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

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ABSTRACT

Objective. Indoleamine 2,3-dioxygenase-1 (IDO1) is a key regulator of immune tolerance in ovarian cancer. This study investigated efficacy and safety of the IDO1 enzyme inhibitor epacadostat versus tamoxifen in patients with biochemical-only recurrence (CA-125 elevation) following complete remission after first-line chemotherapy for advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer.

Methods. In this open-label, phase 2 study (NCT01685255), patients were randomised 1:1 to epacadostat 600 mg or tamoxifen 20 mg twice daily for successive 28-day cycles and stratified by time since completion of first-line chemotherapy to first CA-125 elevation (3 to <12 or ≥12 months). The primary endpoint was investigator-assessed progression-free survival (PFS; RECIST v1.1). Secondary endpoints included CA-125 response (Gynecologic Cancer InterGroup criteria), overall survival, safety, and tolerability.

Results. The study was terminated primarily due to slow accrual and lack of evidence of superiority. Median PFS was 3.75 months for epacadostat (n=22) versus 5.56 months for tamoxifen (n=20; HR, 1.34 [95% CI, 0.58–3.14]; *P*=0.54). Of evaluable patients, 1 (5.0%) epacadostat and 3 (15.8%) tamoxifen patients had confirmed CA-125 responses. The most common treatment-emergent adverse event was fatigue (epacadostat, 36.4%; tamoxifen, 40.0%). Immune-related adverse events, observed with epacadostat only, were primarily rash (18.2%) and pruritus (9.1%). Epacadostat pharmacokinetics/pharmacodynamics were consistent with its known mechanism of action. IDO1 expression was observed in 94% of archival tumour samples.

Conclusions. This first report of immunotherapy evaluation in biochemical-only relapse ovarian cancer and of IDO1 inhibitor monotherapy in ovarian cancer found no significant difference in efficacy between epacadostat and tamoxifen. Epacadostat was generally well tolerated.

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INTRODUCTION

Ovarian cancer is the leading cause of gynaecologic cancer-related deaths worldwide and has poor long-term survival [1-3]. For patients who relapse ≥6 months after responding to first-line treatment (typically cytoreductive surgery and systemic platinum-based chemotherapy [2,4]), retreatment with platinum-based chemotherapy has encouraging response rates [5]; however, the majority of patients experiencing relapse are considered incurable [2,4,6]. There remains a substantial unmet clinical need for better strategies to improve disease-free survival and cure in early treatment of ovarian cancer [5,6].

The development of symptoms is one indicator of disease relapse, prompting biochemical testing with the tumour marker CA-125 and imaging to confirm disease recurrence [5,7]. However, patients are frequently asymptomatic at the time of small-volume recurrence, with suspicion of relapse based solely on rising CA-125 levels [5,7]. In such patients, a watch-and-wait policy is justifiable. Second-line chemotherapy is initiated according to symptoms, extent of disease and CA-125 level, among other considerations [5]. When patients present with a biochemical relapse without clinical evidence of disease, there may be an opportunity to improve outcomes by extending the time that the cancer remains under control, potentially delaying progression and the need for further cytotoxic therapy.

Ovarian cancer is an immunogenic malignancy [8,9], supporting the rationale for immunomodulatory agents (eg, checkpoint inhibitors) as potentially effective therapeutic agents. Recruitment of regulatory T cells in ovarian cancer leads to immunosuppression [10], which has been associated with decreased survival, paclitaxel resistance, and increased levels of vascular endothelial growth factor

[8,10]. In patients with stage III/IV ovarian cancer, survival is also strongly correlated with the presence of tumour-infiltrating lymphocytes (TILs) [11], with a 5-year survival of 38% when TILs are present versus 4.5% when they are absent [12].

The intracellular indoleamine 2,3-dioxygenase-1 (IDO1) enzyme is a key regulator of the immunosuppression responsible for tumour escape from immune surveillance [15-17] and is predominantly expressed by tumour epithelial cells, antigen-presenting cells in primary tumours and tumour-draining lymph nodes in a variety of cancers [13,14]. IDO1 catalyses the degradation of tryptophan via oxidation to kynurenine (Kyn), which results in strong inhibitory effects on T-cell–mediated responses, including blocking T-cell activation and inducing T-cell apoptosis [18]. High intratumoural IDO1 expression in ovarian cancer has been found to correlate with a reduced number of TILs [19], advanced disease stage, paclitaxel resistance, and decreased survival [15-17,19]. Taken together, these findings strongly support IDO1 as a rational target to reactivate the antitumour immunity in patients with ovarian cancer. Epacadostat (INCB024360), a selective IDO1 enzyme inhibitor, has been developed and is currently under clinical investigation in various tumour types [20-23].

Ovarian cancer treatment guidelines suggest that patients with biochemical relapse (serially increasing CA-125 levels and no clinical evidence of disease) have several options: (1) delay therapy until clinical relapse; (2) enrol in a clinical trial; or (3) undergo treatment with a second-line therapy that has an acceptable side-effect profile, such as biologic therapies (eg, tamoxifen) over cytotoxic therapies [2]. We hypothesised that these patients would be good candidates for immune-targeted therapies and investigated the effects of treatment with epacadostat in patients with

a low cancer burden. Thus, the objective of this study was to determine the efficacy of epacadostat compared with tamoxifen in biochemical-recurrent–only epithelial ovarian, primary peritoneal, or fallopian tube cancer.

METHODS

Study Design and Treatment

This international, multicentre, randomised, open-label phase 2 study conducted in 6 countries (United States, United Kingdom, Russia, Ukraine, Australia, and Canada) evaluated epacadostat versus tamoxifen for efficacy, safety, and tolerability in women with ovarian cancer and CA-125 elevation following complete remission with first-line chemotherapy. At study initiation, the intention was to enrol 110 patients randomised 1:1 to receive epacadostat or tamoxifen and stratified based on the number of months since prior first-line chemotherapy to the time of their first CA-125 elevation (3 to <12 months or ≥12 months). The study (ClinicalTrials.gov: NCT01685255) was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Conference on Harmonisation guidelines, and was approved by the institutional review board or ethics committee at each participating institution. All patients provided written informed consent before initiation of treatment.

