatic central nervous system metastases and/or carcinomatous meningitis, lack of recovery to grade ≤ 1 from the toxic effects of prior therapy and/or complications from a previous surgical intervention before starting study treatment, clinically significant cardiac disease (eg, unstable angina, arrhythmia requiring therapy), and use of monoamine oxidase inhibitors (MAOIs) or drugs that have significant MAOI activity (eg, meperidine, linezolid, methylene blue) in the 21 days prior to screening.

Study Design and Treatment

ECHO-207/KEYNOTE-723 (NCT03085914) was an open-label, nonrandomized phase I/II study performed at 9 sites in the US (Fig. 1). The phase I portion of the study used a 3+3+3 design. Participants received one of 7 distinct chemotherapy regimens in combination with epacadostat and pembrolizumab (treatment groups A–G). All treatment groups were tested in parallel during phase I. The chemotherapy regimen most appropriate for the presenting tumor type was selected by the treating investigator. Pembrolizumab 200 mg was infused intravenously every 3 weeks. Epacadostat 100 mg was administered orally twice daily. Patients received study treatment until the completion of 35 pembrolizumab infusions (approximately 2

years), disease progression, unacceptable toxicity, or other discontinuation criterion was met. Dose modification of epacadostat, pembrolizumab, or both was permitted for the management of immune-related adverse events (AEs). Dose interruptions and discontinuation were permitted for pembrolizumab, but not changes in dose. Chemotherapy dose adjustment followed standard guidelines. The phase I portion of the study sought to determine the maximum tolerated dose (MTD) or pharmacologically active dose (PAD) of epacadostat when combined with pembrolizumab and chemotherapy.

To further evaluate the safety, tolerability, and efficacy of epacadostat at the MTD or PAD identified in phase I, the phase II portion of the study was designed to enroll efficacy-expansion cohorts in select tumor types (treatment groups A, B, C, D, F, and G) and of patients with advanced or metastatic solid tumors who experienced progression during prior treatment with a PD-1/PD-L1 inhibitor (treatment group E). To assess changes in the tumor and tumor microenvironment, mandatory-biopsy cohorts were planned for phase II.

Study Conduct

The study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and applicable national and local regulatory requirements. The study protocol was approved by the independent ethics committee/institutional review board at each participating site, and all patients provided written informed consent. The first patient was dosed on May 2, 2017. On October 25, 2018, a decision was made to permanently stop enrollment. This decision was based on results from the phase III ECHO-301/KEYNOTE-252 study, which compared epacadostat (100 mg twice daily) plus pembrolizumab versus placebo plus pembrolizumab in patients with advanced melanoma.

Endpoints

The primary endpoint of the phase I portion of the study was safety and tolerability. The secondary endpoint was investigator-assessed objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) per RECIST version 1.1. In the phase II portion of the study, the primary endpoint was investigator-assessed ORR, and the secondary endpoint was safety and tolerability. Adverse events (AEs) were coded per Medical Dictionary for Regulatory Activities version 20.0 and graded per Common Terminology Criteria for Adverse Events

version 4.03. Exploratory endpoints in phase I and phase II included (1) the pharmacokinetics of epacadostat and (2) analysis of changes in immune status and of biomarkers of treatment response. Plasma samples for the pharmacokinetic analyses were obtained pre- and post-dose of epacadostat on cycle 1/day 1, cycle 1/day 8, and cycle 2/day 1. Whole blood and plasma samples for the immune status/biomarkers analyses were obtained on days 1, 8, and 15 of cycle 1; day 1 of cycles 2 and 3; and every 3 cycles thereafter starting with cycle 6. Tumor biopsies were obtained at screening and on treatment from patients in the mandatory-biopsy cohorts.

Following study termination, on-treatment biopsies were no longer required. Thus, analyses of changes in immune status and biomarkers of treatment response were not conducted.

Statistics

The analysis population was comprised of patients who received ≥ 1 dose of any study drug. All outcomes were summarized using descriptive statistics. Data collected from phase I and phase II were pooled and summarized by treatment group.

DRUG INFORMATION: GROUP A	
Drug 1	
Generic/working name	Epacadostat
Company name	Incyte Corporation
Drug type	Small molecule
Drug class	IDO1 inhibitor
Dose	100
Unit	mg
Route	Oral (po)
Schedule of administration	Twice-daily (bid)
Drug 2	
Generic/working name	Pembrolizumab
Company name	Merck & Co., Inc.
Drug type	Antibody
Drug class	Immunotherapy
Dose	200
Unit	mg
Route	Intravenous
Schedule of administration	Every 3 weeks for up to 35 infusions
Drug 3	
Generic/working name	Oxaliplatin
Company name	Generic
Drug type	Platinum compound
Dose	85
Unit	mg/m ²
Route	Intravenous
Schedule of administration	Days 1 and 15 of each 28-day cycle
Drug 4	
Generic/working name	Leucovorin
Company name	
Drug type	Folic acid analog
Dose	400
Unit	mg/m ²
Route	Intravenous
Schedule of administration	Days 1 and 15 of each 28-day cycle
Drug 5	
Generic/working name	5-Fluorouracil
Company name	Generic
Drug type	Antimetabolite
Dose	400 mg/m ² IV bolus, then 1200 mg/m ² per day IV infusion over 46 hours for a total dose of 2400 mg/m ²
Route	Intravenous
Schedule of administration	Days 1 and 15 of each 28-day cycle

DRUG INFORMATION: GROUP B**Drug 1**

Generic/working name	Epacadostat
Company name	Incyte Corporation
Drug type	Small molecule
Drug class	IDO1 inhibitor
Dose	100
Unit	mg
Route	Oral (po)
Schedule of administration	Twice-daily (bid)

Drug 2

Generic/working name	Pembrolizumab
Company name	Merck & Co., Inc.
Drug type	Antibody
Drug class	Immunotherapy
Dose	200
Unit	mg
Route	Intravenous
Schedule of administration	Every 3 weeks for up to 35 infusions

