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CLINICAL TRIAL PROTOCOL

OPERA: a phase II trial of oregovomab plus non-platinum chemotherapy in PARP inhibitor/platinum-resistant ovarian cancer

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ABSTRACT

A consensus regarding subsequent therapeutic strategies for patients with platinum- and poly (ADP-ribose) polymerase inhibitor (PARPi)-resistant ovarian cancer is lacking. These patients typically receive non-platinum-based chemotherapy; however, survival outcomes remain poor. Compared with chemotherapy alone, combination therapy with novel target agents can provide additional benefits to these patients. Oregovomab, an investigational murine monoclonal antibody against CA-125, has shown promising efficacy in a phase II study in patients with recurrent ovarian cancer. Herein, we described the rationale and design of OPERA/KGOG 3065/APGOT-OV6, a multicenter, investigator-initiated, two-cohort, single-arm phase II trial, aimed at examining the efficacy of oregovomab plus non-platinum-based chemotherapy in patients with PARPi/platinum-resistant ovarian cancer. The primary end point was the objective response rate, according to RECIST 1.1.
Clinical Trial Registration: NCT05407584 (ClinicalTrials.gov)

PLAIN LANGUAGE SUMMARY

OPERA/KGOG 3065/APGOT-OV6 is a promising phase II studies that test new drug (oregovomab) on the patients with poly (ADP-ribose) polymerase inhibitor (PARPi)/platinum-resistant epithelial ovarian cancer. PARPis have changed the treatment landscape of ovarian cancer in a relatively short time. PARPi/platinum-resistant epithelial ovarian cancer refer to a subtype of recurrent epithelial cancer of ovarian, tubal or peritoneal origin who experienced disease progression despite treatment with a PARPi or platinum-based chemotherapy drugs. Although various new drugs have been tested to improve the treatment response in resistant patients, a consensus regarding the international standard of treatment is yet to be established, despite the poor survival outcomes of these patients. OPERA/KGOG 3065/APGOT-OV6 has been designed to add oregovomab, a murine monoclonal antibody to cancer antigen-125 (CA-125), to non-platinum chemotherapy (pegylated liposomal doxorubicin or paclitaxel) for patients with ovarian cancer determined as PARPi/platinum-resistant and ineligible for bevacizumab treatment. The results of this study will aid in developing effective treatment strategies for patients with PARPi/platinum-resistant ovarian cancer.

TWEETABLE ABSTRACT

OPERA/KGOG 3065/APGOT-OV6: a multicenter, investigator-initiated, two-cohort, single-arm phase II trial, aimed at examining the efficacy of oregovomab plus non-platinum-based chemotherapy in patients with poly (ADP-ribose) polymerase inhibitor/platinum-resistant ovarian cancer.

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Antibody anti-CA125; indirect immunization; oregovomab; ovarian neoplasms; recurrence; resistant

1. Background

1.1. Background & rationale

Epithelial ovarian cancer (EOC) is the most fatal gynecological cancer, accounting for more than 200,000 deaths annually worldwide [1]. Most patients present with advanced disease at diagnosis and undergo platinum-based chemotherapy and cytoreductive surgery [2]. Despite considerable progress in treatment strategies, most patients with advanced EOC relapse and eventually develop resistance to therapy, following a frequent relapse–response pattern [3]. Traditionally, platinum resistance has been defined based on the duration of the response to platinum-containing chemotherapy. Patients with a treatment-free interval of less than 6 months are classified as platinum-resistant and generally treated with non-platinum-based chemotherapy [4]. However, the current classification of platinum resistance has several limitations. In the era of maintenance therapy, the use of bevacizumab or poly-ADP-ribose polymerase

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inhibitors (PARPi) for patients responding to recent platinum chemotherapy was shown to substantially prolong progression-free survival (PFS) [5–13], rendering the evaluation of platinum response difficult. Furthermore, for patients experiencing recurrence following PARPi maintenance therapy, the platinum-free interval was not predictive of PFS for subsequent therapy [14,15]. Furthermore, a poor response to subsequent platinum-based treatment has been documented in patients who relapse after PARPi maintenance therapy [14–17]. These results support the hypothesis that platinum chemotherapy and PARPi have similar resistance mechanisms. Growing evidence suggests that PARPi resistance is related to platinum resistance [16,18]. Therefore, patients who experience disease progression despite PARPi maintenance therapy within 6–12 months after remission may be categorized as having PARPi-resistant or platinum-resistant disease.