Study treatment was administered orally as continuous 28-day cycles of either epacadostat 600 mg twice daily (BID) or tamoxifen 20 mg BID. Dose reductions, interruptions, or discontinuations were allowed at any time for safety reasons **(Supplement Table 1)**. However, only 2 dose reductions of epacadostat were

allowed (400 mg BID and 300 mg BID). The study comprised a screening phase, treatment phase, and safety follow-up phase. During the treatment phase, patients received study drug in successive 28-day cycles until they met any criterion for withdrawal. Patients were monitored for 60 days after the last dose of epacadostat or tamoxifen during the safety follow-up. After this, patients were monitored for survival at approximately 12-week intervals.

Study Population

Eligible patients were women aged 18 years or older with Eastern Cooperative Oncology Group performance status 0 or 1; histologically confirmed Federation of International Gynecologists and Obstetricians (FIGO) [24] stage IC, II, III, or IV epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer at diagnosis; biochemical recurrence; and no other objective evidence of disease recurrence as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Biochemical recurrence of disease (Gynecologic Cancer InterGroup [GCIG] criteria) was defined as 2 consecutive measurements of CA-125 above the upper limit of normal (ULN) that were ≥2 weeks apart, with the second measurement showing a further increase from the first measurement. If the first CA-125 measurement is ≥2× ULN, the confirmatory CA-125 measurement only needs to be ≥1 week later. In the United Kingdom (UK-only requirement), biochemical recurrence of disease was defined as elevated CA-125 levels ≥2× ULN on 2 occasions that were ≥1 week apart without evidence of disease as defined by RECIST 1.1. Before entering the study, patients must have had a complete response to chemotherapy and must have received a first-line platinum-containing chemotherapy regimen with

documentation of CA-125 elevation at first diagnosis and at least 1 normal CA-125 level during or after first-line therapy.

Key exclusion criteria included protocol-specified active or inactive autoimmune processes (except vitiligo, thyroiditis, or eczema) and unstable cardiovascular disease ≤6 months before starting study treatment. Patients were also excluded if they had received prior antitumour systemic therapy besides first-line chemotherapy; prior radiotherapy within 3 months of randomisation with unresolved toxicities; prior investigational drug or immunologically based treatment for any reason, including chronic use of systemic steroid ≥7.5 mg/d prednisone equivalents (except completed adjuvant therapy or use of inhaled or topical steroids); potent cytochrome P450 3A4 inducers or inhibitors; monoamine oxidase inhibitors within the 21 days before screening; prior serotonin syndrome after receiving ≥1 serotonergic drug; and contraindication to tamoxifen therapy.

Endpoints and Assessments

The primary endpoint was efficacy by investigator-assessed progression-free survival (PFS; RECIST v1.1). Per RECIST v1.1, progressive disease was defined by the appearance of any new lesion, whether target or non-target. Disease and tumour assessments were conducted every 8 weeks for the first 12 months, then every 12 weeks thereafter, and at end of treatment or early termination.

Secondary endpoints included evaluation of CA-125 response or non-response (GCIG criteria; CA 125 already progressing at study entry), overall survival, and evaluation of the safety and tolerability of epacadostat. A CA-125 response (GCIG criteria) was defined as ≥50% reduction in CA-125 levels from a pretreatment sample that was confirmed and maintained for ≥28 days. Safety and tolerability

assessments included treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs), and immune-related adverse events (irAEs), vital signs, electrocardiograms (ECGs), physical examination, and clinical laboratory tests. CA-125 and adverse events were assessed at baseline then every 4 weeks thereafter, at end of treatment or early termination, and 30 and 60 days after end of treatment or last dose.

Exploratory endpoints included assessment of epacadostat pharmacokinetics (PK) and pharmacodynamics (PD). Blood samples for PK assessments were obtained on day 15 of cycle 1 and day 1 of cycle 2. Blood samples for PD assessments were obtained on days 1 and 15 of cycle 1, day 1 of cycles 2 to 4, every 4 weeks thereafter, at end of treatment or early termination, and at follow-up. Following whole blood sample stimulation ex vivo with interferon-γ (IFN-γ; 100 ng/mL) and lipopolysaccharide (LPS; 100 ng/mL) for approximately 20 hours, plasma levels of tryptophan and Kyn were evaluated by liquid chromatography with tandem mass spectrometry as previously described [22]. Percentage inhibition of IDO1, as determined by the decrease in Kyn levels, was calculated by comparing predose values with those obtained at different times after dosing. Changes in plasma levels of proteins related to immunity and inflammation were monitored using Evidence Investigator™ Biochip Array technology (Randox Laboratories, Crumlin, County Antrim, UK), a custom-designed multiplex biochip assay that is based on sandwich chemiluminescent immunoassays. Analysis of archival tumour biopsy samples for IDO1 and programmed death-ligand 1 (PD-L1) expression was also performed using immunohistochemistry.

Statistical Methods

Per protocol, target enrolment was 110 patients (55 per treatment group, with the expectation that target enrolment would be reached within 18 months), and a formal interim analysis for futility was planned to occur after 30 deaths or disease progression events were observed. However, 20 months after the study began, actual enrolment was <50% of target enrolment, prompting an earlier, unplanned interim analysis. Based on the results of this analysis (42 patients, 26 progression events), the sponsor terminated the study for lack of evidence of superiority, and no formal interim analysis was conducted.

The modified intent-to-treat population, defined as all randomised patients who received ≥1 dose of study drug, was used for efficacy analyses. Safety analyses included all enrolled patients who received ≥1 dose of study drug. The PK/PD evaluable population included patients who received ≥1 dose of epacadostat or tamoxifen and provided ≥1 postdose plasma sample for PK/PD measurement.

SAS® software, version 9.2 (SAS Institute, Cary, NC) was used to generate all tables, graphs, and statistical analyses. Descriptive statistics were used to present summaries of continuous and categorical variables. Safety, PK, PD, and immunologic marker data were analysed using summary statistics (eg, means and frequencies).

Standard noncompartmental PK methods were used to analyse epacadostat plasma concentration data using Phoenix WinNonlin® version 6.0 (Pharsight Corporation, Mountain View, CA).

RESULTS

Study Population

Forty-two women were enrolled in the study between March 7, 2013, and October 23, 2014 (epacadostat, n=22; tamoxifen, n=20). All 42 patients were evaluated for efficacy and safety. All 42 patients discontinued from study drug treatment. The most common reason for discontinuation was disease progression (epacadostat, n=10 [45.5%]; tamoxifen, n=11 [55.0%]). Six patients (27.3%) in the epacadostat group discontinued because of an adverse event (TEAE in 2 patients; TRAE in 4 patients). No tamoxifen-treated patients discontinued because of TEAEs. The remaining 6 epacadostat-treated patients (27.3%) and 9 tamoxifen-treated patients (45.0%) discontinued study drug because of the sponsor's decision to terminate the study early because of slow accrual and a lack of superior efficacy with epacadostat at time of interim analysis **(Supplement Table 2)**. These 15 patients were censored for the unplanned interim analysis.