Drug 3

Generic/working name	<i>nab</i> -Paclitaxel
Company name	Celgene
Drug type	Drug conjugate
Drug class	Tubulin/microtubules targeting agent
Dose	125
Unit	mg/m ²
Route	Intravenous
Schedule of administration	Days 1, 8, and 15 of each 28-day cycle

Drug 4

Generic/working name	Gemcitabine
Company name	Generic
Drug type	Small molecule
Drug class	DNA synthesis inhibitor
Dose	1000
Unit	mg/m ²
Route	Intravenous
Schedule of administration	Days 1, 8, and 15 of each 28-day cycle

DRUG INFORMATION: GROUP C**Drug 1**

Generic/working name	Epacadostat
Company name	Incyte Corporation
Drug type	Small molecule
Drug class	IDO1 inhibitor
Dose	100
Unit	mg
Route	Oral (po)
Schedule of administration	Twice-daily (bid)

Drug 2

Generic/working name	Pembrolizumab
Company name	Merck & Co., Inc.
Drug type	Antibody
Drug class	Immunotherapy
Dose	200
Unit	mg
Route	Intravenous
Schedule of administration	Every 3 weeks for up to 35 infusions

Drug 3	
Generic/working name	Paclitaxel
Company name	Generic
Drug type	Small molecule
Drug class	Tubulin/microtubule targeting agent
Dose	200
Unit	mg/m ²
Route	Intravenous
Schedule of administration	Day 1 of each 21-day cycle for a minimum of 4 cycles and a maximum of 6 cycles
Drug 4	
Generic/working name	Carboplatin
Company name	Generic
Drug type	Platinum compound
Drug class	Alkylating agent
Dose	6
Unit	AUC
Route	Intravenous
Schedule of administration	Day 1 of each 21-day cycle for a minimum of 4 cycles and a maximum of 6 cycles

DRUG INFORMATION: GROUP D

Drug 1	
Generic/working name	Epacadostat
Company name	Incyte Corporation
Drug type	Small molecule
Drug class	IDO1 inhibitor
Dose	100
Unit	mg
Route	Oral (po)
Schedule of administration	Twice-daily (bid)
Drug 2	
Generic/working name	Pembrolizumab
Company name	Merck & Co., Inc.
Drug type	Antibody
Drug class	Immunotherapy
Dose	200
Unit	mg
Route	Intravenous
Schedule of administration	Every 3 weeks for up to 35 infusions
Drug 3	
Generic/working name	Pemetrexed
Company name	Generic
Drug type	Small molecule
Drug class	Antimetabolite
Dose	500
Unit	mg/m ²
Route	Intravenous
Schedule of administration	Day 1 of each 21-day cycle for a minimum of 4 cycles and a maximum of 6 cycles
Drug 4	
Generic/working name	Carboplatin or cisplatin
Company name	Generic
Drug type	Platinum compound
Drug class	Alkylating agent
Dose/unit	Carboplatin AUC 5 or cisplatin 75 mg/m ²
Route	Intravenous
Schedule of administration	Day 1 of each 21-day cycle for a minimum of 4 cycles and a maximum of 6 cycles

DRUG INFORMATION: GROUP E**Drug 1**

Generic/working name	Epacadostat
Company name	Incyte Corporation
Drug type	Small molecule
Drug class	IDO1 inhibitor
Dose	100
Unit	mg
Route	Oral (po)
Schedule of administration	Twice-daily (bid)

Drug 2

Generic/working name	Pembrolizumab
Company name	Merck & Co., Inc.
Drug type	Antibody
Drug class	Immunotherapy
Dose	200
Unit	mg
Route	Intravenous
Schedule of administration	Every 3 weeks for up to 35 infusions

Drug 3

Generic/working name	Cyclophosphamide
Company name	Generic
Drug type	Small molecule
Drug class	Alkylating agent
Dose	50
Unit	mg
Route	Oral
Schedule of administration	Daily

DRUG INFORMATION: GROUP F**Drug 1**

Generic/working name	Epacadostat
Company name	Incyte Corporation
Drug type	Small molecule
Drug class	IDO1 inhibitor
Dose	100
Unit	mg
Route	Oral (po)
Schedule of administration	Twice-daily (bid)

Drug 2

Generic/working name	Pembrolizumab
Company name	Merck & Co., Inc.
Drug type	Antibody
Drug class	Immunotherapy
Dose	200
Unit	mg
Route	Intravenous
Schedule of administration	Every 3 weeks for up to 35 infusions

Drug 3

Generic/working name	Gemcitabine
Company name	Generic
Drug class	DNA synthesis inhibitor
Dose	1000
Unit	mg/m ²
Route	Intravenous
Schedule of administration	Days 1 and 8 in a 21-day cycle for a maximum of 6 cycles

Drug 4	
Generic/working name	Carboplatin or cisplatin
Company name	Generic
Drug type	Platinum compound
Drug class	Alkylating agent
Dose/unit	Carboplatin AUC 5 or cisplatin 70 mg/m ²
Route	Intravenous
Schedule of administration	Day 1 of a 21-day cycle for a maximum of 6 cycles

DRUG INFORMATION: GROUP G

Drug 1	
Generic/working name	Epacadostat
Company name	Incyte Corporation
Drug type	Small molecule
Drug class	IDO1 inhibitor
Dose	100
Unit	mg
Route	Oral (po)
Schedule of administration	Twice-daily (bid)

Drug 2	
Generic/working name	Pembrolizumab
Company name	Merck & Co., Inc.
Drug type	Antibody
Drug class	Immunotherapy
Dose	200
Unit	mg
Route	Intravenous
Schedule of administration	Every 3 weeks for up to 35 infusions