The current management of platinum-resistant disease involves non-platinum chemotherapy, including pegylated liposomal doxorubicin (PLD) [19,20], weekly paclitaxel chemotherapy [21,22], gemcitabine [20] or topotecan alone [19,21,23]. The efficacy rate in most patients is approximately 10–20%, with a median PFS of 3–4 months and a median overall survival (OS) of 9–12 months [24,25]. Bevacizumab, a monoclonal antivascular endothelial growth factor-A antibody, has been investigated and widely adopted for treating recurrent ovarian cancer based on the results of the phase III AURELIA trial [26]. The AURELIA trial revealed that combining non-platinum chemotherapy (weekly paclitaxel, liposomal doxorubicin and topotecan) with bevacizumab could markedly increase the objective response rate (ORR; 11.8 vs 27.3%) and improve median PFS (3.4 vs 6.7 months) [26]. Therefore, bevacizumab combined with PLD, weekly paclitaxel or topotecan has been approved for treating patients with platinum-resistant disease who have received no more than two previous lines of chemotherapy. However, there are no effective therapeutic options for patients with ovarian cancer who are PARPi/platinum-resistant and ineligible for bevacizumab treatment. Therefore, there is an urgent need to establish additional therapeutic options for this patient population.

Oregovomab is a murine monoclonal antibody specifically targeting cancer antigen (CA)-125. Oregovomab activates humoral and cellular immune responses by enhancing antigen uptake and cross-presentation to T cells. Oregovomab has been investigated in phase II trials in newly diagnosed or recurrent ovarian cancer (Table 1). In the recurrence setting, 20 patients received oregovomab before and concurrently with standard chemotherapy. The median progression-free interval was 11 weeks (2.6–114.6 weeks), and the median OS was 70.4 weeks (4.6–141.6 weeks). Patients with a T-cell response to CA125 and/or autologous tumors had substantially improved survival [27]. In a phase II pilot trial, 30 patients with recurrent ovarian cancer received oregovomab without concomitant chemotherapy. Although no complete or partial responses were observed, three of the 13 patients experienced stable disease for over 2 years with robust immune responses [28].

Based on the potential efficacy of oregovomab, an international phase III randomized trial was conducted in a frontline ovarian cancer maintenance setting. However, the primary end point, time to recurrence, was not significant [32]. More recently, a phase III, double-blind, placebo-controlled, multicenter FLORA-5 study comparing the efficacy of oregovomab and placebo in combination with a standard regimen of paclitaxel and carboplatin in frontline advanced EOC is ongoing [33]. However, no study has explored the efficacy of oregovomab, particularly in combination with non-platinum chemotherapy, in patients with PARPi/platinum-resistant EOC.

1.2. Objectives

Based on the immunogenic activity of PLD and paclitaxel observed in previous studies [34,35], we hypothesized that the addition of oregovomab would enhance the efficacy of PLD or weekly paclitaxel. Accordingly, in OPERA/KGOG 3065/APGOT-OV6, we plan to investigate the efficacy of oregovomab plus non-platinum-based chemotherapy in patients with PARPi-resistant EOC unsuitable for platinum-based therapy.

1.3. Trial design

The OEPRA is a multicenter, investigator-initiated, two-cohort, single-arm phase II trial to evaluate the efficacy and safety of oregovomab in combination with PLD or weekly paclitaxel in patients with PARPi-resistant EOC deemed ineligible for platinum-based chemotherapy (NCT05407584). Patients who received one to three prior lines of chemotherapy will be assigned to Cohort 1 (oregovomab 2 mg [C1,2,3,5,7 for five doses] + PLD 40 mg/m^2 q4w, n = 28), whereas patients who received more than three prior lines of chemotherapy will be assigned to Cohort 2 (oregovomab 2 mg [C1,2,3,5,7 for five doses] + weekly paclitaxel 80 mg/m^2 [D1,8,15 q4w], n = 28) (Table 2). In total, 56 patients will be recruited and treated with oregovomab + PLD/weekly paclitaxel until disease progression, unacceptable toxicity, or withdrawal of patient consent (Figure 1). The primary end point is the ORR, according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. This study plans to enroll a total of 56 subjects from four sites in South Korea.

Table 1. Published phase II and III clinical trials evaluating oregovomab.