The majority of patients were white (epacadostat, 100%; tamoxifen, 90.0%), and the median age overall was 59.0 years. Baseline demographics and disease characteristics were generally well balanced across the 2 treatment groups, including primary cancer site, number of months from completion of prior first-line chemotherapy to the first CA-125 elevation, prior surgery, prior systemic therapy, and breast cancer susceptibility gene (*BRCA*) status. The most common FIGO stage at diagnosis was stage IIIC for both treatment groups (64.3% overall; **Table 1**).

Efficacy

At early study termination, epacadostat was not associated with superiority over tamoxifen as measured by investigator-assessed PFS. Median PFS was 3.75 months in the epacadostat group versus 5.56 months in the tamoxifen group. The

hazard ratio (HR) for death or disease progression was 1.34 (95% CI, 0.58–3.14; *P*=0.54; **Figure 1**). For patients who had their first CA-125 elevation 3 to <12 months after completion of first-line chemotherapy (baseline stratification factors), median PFS was 2.24 months for epacadostat versus 5.48 months for tamoxifen (HR, 1.63 [95% CI, 0.48–5.50]; *P*=0.41). For patients with their first CA-125 elevation at ≥12 months, median PFS was 3.98 and 5.56 months in epacadostat and tamoxifen arms (HR, 0.85 [95% CI, 0.26–2.80]; *P*=0.78), respectively.

Of evaluable patients, 1 (5.0%) in the epacadostat group and 3 (15.8%) in the tamoxifen group had confirmed CA-125 responses. Two additional patients (10.0%) in the epacadostat group and 2 (10.5%) in the tamoxifen group had CA-125 responses but were unconfirmed (ie, ≥50% reduction of CA-125 at only 1 time point; **Supplement Table 3**). The mean best percentage change from baseline in CA-125 was 36.6% for epacadostat-treated patients and 59.9% for tamoxifen-treated patients **(Figure 2).**

Overall survival was assessed over the treatment and follow-up phases, during which 21 patients (95.5%) receiving epacadostat and all 20 patients (100%) receiving tamoxifen discontinued from the study and were censored from the overall survival analysis. The remaining 1 patient (4.5%) in the epacadostat group completed study drug treatment and the 60-day safety follow-up but subsequently died because of disease progression during the survival follow-up, before the sponsor’s decision to terminate the study. No tamoxifen-treated patients died at time of follow-up before study termination.

Safety and Tolerability

Epacadostat was generally well tolerated. Twenty-two patients received ≥1 dose of epacadostat, with a median exposure of 56.0 days and a median total daily dose of 1200 mg. Twenty patients received ≥1 dose of tamoxifen, with a median exposure of 61.0 days and a median total daily dose of 40 mg.

Seventeen patients (77.3%) in the epacadostat group and 15 patients (75.0%) in the tamoxifen group experienced TEAEs **(Table 2A)**. The most frequently reported all-grade TEAE in both groups was fatigue (epacadostat, 36.4%; tamoxifen, 40.0%). Six patients (27.3%) in the epacadostat group discontinued study drug because of an adverse event; the most frequently reported reason was rash (n=3; all TRAEs). No patient in the tamoxifen group discontinued because of an adverse event.

Seven patients (31.8%) in the epacadostat group and 2 patients (10%) in the tamoxifen group had TEAEs of grade ≥3. The most frequently reported grade ≥3 TEAE in the epacadostat group was maculopapular rash (n=2 [9.1%]). No individual TEAE grade ≥3 was reported in >1 patient in the tamoxifen group.

There were no TEAEs leading to death. One patient in each treatment group had a serious adverse event (epacadostat, abdominal pain [4.5%]; tamoxifen, ascites [5.0%]).

As expected based on its mechanism of action, no irAEs were reported in patients receiving tamoxifen. In the epacadostat group, the most frequently reported irAEs were skin related: 4 patients (18.2%) had rash and 2 patients (9.1%) had pruritus **(Table 2B)**. Two patients (9.1%) receiving epacadostat had a grade ≥3 irAE of maculopapular rash.

The majority of patients had normal haematology and clinical chemistry laboratory assessments at baseline, and the values remained normal throughout the study. Overall, no clinically meaningful changes or trends in vital signs or ECG findings were observed. There were no reports of serotonin syndrome at any time during the study.

Pharmacokinetics

After oral administration of epacadostat 600 mg BID (n=15), mean (SD) epacadostat maximum observed plasma concentration (C_{max}), minimum observed plasma concentration (C_{min}), and area under the plasma concentration-time curve ($AUC_{0-\tau}$) were 6.20 (2.68) μM, 0.868 (0.516) μM, and 31.7 (11.7) μM·h, respectively, on day 15 of cycle 1. Median time to C_{max} (t_{max}) was 1.9 hours postdose **(Figure 3)**.

Pharmacodynamics

Samples from 29 patients were available for IDO1 inhibition analysis. In the epacadostat group (n=16), the average Kyn level was reduced by 39% from 2010 nM at cycle 1 day 1 to 1227 nM at cycle 2 day 1, suggesting that treatment with epacadostat reduced plasma Kyn levels to within the observed range in healthy volunteers (median Kyn, 1499 nM) [25]. In contrast, the average Kyn level was reduced by 13% in the tamoxifen group (n=13) during the same period (from 2192 to 1897 nM).

In the ex vivo PD analysis that evaluated IDO1 inhibition in IFN-γ– and LPS-stimulated whole blood samples, >90% Kyn reduction was observed for at least the first 6 hours after epacadostat administration on day 1 of cycle 1 and at all time points after epacadostat administration on day 15; average inhibition over the 6

hours ranged from 95% to 98% **(Figure 4A, 4B)**. Meanwhile, reductions in Kyn levels in the tamoxifen group appeared to be more modest and inconstant, evidenced by an average inhibition of 0% to 40% over the 6 hours (data not shown).