Drug 3	
Generic/working name	5-Fluorouracil
Company name	Generic
Drug class	Antimetabolite
Dose	1000
Unit	mg/m ²
Route	Intravenous
Schedule of administration	Each day on days 1-4 in a 21-day cycle for a maximum of 6 cycles

Drug 4	
Generic/working name	Carboplatin or cisplatin
Company name	Generic
Drug type	Platinum compound
Drug class	Alkylating agent
Dose/unit	Carboplatin AUC 5 or cisplatin 100 mg/m ²
Route	Intravenous
Schedule of administration	Day 1 in a 21-day cycle for a maximum of 6 cycles

PATIENT CHARACTERISTICS (FOR ALL PATIENTS; TABLE 1 SHOWS CHARACTERISTICS BY TREATMENT GROUP)

Number of patients, male	34
Number of patients, female	36
Stage	69 patients had metastatic disease; 1 patient had advanced disease
Age: median (range)	59 (28-80) years
Number of prior systemic therapies: median (range)	1 (1-7)
Performance status: ECOG	0 or 1: all patients had ECOG performance status less than or equal to 1

Cancer types or histologic subtypes	Number
Adrenal cancer	1
Anal cancer	2
Breast cancer	3
Cervical cancer	1
Cholangiocarcinoma	2
Colorectal cancer	10
Endometrial cancer	5
Esophageal cancer	1
Gall bladder cancer	2
Gastric cancer	2
Gastroesophageal/gastroesophageal junction cancer	3
Head and neck squamous cell carcinoma	1
Melanoma	1
Mesothelioma	2
Nasopharyngeal cancer	1
Non-small cell lung cancer	9
Ovarian cancer	3
Pancreatic ductal adenocarcinoma	9
Renal cell carcinoma	1
Salivary gland cancer	3
Sarcoma	1
Small cell lung cancer	1
Urothelial cancer	1
Uterine cancer	1
Other	4

PRIMARY ASSESSMENT METHOD: ALL PATIENTS

Title	Response evaluation
Number of patients screened	85
Number of patients enrolled	70
Number of patients evaluable for toxicity	70
Number of patients evaluated for efficacy	70
Evaluation Method	RECIST 1.1
Response assessment, CR	1 (1.4%)
Response assessment, PR	21 (30%)
Response assessment, SD	23 (32.9%)
Response assessment, PD or death	24 (34.3%)
Outcome notes	<p>Table 2 shows a summary of AEs.</p> <p>Table 3 shows response by treatment group.</p> <p>Table 4 shows pharmacokinetic parameters.</p> <p>Table 5 shows response by tumor histology.</p>

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion	Study terminated prior to completion
Investigator's assessment	Inconclusive due to early study termination

The phase I/II ECHO-207/KEYNOTE-723 study investigated epacadostat in combination with pembrolizumab plus chemotherapy for the treatment of patients with advanced solid tumors (Fig. 1). Epacadostat is an orally available selective inhibitor of indoleamine 2,3-dioxygenase (IDO1), a key enzyme involved in the metabolism of tryptophan to kynurenine. Whereas tryptophan supports T-cell antitumor functions, kynurenine has been shown to trigger immunosuppression.

Preclinical models show that IDO1 and immune checkpoints have complementary roles in regulating the antitumor activity of tumor-specific T cells.^{4,6} Although this biology has not been demonstrated in humans, whole blood assays have shown that epacadostat effectively inhibits the metabolism of tryptophan to kynurenine in patients with advanced solid tumors.⁷

A CONSORT diagram summarizing all enrolled patients is shown in Fig. 2. The addition of epacadostat (100 mg twice

daily) to pembrolizumab plus a tumor-appropriate chemotherapy regimen was associated with acceptable safety/tolerability and preliminary clinical activity. The proportion of patients who experienced AEs leading to dose reduction of epacadostat (4.3%) or to discontinuation of epacadostat or pembrolizumab (15.7%) was low (Table 2). No new safety concerns were identified for any of the 7 treatment regimens studied. The ORR was 31.4%, with the highest response rate (55.6%) observed in treatment group A (epacadostat + pembrolizumab + mFOLFOX6) and treatment group B (epacadostat + pembrolizumab + nanoparticle albumin-bound [nab]-paclitaxel + gemcitabine) (Table 3). However, in the absence of a control arm (ie, chemotherapy plus pembrolizumab only), it is not possible to assess the extent to which epacadostat contributed to the observed treatment responses. Pharmacokinetic data showed that plasma exposures to epacadostat when administered in combination with pembrolizumab and chemotherapy were comparable to epacadostat monotherapy⁷ (Table 4). The general similarity of the pharmacokinetics of epacadostat across the 7 treatment groups suggests that chemotherapy does not impact the pharmacokinetic profile of epacadostat. The lower exposures observed in treatment group D relative to treatment group C and treatment group E were likely due to variability, because no mechanistic basis for a drug–drug interaction has been identified. The clearance mechanisms of epacadostat and pemetrexed (treatment group D) do not overlap, with epacadostat cleared predominantly by hepatic glucuronidation and pemetrexed cleared by renal excretion. Overall, the findings from this study show that epacadostat can be safely combined with pembrolizumab and chemotherapy in the treatment of multiple solid tumor histologies.

Following the sponsor's review of combination treatment with epacadostat and pembrolizumab and considering the results from the ECHO-301/KEYNOTE-252 phase III study, this phase I/II study was closed to accrual and terminated. ECHO-301/KEYNOTE-252 randomized patients with advanced melanoma to receive epacadostat (100 mg twice daily) plus pembrolizumab or placebo plus pembrolizumab.¹ Although no new safety concerns were seen with epacadostat plus pembrolizumab compared with pembrolizumab monotherapy, no statistically significant differences between the 2 treatment arms were observed for either of the dual primary endpoints: PFS (epacadostat plus pembrolizumab, 4.7 months; placebo plus pembrolizumab, 4.9 months, one-sided $P = .52$) and OS (median not reached in either arm after a median follow-up of 12.4 months).