Trial	Phase	Number of patients	Setting	Primary end point	Clinical results	Refs.
Berek et al. 2004	II	145	Maintenance first-line	TTR	13.3 vs 10.3 months (oregovomab vs placebo, $p = 0.71$)	[29]
Braly et al. 2009	II	40	Concomitant or maintenance first-line	Antibody response to oregovomab	SIM arm: mPFS 17.9 months, 12-month PFS 89%; OWD arm: mPFS 16.1 months, 12-month PFS 60%	[30]
Brewer et al. 2020	II	97	Concomitant first-line	Translational assessment of a cellular immune response	mPFS: 41.8 months for CPO vs 12.2 months for CP ($p = 0.0027$, HR 0.46, CI 0.3–0.7).	[31]
Gordon et al. 2004	II	20	Recurrent disease with or without chemotherapy	Humoral and cellular immune responses	mPFI: 11 weeks (2.6–14.6); Median survival 70.4 weeks (4.6–41.6) Significantly improved survival ($p = 0.002$) in patients with a T-cell response to CA125 and/or autologous tumor.	[27]
Ehlen et al. 2005	II	13	Recurrent disease without chemotherapy	Objective clinical response	Stable disease and survival >2 years in 3/13 patients associated with robust immune responses; Median survival: 37 weeks (11–110).	[28]
Berek et al. 2009	III	373	Maintenance first-line	TTR	mTTR 10.3 months for oregovomab vs 12.9 months for placebo ($p = 0.29$)	[32]

CI: Confidence interval; CP: Carboplatin + paclitaxel; CPO: Carboplatin + paclitaxel + oregovomab; HR: Hazard ratio; mPFI: Median progression-free survival; mPFS: Median progression-free survival; NE: Non-evaluable; OWD: One week delayed; SIM: Simultaneous infusion; TTR: Time to relapse.

Table 2. Trial treatment.

Drug	Dose/potency	Dose frequency	Route of administration	Regimen/treatment period
Oregovomab	2 mg	5 doses	iv. infusion	Day 1 of each 1,2,3,5,7 cycle
PLD	40 mg/m^2	Q4W	iv. infusion	Q4W; Day 1 of each 4-week cycle
Paclitaxel	80 mg/m^2	D1,8,15 Q4W	iv. infusion	Q4W; Day 1, 8, 15 of each 4-week cycle

iv.: Intravenous; PLD: Pegylated liposomal doxorubicin; Q4W: Every 4 weeks.

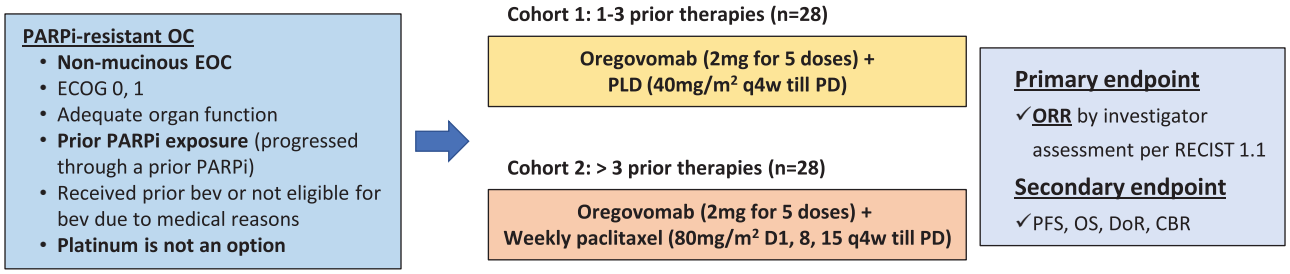

Figure 1. Trial scheme.
Bev: Bevacizumab; CBR: Clinical benefit rate; DoR: Duration of response; ECOG: Eastern Cooperative Oncology Group; EOC: Epithelial ovarian cancer; ORR: Objective response rate; OS: Overall survival; OV: Ovarian cancer; PARPi: Poly (ADP-ribose) polymerase inhibitor; PD: Progressive disease; PFS: Progression-free survival; PLD: Pegylated liposomal doxorubicin.

2. Methods

2.1. Study setting

The OPERA/KGOG 3065/APGOT-OV6 is a multicenter, investigator-initiated, two-cohort, single-arm phase II trial.

2.2. Eligibility criteria

Inclusion/exclusion criteria for enrollment are presented in Table 3. Briefly, the trial will include patients with CA125-associated advanced, recurrent epithelial cancer of ovarian, tubal or peritoneal origin who experienced disease progression despite treatment with a PARPi, received prior bevacizumab or were ineligible for bevacizumab. There is no upper limit on the number of previous chemotherapy courses received. Participants must have adequate organ function, and all screening laboratory tests should be performed within 10 days prior to the start of the study treatment.