There were no significant differences in inflammatory markers between treatment groups at baseline; however, these baseline markers, including C-reactive protein (CRP) and interleukin-6, were elevated in both treatment groups compared with healthy volunteers (data not shown). This was not unexpected because patients with cancer generally have been shown to have elevated CRP and evidence of a chronic systemic inflammatory response [26,27]. Although minor changes were observed in some analytes during treatment, they were not statistically significant.

A large number of archival biopsy tissue samples (30 of 32 samples; 94%) were positive for IDO1 expression in tumour cells, although relatively low levels of expression were detected in the majority of IDO1-positive patients. PD-L1 expression was observed in only 11 of 31 evaluable samples (35%); all PD-L1–positive samples were also IDO1-positive. Only 2 samples (6%) were negative for expression of both IDO1 and PD-L1. Eighteen samples (58%) were positive for IDO1 but negative for PD-L1 **(Supplement Table 4)** .

DISCUSSION

This was an international, multicentre, randomised, open-label phase 2 study of the efficacy, safety, and tolerability of epacadostat versus tamoxifen in women with histologically confirmed epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer who had biochemical recurrence of disease (CA-125 elevation)

and no other objective evidence of disease recurrence after complete response with first-line chemotherapy. This is the first report, to our knowledge, of the use of immunotherapy in patients with early relapse of ovarian cancer and the first study of a small-molecule IDO1 enzyme inhibitor as monotherapy in ovarian cancer. Study enrolment was stopped at 42 patients out of the planned 110 upon early termination by the sponsor based on slow accrual and lack of evidence of superiority for epacadostat. The majority of patients who discontinued did so because of disease progression.

At the time of the interim analysis at study termination (with 14 progression events on epacadostat, 12 progression events on tamoxifen, and 8 censored events in each arm), there was no significant difference in efficacy between epacadostat and tamoxifen as measured by investigator-assessed PFS, and PFS was shorter in both treatment groups for patients who had early (3 to <12 months) versus later (≥12 months) CA-125 relapse following previous complete responses. PFS data were similar to those reported in a comparable patient sample from a phase 3 trial evaluating tamoxifen 20 mg BID versus thalidomide 220 mg daily, suggesting that the efficacy of tamoxifen in this study was as expected in this patient population [28].

Epacadostat was generally well tolerated. The majority of patients in the epacadostat and tamoxifen groups experienced ≥1 TEAE during the study, with fatigue being the most frequently reported TEAE in both groups. As expected, given the mechanism of action of epacadostat, irAEs were observed in the epacadostat group and were primarily skin-related events. There were no TEAEs leading to death. Epacadostat PK parameters in this study were comparable to those observed in the 600-mg BID dose group in a dose-escalation study (NCT01195311) in which epacadostat

monotherapy (dose range, 50 mg once daily to 700 mg BID) was evaluated in patients with advanced malignancies [23].

Despite epacadostat not showing single-agent activity, it is important to consider the timing of this study in the context of immunotherapy development in advanced ovarian cancer. Not only is this the first reported study investigating a small-molecule IDO1 enzyme inhibitor in ovarian cancer, the protocol development predated other clinical investigations with checkpoint inhibitors in this cancer setting. In addition, all immune responses are accompanied by (and limited by) the generation of negative feedback mechanisms that may suppress immunity; IDO1 is one of many such negative feedback mechanisms [29]. IDO1 expression, which is inducible by interferon, is part of adaptive immune resistance mechanisms to limit physiologic inflammation [30,31] and may have a broad role in combination immunotherapies for human malignancies. The concept of evaluating the predictive role of quantitative or qualitative IDO1 expression in tumour tissue and immune cells in the tumour microenvironment at baseline or during therapy has not been defined but is a goal of ongoing studies. Importantly, this study demonstrated a clinically manageable safety profile with epacadostat (including irAEs), effective IDO1 inhibition activity at 600 mg BID, and frequent IDO1 expression and coexpression with PD-L1 in tumour samples, which are all significant considerations given the potential future use of epacadostat in this cancer setting – likely as part of immune-based combination therapy. Preclinical evidence suggests that IDO1 inhibition may dramatically increase the efficacy of various chemotherapeutic agents without increased toxicity, including platinum-based compounds and taxanes [32], both of which are recommended for ovarian cancers [2]. Although the mechanisms responsible for this potentiation are not fully understood, these effects were not observed in T-cell–deficient animals,

suggesting that the effects may be due to the disabling of immunosuppressive mechanisms within the tumour microenvironment [32]. In addition, the combination of high-dose PD-L1 inhibition and cisplatin was associated with tumour burden reduction in preclinical models of ovarian cancers [33]. Ongoing clinical studies are evaluating anti–PD-1/PD-L1 agents, including pembrolizumab, atezolizumab, and avelumab, in combination with chemotherapy in previously untreated patients with ovarian cancers or patients who have recurrent disease (NCT02608684, NCT02440425, NCT02659384, and NCT02718417) [34]. In the current study, coexpression of IDO1 and PD-L1 was apparent in tumour biopsy samples, suggesting that combination treatment of a small-molecule IDO1 enzyme inhibitor, such as epacadostat, with an immunomodulatory checkpoint inhibitor may be an important therapeutic strategy for cancer treatment beyond this clinical setting. Early data from the phase 1/2 dose-escalation study of epacadostat plus ipilimumab in patients with unresectable or metastatic melanoma (NCT01604889) are promising [35] and suggest that combination therapy of IDO1 inhibition and cytotoxic T-lymphocyte antigen-4 blockade may be considered in advanced ovarian cancer. Other studies are currently being conducted to evaluate epacadostat in combination with various immunomodulatory agents, including pembrolizumab (in select advanced cancers; NCT02178722), nivolumab (in select advanced cancers; NCT02327078), durvalumab (in select advanced cancers; NCT02318277), and atezolizumab (in non–small-cell lung cancer; NCT02298153). A phase 3 trial of epacadostat combined with pembrolizumab in patients with unresectable or metastatic melanoma was initiated in 2016 (NCT02752074).

In conclusion, this is the first study of the IDO1 enzyme inhibitor epacadostat in ovarian cancer and also the first report of immunotherapy use in early-relapse

ovarian cancer. Epacadostat was generally well tolerated, with manageable irAEs and other adverse events. Although epacadostat monotherapy did not exhibit activity at the time of interim analysis, additional studies are in progress to assess the activity of epacadostat in combination with other immunomodulatory agents. Study findings suggest that tamoxifen may play a role in early-relapse ovarian cancer, and support the use of tamoxifen as an appropriate control for trials in this patient population.