The early termination of this phase I/II study prevented analysis of biological correlates of response. In addition, given the small number of patients within any given tumor type, it was not possible to conclusively assess responses by tumor histology, and the optimal cytotoxic agent(s) to combine with epacadostat remains unknown. Also, >30% of enrolled patients had tumor types that have been historically associated with poor responsiveness to immune checkpoint inhibition (eg, PDAC, CRC, cholangiocarcinoma, gastroesophageal cancer) (Table 5). Overall, these preliminary safety and efficacy data support further exploration of epacadostat in combination with pembrolizumab plus chemotherapy in patients with solid tumors.

Epacadostat 100 mg twice daily was selected for clinical evaluation because it was predicted to achieve IC₉₀ inhibition of IDO1 in peripheral blood, but it is unclear whether this dose results in IC₉₀ inhibition of IDO1 in tumor tissues.

Thus, the 100 mg twice-daily dose of epacadostat may have been insufficient to achieve optimal blockade of IDO1, particularly within the tumor microenvironment.² In a phase I study of epacadostat in patients with advanced solid tumors, the percentage decrease in kynurenine levels from baseline to day 15 was found to be dose dependent, suggesting that doses higher than 100 mg twice daily may result in more potent antitumor immune effects.⁷ Consistent with this, pembrolizumab has been found to increase the production of plasma kynurenine levels requiring epacadostat dosing at 600 mg BID, the maximally tolerated dose, for suppression of plasma kynurenine production.³ Future studies assessing pharmacodynamic markers, such as serum and tumor kynurenine levels, should provide further insight into this research question, especially given the anticipated importance of sustained suppression of intratumoral kynurenine. It will also be important to consider inhibition of parallel pathways of tryptophan metabolism, such as tryptophan 2,3-dioxygenase 2.⁸

In contrast to epacadostat,⁷ both pembrolizumab and chemotherapy have single-agent antitumor activity. In this study, we hypothesized that epacadostat would improve the therapeutic efficacy of pembrolizumab plus chemotherapy. Analyses of biomarkers and of the effects of epacadostat would be needed to understand the impact on the immunomodulatory activity of pembrolizumab plus chemotherapy. Such studies could also inform patients most likely to benefit from treatment.^{1,9,10} In our study, PD-L1 expression was not a requirement for enrollment and PD-L1 status was not available on patients to correlate with treatment responses. Overall, the study population was highly heterogeneous, but does provide early data on the activity of epacadostat-based combination therapy and in several uncommon tumor types.

Despite a relatively small sample size ($N = 70$), short duration of follow-up, and limited numbers of each tumor histology enrolled, this phase I/II study shows that epacadostat can be administered in combination with pembrolizumab plus chemotherapy and that this combination may have clinical activity across multiple types of advanced solid tumors.

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Conflict of Interest

John D. Powderly: AstraZeneca, Bristol-Myers Squibb, Merck and Co., Inc., Curis (C/A), Calico, Apros Therapeutics, Inc., AbbVie, AstraZeneca, Bristol-Myers Squibb, Merck and Co., Inc., EMD Serono, MacroGenics, Incyte Corporation, RAPT Therapeutics, Alkermes, Tempest, Curis, Corvus, Top Alliance Biosciences, Precision for Medicine, MT Group, StemCell, Sequenom (RF), Carolina BioOncology Institute, BioCytics (OI, IP); **Samuel J. Klempner:** Merck and Co., Inc., Bristol-Myers Squibb, Eli Lilly, Pieris, Boston Biomedical,

Foundation Medicine, Sanofi-Aventis, Daiichi-Sankyo, Exact Sciences, AstraZeneca (C/A), Turning Point Therapeutics, Nuvalent (OI); **Aung Naing:** National Cancer Institute, EMD Serono, MedImmune, Healios Oncology Nutrition, Atteracor, Amplimmune, ARMO BioSciences, Eli Lilly, Karyopharm Therapeutics, Incyte Corporation, Novartis, Regeneron, Merck and Co., Inc., Bristol-Myers Squibb, Pfizer, CytomX Therapeutics, Neon Therapeutics, Calithera Biosciences, TopAlliance Biosciences, Kymab, PsiOxus, Arcus Biosciences, NeoimmuneTech, ImmuneOncia, Surface Oncology, Jeffery Modell Foundation, Chao-physician scientist (spouse), Baxalta (spouse), Immune Deficiency Foundation (spouse) (RF), ARMO BioSciences (H), CytomXTherapeutics, Novartis, Kymab, Genome, Co, Takeda (spouse), CSL Behring (spouse), Horizon Pharma (spouse) (SAB); **Johanna Bendell:** Gilead, Genentech/Roche, Bristol-Myers Squibb, Five Prime, Lilly, Merck and Co., Inc., MedImmune, Celgene, Taiho, MacroGenics, GlaxoSmithKline, Novartis, OncoMed, LEAP, TG Therapeutics, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Bayer, Incyte Corporation, Apexigen, Array, Sanofi, ARMO, Ipsen, Merrimack, Oncogenex, FORMA, Arch Oncology, Prelude Therapeutics, Phoenix Bio, Cyteir, Molecular Partners, Innate, Torque, Tizona, Janssen, Tolero, TD2 (Translational Drug Development), Amgen, Seattle Genetics, Moderna Therapeutics, Tanabe Research Laboratories, Beigene, Continuum Clinical, Agios, Bicycle Therapeutics, Relay Therapeutics, Evelo, Pfizer, Piper Biotech, Samsung Bioepios (C/A); Gilead, Genentech/Roche, Bristol-Myers Squibb, Five Prime, Lilly, Merck and Co., Inc., MedImmune, Celgene, EMD Serono, Taiho, MacroGenics, GlaxoSmithKline, Novartis, OncoMed, LEAP, TG Therapeutics, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Bayer, Incyte Corporation, Apexigen, Koltan, SynDevRex, Forty Seven, AbbVie, Array, Onyx, Sanofi, Takeda, Eisai, Celldex, Agios, Cytomx, Nektar, ARMO, Boston Biomedical, Ipsen, Merrimack, Tarveda, Tyrogenex, Oncogenex, Marshall Edwards, Pieris, Mersana, Calithera, Blueprint, Evelo, FORMA, Merus, Jacobio, Effector, Novocare, Arrys, Tracon, Sierra, Innate, Arch Oncology, Prelude Oncology, Unum Therapeutics, Vyriad, Harpoon, ADC Therapeutics, Amgen, Pfizer, Millennium, Imclone, Acerta Pharma, Rgenix, Bellicum, Gossamer Bio, Arcus Bio, Seattle Genetics, TempestTx, Shattuck Labs, Synthorx, Revolution Medicines, Bicycle Therapeutics, Zymeworks, Relay Therapeutics, Scholar Rock, NGM Biopharma, Stemcentrx, Beigene, CALGB, Cyteir Therapeutics, Foundation Bio, Innate Pharma, Morphotex, Ongologie, NuMab (RF), Gilead, Genentech/Roche, Bristol-Myers Squibb, Lilly, Merck and Co., Inc., MedImmune, Celgene, Taiho, Novartis, OncoMed, Boehringer Ingelheim, ARMO, Ipsen, Oncogenex, FORMA (H); **Ignacio Garrido-Laguna:** Array, Eisai (C/A), MedImmune, Novartis, Incyte Corporation, GlaxoSmithKline, Bristol-Myers Squibb, Genentech, Bayer, Rafael, Novartis, Tolero, Trishula, Eli Lilly, Amgen, Seattle Genetics (RF); **Daniel V.T. Catenacci:** Genentech/Roche, Amgen, Eli Lilly, Five Prime, Merck and Co., Inc., Bristol-Myers Squibb, Taiho, Astellas, Gritstone, Pieris, Daiichi Sankyo, Zymeworks, QED, Foundation Medicine, Tempus, Guardant Health, Archer (H); **Matthew H. Taylor:** Bristol-Myers Squibb, Eisai (H), Bristol-Myers Squibb, Merck Sharp & Dohme, Pharmacyclics, AstraZeneca, Eisai, Incyte Corporation, EMD Serono, Novartis, Seattle Genetics, AbbVie, Eli Lilly, Genentech/Roche, Acerta Pharma,

