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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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HIGHLIGHTS

- Epacadostat monotherapy was evaluated in biochemically recurrent ovarian cancer.
- Immune-related adverse events were manageable and predominantly low grade.
- No significant efficacy difference between epacadostat and tamoxifen was observed.
- IDO1/PD-L1 coexpression supports evaluation of IDO1 plus checkpoint inhibitors.

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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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1. 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.

2. Methods

2.1. 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.

2.2. 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.

2.3. Endpoints and assessments

The primary endpoint was efficacy by investigator-assessed progression-free survival (PFS; RECIST v1.1). Per RECIST v1.1,

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