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CONFLICT OF INTEREST STATEMENT

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Figure 2. Best percentage change from baseline in CA-125 (modified intent-to-treat population).

Figure 3. Mean (SE) epacadostat plasma concentrations on Day 15 of Cycle 1 in patients receiving epacadostat 600 mg twice daily.

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Table 1. Baseline Demographics and Clinical Characteristics (mITT Population)

Characteristic	Epacadostat 600 mg BID (n=22)	Tamoxifen 20 mg BID (n=20)	Total (N=42)
Median (range) age, y	61.0 (23.0–78.0)	58.5 (43.0–77.0)	59.0 (23.0–78.0)
Race, n (%)			
White	22 (100)	18 (90.0)	40 (95.2)
Asian	0	2 (10.0)	2 (4.8)
Primary cancer site, n (%)			
Epithelial ovarian cancer	14 (63.6)	13 (65.0)	27 (64.3)
Primary peritoneal carcinoma	2 (9.1)	2 (10.0)	4 (9.5)
Primary fallopian tube	2 (9.1)	2 (10.0)	4 (9.5)
Adenocarcinoma, not specified	2 (9.1)	2 (10.0)	4 (9.5)
Other[a]	2 (9.1)	1 (5.0)	3 (7.1)
Grade, n (%)			
I	0	1 (5.0)	1 (2.4)
II	0	0	0
III	10 (45.5)	14 (70.0)	24 (57.1)
Unknown	12 (54.5)	5 (25.0)	17 (40.5)
FIGO stage at screening, n (%)			
IC	1 (4.5)	1 (5.0)	2 (4.8)
IIIA	5 (22.7)	2 (10.0)	7 (16.7)
IIIB	0	4 (20.0)	4 (9.5)
IIIC	16 (72.7)	11 (55.0)	27 (64.3)
IV	0	2 (10.0)	2 (4.8)
BRCA status, n (%)			
BRCA1 mutation only	0	1 (5.0)	1 (2.4)
BRCA2 mutation only	0	0	0
Both *BRCA1* and *BRCA2*	0	0	0
Negative	3 (13.6)	4 (20.0)	7 (16.7)
Unknown	19 (86.4)	15 (75.0)	34 (81.0)
ECOG PS, n (%)			
0	12 (54.5)	15 (75.0)	27 (64.3)
1	10 (45.5)	5 (25.0)	15 (35.7)

Characteristic	Epacadostat 600 mg BID (n=22)	Tamoxifen 20 mg BID (n=20)	Total (N=42)
Time since completion of prior first-line chemotherapy to CA-125 elevation,[b] n (%)			
3–<12 mo	10 (45.5)	9 (45.0)	19 (45.2)
≥12 mo	12 (54.5)	11 (55.0)	23 (54.8)
Prior surgery, n (%)	22 (100)	20 (100)	42 (100)
Prior systemic therapy, n (%)			
Carboplatin[c]	19 (86.4)	16 (80.0)	35 (83.3)
Paclitaxel[d]	15 (68.3)	14 (70.0)	29 (69.0)
Cyclophosphamide	7 (31.8)	4 (20.0)	11 (26.2)
Cisplatin[e]	5 (22.7)	6 (30.0)	11 (26.2)
Bevacizumab	3 (13.6)	1 (5.0)	4 (9.5)
Doxorubicin	2 (9.1)	0	2 (4.8)
Pegylated liposomal doxorubicin hydrochloride	1 (4.5)	0	1 (2.4)
Gemcitabine hydrochloride	0	1 (5.0)	1 (2.4)

BID, twice daily; *BRCA1*, breast cancer 1 gene; *BRCA2*, breast cancer 2 gene; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, Federation of International Gynecologists and Obstetricians; mITT, modified intent-to-treat.

[a]Includes high-grade serous carcinoma and serous tubal intraepithelial carcinoma, ovarian/primary peritoneal, and papillary cystadenocarcinoma.

[b]Two patients (1 in each treatment group) were enrolled under the original protocol (Feb. 28, 2012), which enrolled patients who had a 6- to <12-month duration since completion of prior first-line chemotherapy and CA-125 elevation. Data for these 2 patients were analysed in the 3- to <12-month subgroup.

[c]Includes carboplatin alone and carboplatin + paclitaxel.

[d]Includes paclitaxel alone, paclitaxel + carboplatin, and paclitaxel + cisplatin. Paclitaxel is only counted once, but patients may have received paclitaxel as part of 2 separate regimens (ie, paclitaxel alone followed by paclitaxel + carboplatin).

[e]Includes cisplatin alone and cisplatin + paclitaxel.

Table 2.

A. TEAEs Reported by ≥3 Patients in Either Treatment Group

Preferred Term, n (%)	Epacadostat 600 mg BID (n=22)	Tamoxifen 20 mg BID (n=20)
All-grade TEAE	17 (77.3)	15 (75.0)
Fatigue	8 (36.4)	8 (40.0)
Nausea	6 (27.3)	6 (30.0)
Rash[a]	5 (22.7)	0
Abdominal distension	4 (18.2)	3 (15.0)
Constipation	4 (18.2)	2 (10.0)
Vomiting	4 (18.2)	3 (15.0)
Abdominal pain	3 (13.6)	0
Arthralgia	3 (13.6)	2 (10.0)
Decreased appetite	3 (13.6)	4 (20.0)
Headache	3 (13.6)	3 (15.0)
Insomnia	3 (13.6)	1 (5.0)
Dyspnoea	2 (9.1)	3 (15.0)

BID, twice daily; TEAE, treatment-emergent adverse event.
[a]Includes the following preferred terms: rash maculopapular, rash papular, rash erythematous, and rash.

B. Treatment-Emergent irAEs

Preferred Term, n (%)	Epacadostat 600 mg BID (n=22)	Tamoxifen 20 mg BID (n=20)
Patients with any treatment-emergent irAE	5 (22.7)	0
Rash[a]	4 (18.2)	0
Pruritus	2 (9.1)	0
Hyperthermia	1 (4.5)	0

BID, twice daily; irAE, immune-related adverse event.
[a]Includes the following preferred terms: rash maculopapular, rash erythematous, and rash.

FIGURES

Figure 1. PFS Kaplan-Meier curves by investigator assessment using RECIST 1.1 criteria (mITT population). mITT, modified intent-to-treat; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours.