Genzyme, Pfizer (RF), Bristol-Myers Squibb, Eisai, Novartis, Bayer, Sanofi/Genzyme, Array Biopharma, Loxo Oncology, Blueprint Medicines, Arqule (C/A); **James J. Lee:** Merck and Co., Inc. (RF); **Fred Zheng:** Incyte Corporation (E); **Feng Zhou:** Incyte Corporation (E); **Xiaohua Gong:** Incyte Corporation (E); **Hema Gowda:** Incyte Corporation (E [at the time of study conduct]), AstraZeneca (E [currently]); **Gregory L. Beatty:** Seattle Genetics, Boehringer Ingelheim, Cour Pharmaceutics, Aduro Biotech, AstraZeneca, Bristol-Myers Squibb, Genmab, Incyte Corporation, Janssen, Osona, Merck and Co., Inc., BiolineRx, NanoGhost, Monopteros (C/A), Incyte Corporation, Bristol-Myers Squibb, Monopteros, Verastem, Halozyme, HiberCell, Biothera, Newlink, Novartis, Arcus, Janssen (RF), Novartis (IP).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

Data Availability

Incyte Corporation (Wilmington, DE, USA) is committed to data sharing that advances science and medicine while protecting patient privacy. Qualified external scientific researchers may request anonymized datasets owned by Incyte for the purpose of conducting legitimate scientific research. Researchers may request anonymized datasets from any interventional study (except phase I studies) for which the product and indication have been approved on or after 1 January 2020 in at least one major market (eg, USA, European Union, Japan). Data will be available for request after the primary publication or 2 years after the study has ended. Information on Incyte's clinical trial data sharing policy and instructions for submitting clinical trial data requests are available at: <https://www.incyte.com/Portals/0/Assets/Compliance%20and%20Transparency/clinical-trial-data-sharing.pdf?ver=2020-05-21-132838-960>.

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FIGURES AND TABLES

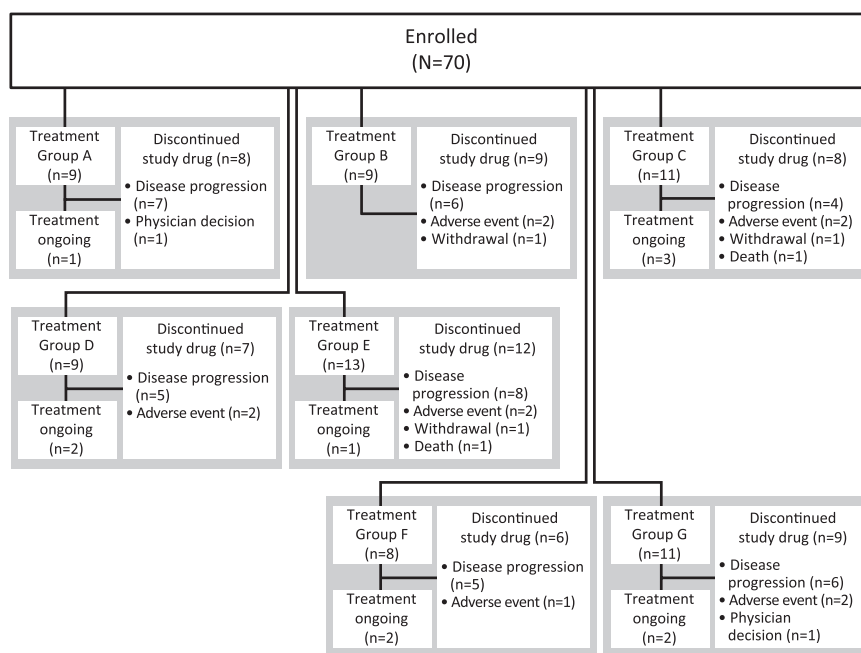


Figure 2. Patient disposition.