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FIGURES

Figure 1.

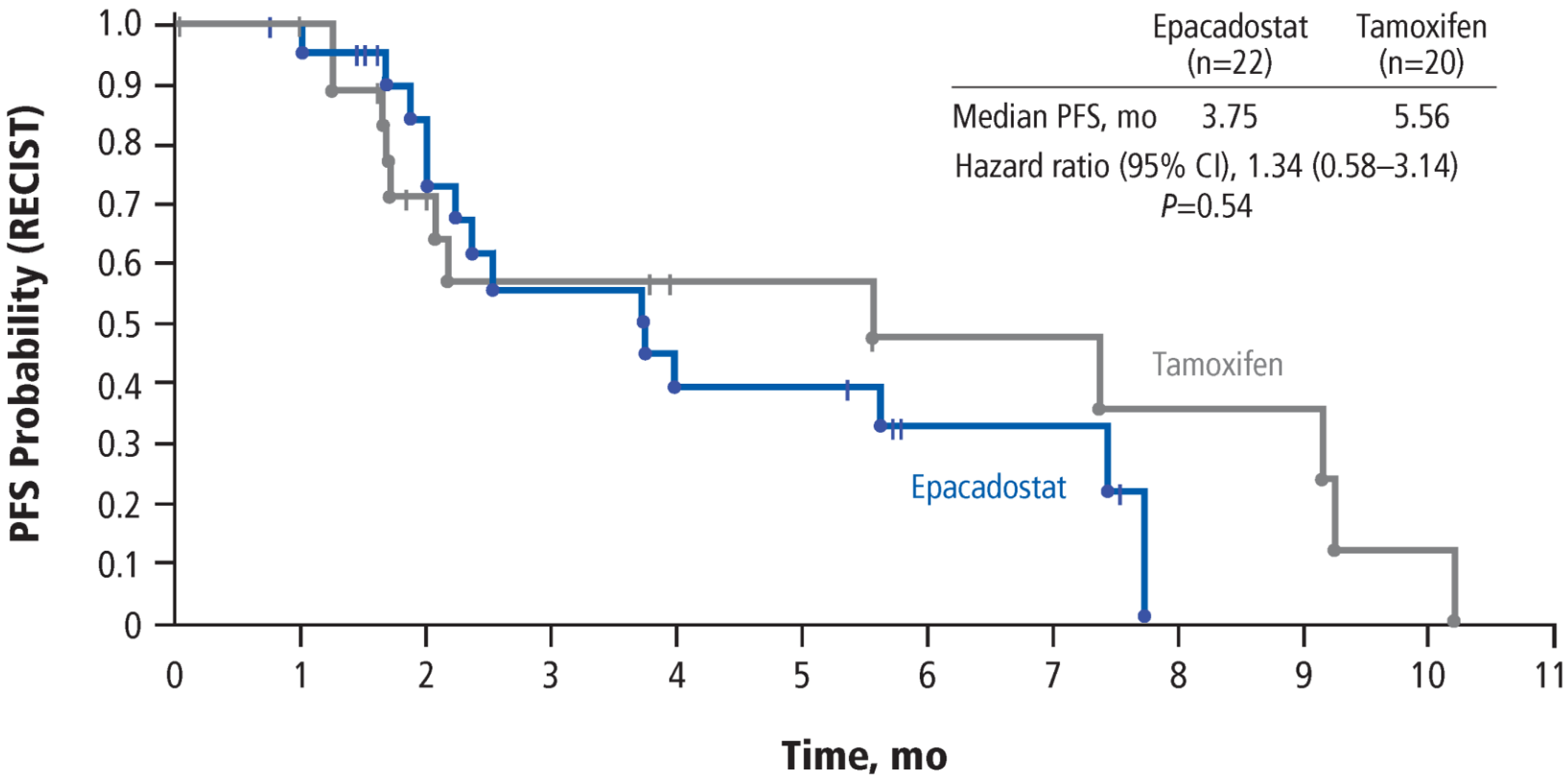


Figure 2.

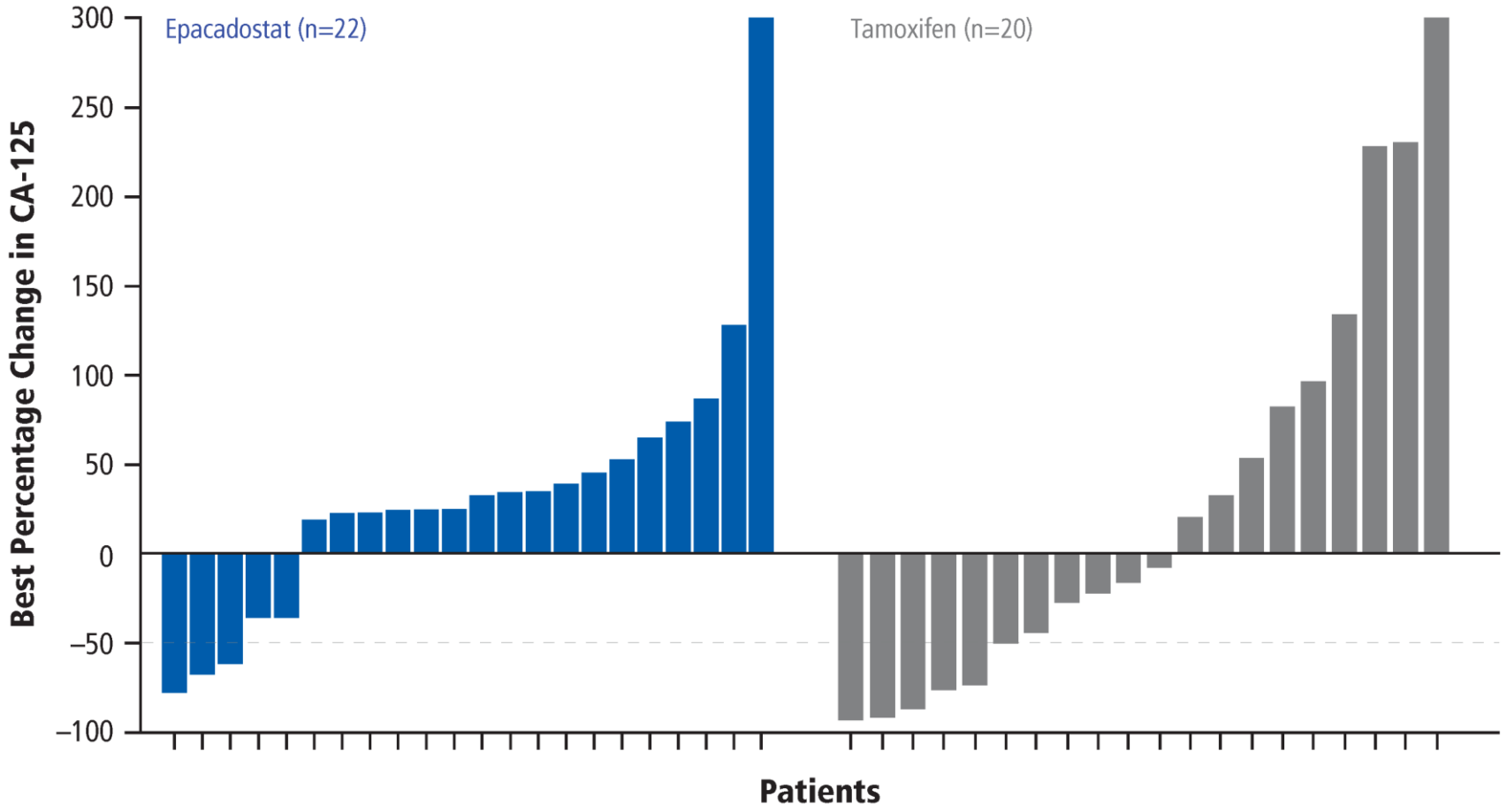

Epacadostat (n=22)
Tamoxifen (n=20)
Best Percentage Change in CA-125
300
250
200
150
100
50
0
−50
−100
Patients

Figure 3.

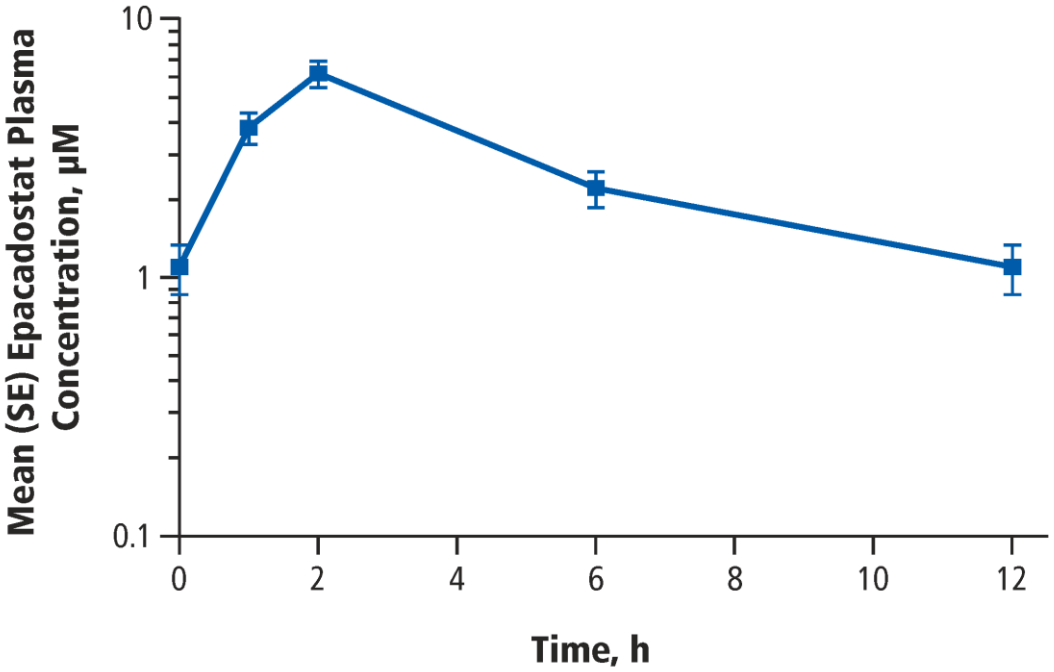
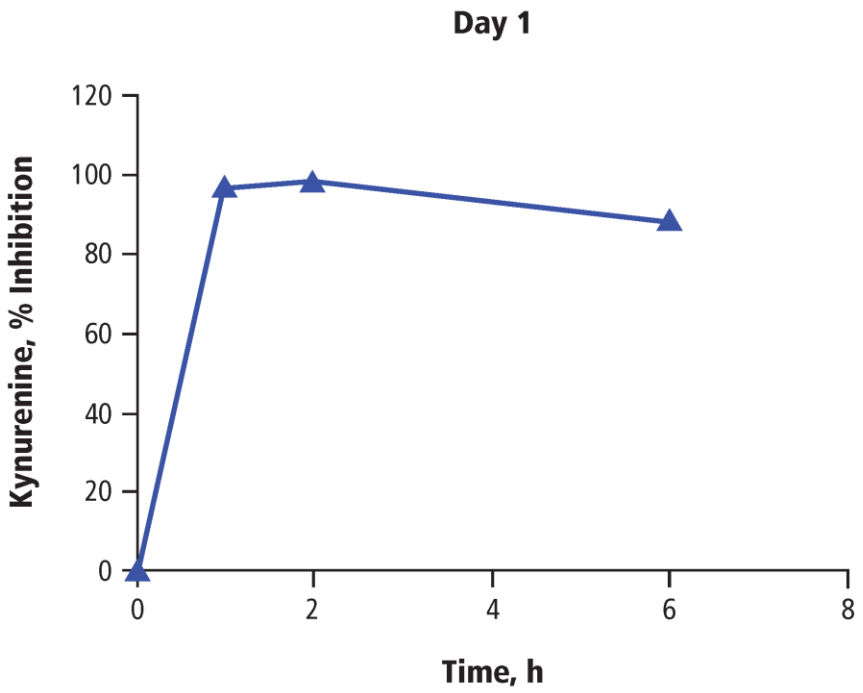
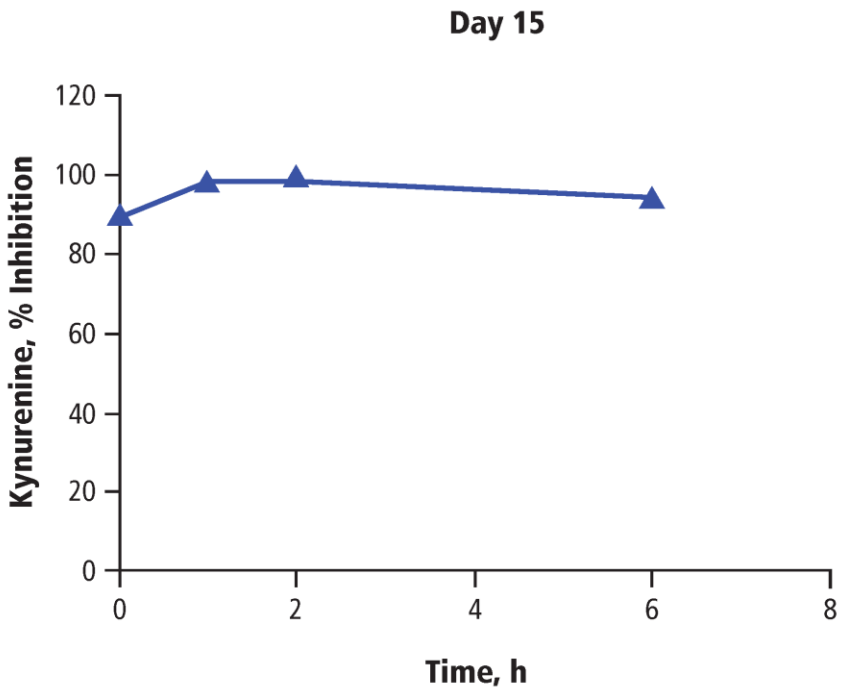