Table 1. Baseline demographics and disease characteristics.

	Treatment group							Total (N = 70)
	A (n = 9)	B (n = 9)	C (n = 11)	D (n = 9)	E (n = 13)	F (n = 8)	G (n = 11)	
Male, n (%)	6 (66.7)	5 (55.6)	5 (45.5)	5 (55.6)	3 (23.1)	3 (37.5)	7 (63.6)	34 (48.6)
Age, mean (SD), years	55.8 (8.03)	46.0 (14.98)	63.7 (12.11)	58.2 (12.96)	62.0 (10.21)	60.3 (12.01)	59.4 (12.24)	58.3 (12.54)
Age ≥65 years, n (%)	1 (11.1)	1 (11.1)	5 (45.5)	3 (33.3)	5 (38.5)	3 (37.5)	4 (36.4)	22 (31.4)
Race, n (%)								
White	7 (77.8)	7 (77.8)	9 (81.8)	8 (88.9)	10 (76.9)	6 (75.0)	8 (72.7)	55 (78.6)
Black/African American	2 (22.2)	1 (11.1)	0	0	1 (7.7)	0	2 (18.2)	6 (8.6)
Other ^a	0	1 (11.1)	2 (18.2)	1 (11.1)	2 (15.4)	2 (25.0)	1 (9.1)	9 (12.9)
Disease stage, n (%)								
Advanced	0	0	1 (9.1)	0	0	0	0	1 (1.4)
Metastatic	9 (100.0)	9 (100.0)	10 (90.9)	9 (100.0)	13 (100.0)	8 (100.0)	11 (100.0)	69 (98.6)
Solid tumor type, n (%)								
Adrenal cancer	0	0	0	0	1 (7.7)	0	0	1 (1.4)
Anal cancer	0	0	1 (9.1)	0	0	0	1 (9.1)	2 (2.9)

Table 1. Continued

	Treatment group							Total (N = 70)
	A (n = 9)	B (n = 9)	C (n = 11)	D (n = 9)	E (n = 13)	F (n = 8)	G (n = 11)	
Breast cancer	0	1 (11.1)	0	0	1 (7.7)	1 (12.5)	0	3 (4.3)
Cervical cancer	0	1 (11.1)	0	0	0	0	0	1 (1.4)
Cholangiocarcinoma	1 (11.1)	0	0	0	0	1 (12.5)	0	2 (2.9)
Colorectal cancer	4 (44.4)	0	0	2 (22.2)	2 (15.4)	0	2 (18.2)	10 (14.3)
Endometrial cancer	0	0	1 (9.1)	0	1 (7.7)	1 (12.5)	2 (18.2)	5 (7.1)
Esophageal cancer	0	1 (11.1)	0	0	0	0	0	1 (1.4)
Gall bladder cancer	1 (11.1)	0	0	0	0	1 (12.5)	0	2 (2.9)
Gastric cancer	1 (11.1)	0	0	0	1 (7.7)	0	0	2 (2.9)
Gastroesophageal/gastroesophageal junction cancer	1 (11.1)	0	0	0	1 (7.7)	0	1 (9.1)	3 (4.3)
Head and neck squamous cell carcinoma	0	0	0	0	0	0	1 (9.1)	1 (1.4)
Melanoma	0	0	0	0	1 (7.7)	0	0	1 (1.4)
Mesothelioma	0	0	0	1 (11.1)	0	1 (12.5)	0	2 (2.9)
Nasopharyngeal cancer	0	0	0	0	0	1 (12.5)	0	1 (1.4)
Non-small cell lung cancer	0	0	4 (36.4)	3 (33.3)	2 (15.4)	0	0	9 (12.9)
Ovarian cancer	0	0	1 (9.1)	2 (22.2)	0	0	0	3 (4.3)
Pancreatic ductal adenocarcinoma	1 (11.1)	4 (44.4)	1 (9.1)	0	1 (7.7)	0	2 (18.2)	9 (12.9)
Renal cell carcinoma	0	0	0	0	0	1 (12.5)	0	1 (1.4)
Salivary gland cancer	0	0	2 (18.2)	0	0	1 (12.5)	0	3 (4.3)
Sarcoma	0	0	0	0	1 (7.7)	0	0	1 (1.4)
Small cell lung cancer	0	1 (11.1)	0	0	0	0	0	1 (1.4)
Urothelial cancer	0	0	1 (9.1)	0	0	0	0	1 (1.4)
Uterine cancer	0	0	0	1 (11.1)	0	0	0	1 (1.4)
Other ^b	0	1 (11.1)	0	0	1 (7.7)	0	2 (18.2)	4 (5.7)
Prior treatment, n (%)								
Systemic therapy	6 (66.7)	7 (77.8)	6 (54.5)	6 (66.7)	13 (100.0)	6 (75.0)	11 (100.0)	55 (78.6)
Monoclonal antibody	2 (22.2)	1 (11.1)	2 (18.2)	4 (44.4)	7 (53.8)	2 (25.0)	3 (27.3)	21 (30.0)
Protein kinase inhibitor	0 (0.0)	2 (22.2)	1 (9.1)	1 (11.1)	2 (15.4)	2 (25.0)	2 (18.2)	10 (14.3)
Anthracyclines and related substances	0	1 (11.1)	0	2 (22.2)	0	0	2 (18.2)	5 (7.1)
Platinum compounds	4 (44.4)	6 (66.7)	5 (45.5)	5 (55.6)	7 (53.8)	4 (50.0)	9 (81.8)	40 (57.1)
Pyrimidine analogs	6 (66.7)	3 (33.3)	2 (18.2)	3 (33.3)	6 (46.2)	2 (25.0)	6 (54.5)	28 (40.0)
Taxanes	1 (11.1)	4 (44.4)	2 (18.2)	3 (33.3)	5 (38.5)	3 (37.5)	5 (45.5)	23 (32.9)
Radiotherapy	3 (33.3)	6 (66.7)	6 (54.5)	4 (44.4)	5 (38.5)	4 (50.0)	9 (81.8)	37 (52.9)
Surgery	5 (55.6)	5 (55.6)	9 (81.8)	7 (77.8)	10 (76.9)	5 (62.5)	7 (63.6)	48 (68.6)
Median prior lines of therapy, n	1	1	1	1	2	2	2	1