Mean (SE) Epacadostat Plasma Concentration, µM
10
1
0.1
0
2
4
6
8
10
12
Time, h

Figure 4.

A


Day 1
Kynurenine, % Inhibition
120
100
80
60
40
20
0
0
2
4
6
8
Time, h

B


Day 15
Kynurenine, % Inhibition
120
100
80
60
40
20
0
0
2
4
6
8
Time, h

SUPPLEMENT

Table 1. Dose Interruptions, Continuations, and Reductions

Adverse Event	CTCAE 4.03 Grade	Action with Respect to Epacadostat
Non-irAE clearly not related to underlying malignancy or intercurrent illness	3	Interrupt until event is resolved to ≤ grade 1; restart after a dose reduction to 400 mg BID[a]
Non-irAE clearly not related to underlying malignancy or intercurrent illness	3 (second occurrence of same event after restart at lower dose)	Discontinue treatment and withdraw from study; treat symptomatically; schedule follow-up visit
Non-irAE clearly not related to underlying malignancy or intercurrent illness	4	Discontinue treatment and withdraw from study; schedule follow-up visit
Immune-mediated AE[b] such as enterocolitis, hepatitis, neuropathies or dermatitis	2	Interrupt until event is resolved to ≤ grade 1; restart after a dose reduction to 400 mg BID[a]
Any immune-mediated AE[b]	3 or higher	Discontinue treatment and withdraw from study (except endocrinopathies)[c]; treat symptomatically; schedule follow-up visit
Immune-mediated, vision threatening ocular manifestations such as uveitis, episcleritis and iritis	2 or higher	Discontinue treatment and withdraw from study; treat symptomatically; schedule follow-up visit

AE, adverse event; ANA, antinuclear antibody; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; irAE, immune-related adverse event; SMA, smooth muscle antibody.
[a]If necessary a 2nd dose reduction to 300 mg BID is permitted if the event recurs. However only 2 dose reductions are permitted and if a second dose reduction is required this must be discussed with the medical monitor before resuming treatment.
[b]Immune-related AEs include (but are not limited to) rash/mucositis (including diffuse maculopapular rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations), enterocolitis, autoimmune hepatitis (including positive ANA and SMA), endocrinopathies (including thyroiditis with either hypo- or hyperthyroidism, hypophysitis, and either adrenal insufficiency or Cushing's syndrome), neuropathy (including peripheral motor or sensory neuropathy as well as Guillain-Barré syndrome), ocular events (uveitis, episcleritis, or iritis), pancreatitis, and sarcoid-like syndrome (diffuse lymphadenopathy with non-caseating granulomas on biopsy). Other etiologies for organ dysfunction should be ruled out as part of the evaluation.
[c]Subjects who develop immune-related endocrinopathies may resume therapy once replacement therapy has been initiated.

SUPPLEMENT

Table 2. Patient Disposition (mITT Population)

Disposition Status, n (%)	Epacadostat 600 mg BID (n=22)	Tamoxifen 20 mg BID (n=20)	Total (N=42)
Patients who discontinued study drug	22 (100)	20 (100)	42 (100)
Primary reason for discontinuation from study drug[a]			
Disease progression	10 (45.5)	11 (55.0)	21 (50.0)
Adverse event	6 (27.3)	0	6 (14.3)
Termination by the sponsor	6 (27.3)	9 (45.0)	15 (35.7)

BID, twice daily; mITT, modified intent-to-treat.

[a]No patients withdrew from the study for reasons of death, consent withdrawal, protocol deviation, lost to follow-up, noncompliance, patient decision, investigator decision, pregnancy, lack of efficacy, physician decision, missing, or other.

SUPPLEMENT

Table 3. CA-125 Response Rate (mITT Population)

	Epacadostat 600 mg BID (n=22)	Tamoxifen 20 mg BID (n=20)	*P* Value[a]
CA-125 response, n (%)			
Total evaluable patients	20 (90.9)	19 (95.0)	
Confirmed response	1 (5.0)	3 (15.8)	0.342
Unconfirmed response[b]	2 (10.0)	2 (10.5)	
Non-responders	17 (85.0)	14 (73.7)	
Patients with normal CA-125 postbaseline, n (%)	1 (4.5)	4 (20.0)	
Mean (range) best change from baseline in CA-125, %	36.6 (−78.2 to 359.1)	59.9 (−93.7 to 914.4)	

BID, twice daily; mITT, modified intent-to-treat.
[a]Calculated based on the Fisher exact test comparing the overall response rate between epacadostat and tamoxifen.
[b]Patients with a decreased CA-125 response that was not confirmed at a second time point.

SUPPLEMENT

Table 4. Protein Expression in Archival Tumour Biopsy Tissue Samples

Protein Expression, n	IDO1-Positive	IDO1-Negative	Total
PD-L1–positive	11	0	11
PD-L1–negative	18	2	20
PD-L1–not evaluable	1	0	1
Total	30	2	32

IDO1, indoleamine 2,3-dioxygenase-1; PD-L1, programmed death-ligand 1.