Treatment group A, mFOLFOX6 (oxaliplatin, leucovorin calcium [folinic acid], and 5-fluorouracil); treatment group B, nab-paclitaxel and gemcitabine; treatment group C, paclitaxel and carboplatin; treatment group D, pemetrexed and platinum agent; treatment group E, cyclophosphamide; treatment group F, gemcitabine and platinum agent; treatment group G, 5-fluorouracil and platinum agent.

^aAsian, Native Hawaiian/Pacific Islander, or Other.

^bThe "other" tumor types were malignant fibrous tumor of the left pleura, basal cell carcinoma, mucoepidermoid carcinoma, and adenoid cystic carcinoma. Abbreviations: Nab, nanoparticle albumin-bound; SD, standard deviation.

Table 2. Safety summary.

Patients, <i>n</i> (%)	Treatment group							Total (<i>N</i> = 70)
	A (<i>n</i> = 9)	B (<i>n</i> = 9)	C (<i>n</i> = 11)	D (<i>n</i> = 9)	E (<i>n</i> = 13)	F (<i>n</i> = 8)	G (<i>n</i> = 11)	
Any-grade TEAE ^a	9 (100.0)	9 (100.0)	11 (100.0)	9 (100.0)	13 (100.0)	8 (100.0)	11 (100.0)	70 (100.0)
Nausea	2 (22.2)	6 (66.7)	8 (72.7)	7 (77.8)	5 (38.5)	4 (50.0)	8 (72.7)	40 (57.1)
Fatigue	7 (77.8)	5 (55.6)	6 (54.5)	6 (66.7)	6 (46.2)	4 (50.0)	4 (36.4)	38 (54.3)
Diarrhea	4 (44.4)	6 (66.7)	6 (54.5)	4 (44.4)	4 (30.8)	0	5 (45.5)	29 (41.4)
Anemia	3 (33.3)	5 (55.6)	4 (36.4)	3 (33.3)	6 (46.2)	4 (50.0)	3 (27.3)	28 (40.0)
Neutropenia	2 (22.2)	5 (55.6)	5 (45.5)	2 (22.2)	2 (15.4)	6 (75.0)	3 (27.3)	25 (35.7)
Vomiting	1 (11.1)	4 (44.4)	4 (36.4)	3 (33.3)	4 (30.8)	3 (37.5)	4 (36.4)	23 (32.9)
Neuropathy peripheral	6 (66.7)	3 (33.3)	5 (45.5)	3 (33.3)	0	0	1 (9.1)	18 (25.7)
Stomatitis	3 (33.3)	3 (33.3)	2 (18.2)	2 (22.2)	1 (7.7)	0	6 (54.5)	17 (24.3)
ALT increased	3 (33.3)	3 (33.3)	3 (27.3)	3 (33.3)	1 (7.7)	2 (25.0)	1 (9.1)	16 (22.9)
Thrombocytopenia	1 (11.1)	7 (77.8)	0	1 (11.1)	0	5 (62.5)	2 (18.2)	16 (22.9)
AST increased	3 (33.3)	3 (33.3)	3 (27.3)	3 (33.3)	1 (7.7)	1 (12.5)	0	14 (20.0)
Leukopenia	1 (11.1)	1 (11.1)	3 (27.3)	2 (22.2)	1 (7.7)	5 (62.5)	1 (9.1)	14 (20.0)
Treatment-related AE	9 (100.0)	9 (100.0)	11 (100.0)	9 (100.0)	10 (76.9)	8 (100.0)	11 (100.0)	67 (95.7)
Grades 3 and 4 TEAE ^a	7 (77.8)	9 (100.0)	10 (90.9)	5 (55.6)	8 (61.5)	8 (100.0)	8 (72.7)	55 (78.6)
Neutropenia	1 (11.1)	5 (55.6)	2 (18.2)	1 (11.1)	1 (7.7)	4 (50.0)	3 (27.3)	17 (24.3)
Disease progression	1 (11.1)	0	2 (18.2)	1 (11.1)	1 (7.7)	1 (12.5)	1 (9.1)	7 (10.0)
Serious TEAE	5 (55.6)	5 (55.6)	4 (36.4)	2 (22.2)	6 (46.2)	4 (50.0)	6 (54.5)	32 (45.7)
TEAE leading to death	1 (11.1)	3 (33.3)	3 (27.3)	1 (11.1)	4 (30.8)	2 (25.0)	2 (18.2)	16 (22.9)
TEAE leading to dose reduction of epacadostat	1 (11.1)	1 (11.1)	0	0	1 (7.7)	0	0	3 (4.3)
TEAE leading to dose interruption of epacadostat or pembrolizumab	6 (66.7)	9 (100.0)	7 (63.6)	5 (55.6)	4 (30.8)	6 (75.0)	6 (54.5)	43 (61.4)
TEAE leading to discontinuation of epacadostat or pembrolizumab	0	2 (22.2)	2 (18.2)	2 (22.2)	2 (15.4)	1 (12.5)	2 (18.2)	11 (15.7)
Dose-limiting toxicity	0	2 (22.2)	0	0	0	0	3 (27.3)	5 (7.1)

^aOnly preferred terms were used. Specific AEs are shown if they occurred in ≥20% (any-grade) or ≥10% (grades 3 and 4) of patients.

Table 3. Objective response rate.

Patients, <i>n</i> (%)	Treatment group							Total (<i>N</i> = 70)
	A (<i>n</i> = 9)	B (<i>n</i> = 9)	C (<i>n</i> = 11)	D (<i>n</i> = 9)	E (<i>n</i> = 13)	F (<i>n</i> = 8)	G (<i>n</i> = 11)	
Best response								
Complete response	0	0	1 (9.1)	0	0	0	0	1 (1.4)
Partial response	5 (55.6)	5 (55.6)	2 (18.2)	3 (33.3)	2 (15.4)	3 (37.5)	1 (9.1)	21 (30.0)
Stable disease	2 (22.2)	2 (22.2)	7 (63.6)	4 (44.4)	2 (15.4)	2 (25.0)	4 (36.4)	23 (32.9)
Progressive disease or death	2 (22.2)	2 (22.2)	0	2 (22.2)	9 (69.2)	3 (37.5)	6 (54.5)	24 (34.3)
Not evaluable	0	0	1 (9.1)	0	0	0	0	1 (1.4)
Objective response rate	5 (55.6)	5 (55.6)	3 (27.3)	3 (33.3)	2 (15.4)	3 (37.5)	1 (9.1)	22 (31.4)

Table 4. Epacadostat pharmacokinetic parameters at steady state (cycle 1/day 8) per noncompartmental analysis.

Treatment group	N	C _{max} , nM	t _{max} , h	C _{min} , nM	AUC ₀₋₁ , h* nM	AUC _{0-τ} , h* nM	t _{1/2} , h	CL _{ss} /F, L/h
A mFOLFOX6	6	586 ± 256 (535)	2.9 (1-4.1)	73.5 ± 31.2 (68.5)	1890 ± 762 (1760)	2790	1.78	81.7
B Nab-paclitaxel and gemcitabine	7	842 ± 377 (731)	2 (1-4)	174 ± 183 (123)	2890 ± 1630 (2480)	2760	1.42	82.6
C Paclitaxel and carboplatin	7	885 ± 328 (832)	2 (1-4)	75.1 ± 62.3 (NC)	2450 ± 628 (2380)	3240, 2440	2.62, 1.07	70.4, 93.5
D Pemetrexed and platinum agent	5	505 ± 232 (448)	2 (1-6.2)	30 ± 21.3 (NC)	1540 ± 442 (1470)	1810	1.3	126
E Cyclophosphamide	7	888 ± 459 (791)	2 (1-6)	98 ± 54.5 (83.1)	2830 ± 1660 (2420)	3410 ± 1310 (3220; n = 3)	1.84 ± 0.134 (1.84; n = 3)	75.5 ± 34.4 (70.8; n = 3)
F Gemcitabine and platinum agent	7	980 ± 331 (925)	2.1 (0-4)	194 ± 206 (NC)	3130 ± 1050 (2940)	3770 ± 3040 (3020; n = 3)	56.4 ± 95 (7.46; n = 3)	92.1 ± 63.8 (75.6; n = 3)
G 5-FU and platinum agent	8	752 ± 552 (588)	3.1 (1-6)	104 ± 108 (80.8)	2070 ± 1220 (1760)	2970, 2810	1.35, 1.30	76.8, 81.3
Overall	47	792 ± 395 (686)	2 (0-6.2)	111 ± 124 (NC)	2440 ± 1220 (2150)	3110 ± 1470 (2860; n = 13)	14.3 ± 45.6 (2.27; n = 13)	85.8 ± 32.9 (79.9; n = 13)

If $n > 2$, data are mean ± standard deviation (geometric mean), except for t_{max} , which is reported as median (range). If $n \leq 2$, individual values are listed. 5-FU, 5-fluorouracil; AUC_{0-τ}, area under the plasma drug concentration–time curve up to time “τ”; AUC_{0-t}, area under the plasma drug concentration–time curve over the dosing interval; CL_{ss}/F, apparent total body clearance after oral administration at steady state; C_{max}, maximum observed plasma concentration; C_{min}, minimum (trough) steady-state plasma concentration; mFOLFOX6, oxaliplatin, leucovorin calcium (folinic acid), and 5 fluorouracil; nab, nanoparticle albumin-bound; NC, not calculable; t_{max}, time to maximum concentration; t_{1/2}, half-life; tmax, time to maximum concentration.

Table 5. Responses by tumor histology.^a

Tumor type, <i>n</i> (%)	Responders						
	A (<i>n</i> = 5)	B (<i>n</i> = 5)	C (<i>n</i> = 3)	D (<i>n</i> = 3)	E (<i>n</i> = 2)	F (<i>n</i> = 3)	G (<i>n</i> = 1)
Breast cancer		1 (20.0)			1 (50.0)		
Colorectal cancer	4 (80.0)						
Esophageal cancer		1 (20.0)					
Gallbladder cancer	1 (20.0)					1 (33.3)	
Gastric cancer					1 (50.0)		
Mesothelioma				1 (33.3)		1 (33.3)	
Nasopharyngeal cancer						1 (33.3)	
Non–small cell lung cancer			2 (66.7)	1 (33.3)			
Ovarian cancer			1 (33.3)	1 (33.3)			
Pancreatic cancer		3 (60.0)					
Mucoepidermoid carcinoma							1 (100.0)

Treatment group A, mFOLFOX6 (oxaliplatin, leucovorin calcium [folinic acid], and 5-fluorouracil); treatment group B, nanoparticle albumin-bound (nab)-paclitaxel and gemcitabine; treatment group C, paclitaxel and carboplatin; treatment group D, pemetrexed and platinum agent; treatment group E, cyclophosphamide; treatment group F, gemcitabine and platinum agent; treatment group G, 5-fluorouracil and platinum agent.

^aWith the exception of one patient with non–small cell lung cancer in treatment group C who developed a complete response, all other responses were partial responses.