Table 3. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
► Age ≥20 years ► Epithelial adenocarcinoma of ovarian, fallopian tube or peritoneal origin. ► Histology: HGSC, high grade endometrioid adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma and low-grade adenocarcinoma or adenocarcinoma not otherwise specified (only up to five patients with non-HGSC will be included) ► Prior PARP inhibitor exposure • Progressed through a prior PARP inhibitor ► CA-125 ≥50 U/ml ► Prior platinum-based chemotherapy. • Cohort 1: 1–3 prior lines of therapies • Cohort 2: 4th line or more lies of therapies ► Not eligible for platinum re-treatment • Previous allergic reactions or residual toxicity • Patients not able to receive further platinum, or not willing to receive further platinum • Platinum-resistant patients ► Received prior bevacizumab or not eligible for bevacizumab due to medical reasons ► Adequate bone marrow and organ function ► ECOG performance status 0–1 ► Informed consent	► Histology: mucinous, germ line or borderline tumor ► Active autoimmune disease ► Known allergy to murine proteins ►Hypersensitivity to PLD ►Chronic therapeutic corticosteroid use • >5 days of prednisone or equivalent ► Known additional malignancy that is progressing or has required active treatment within the past 2 years. ► Contraindications to the use of pressor agents ► Clinically significant active infection(s) at the time of screening ► Any of the following cardiovascular conditions • Acute myocardial infarction within 6 months before the first dose of study treatment. • Current history of NYHA Class III or IV heart failure. • Evidence of current uncontrolled cardiovascular conditions ► Uncontrolled or life-threatening diseases compromising safety evaluation ► Inability to attend or comply with treatment of follow-up scheduling ► Unable to read or understand or unable to sign the necessary written consent before starting treatment

ECOG: Eastern Cooperative Oncology Group; HGSC: High-grade serous adenocarcinoma; NYHA: New York Heart Association; PLD: Pegylated liposomal doxorubicin.

2.3. Interventions

Cohort 1 will receive oregovomab 2 mg (C1,2,3,5,7 for five doses) + PLD 40 mg/m^2 q4w, n = 28. Cohort 2 will receive oregovomab 2 mg (C1,2,3,5,7 for five doses) + weekly paclitaxel 80 mg/m^2 (D1,8,15 q4w).

2.4. Outcomes

The primary end point is an investigator-assessed ORR, according to RECIST 1.1. ORR is defined as the proportion of patients with a partial or complete response to therapy. Analyses will be performed when all enrolled patients have completed 6 months of follow-up and/or when investigator-performed response assessments have been completed. Secondary end points include PFS, OS, time to first subsequent therapy, PFS2, duration of response and safety. PFS (time frame: up to 1 year) is defined as the time from the start of treatment to disease progression or death from any cause. OS (timeframe: up to 1 year) is defined as the date of study enrollment to the date of death due to any cause. Patients without an event will be censored at the date they were last assessed at a clinic or were known to be alive. Time to first subsequent therapy is defined as the time from initiating first-line chemotherapy to starting subsequent therapy or death. PFS2 is defined as the time from the enrollment date to the first documented progression of next-line therapy or death from any cause, whichever occurs first. Duration of response is defined as the time from randomization to disease progression or death in patients who achieve a complete or partial response.

For exploratory end points, comprehensive genomic profiling and immune biomarker exploration will be performed on all samples to identify predictive biomarkers for combination therapy with oregovomab + PLD or oregovomab + paclitaxel. Archival tissue, pretreatment biopsy and post-progression biopsy will also be collected. Additionally, the humoral immune response will be assessed by measuring human antimouse antibodies at time points specified in the protocol. Peripheral blood mononuclear cells will be collected at time points specified in the protocol and analyzed using multicolor flow cytometry to evaluate dynamic changes in immune properties during treatment.

2.5. Statistical methods

For platinum-resistant EOC with conventional monotherapy, the assumed ORR is 10% [20,25,36]. This rate was expected to increase to 30% with the addition of oregovomab (a combination of oregovomab + PLD/weekly paclitaxel). Using a single-stage phase II design with a one-sided 5% level of significance and 80% statistical power, a minimum sample size of 25 is required. Considering subjects whose treatment is discontinued before sufficient assessment of tumor response and a follow-up loss rate of 10%, a total of 28 patients are needed in each cohort. Therefore, the total sample size for this study is expected to be 56. Survival analyses will be performed

using Kaplan–Meier plots and Cox regression analyses to generate hazard ratios, along with a log-rank test on the modified intent-to-treat approach (patients should receive at least one treatment dose). Safety analyses will be based on the safety population (participants treated with at least one dose of the study drug). Adverse events will be graded according to the Common Terminology Criteria for Adverse Events version 5.0.

3. Conclusion

Most patients with EOC typically receive PARPi or bevacizumab as first-line or second-line maintenance therapy to prevent recurrence. However, certain patients experience disease progression despite maintenance therapy, become PARPi/platinum-resistant and show a dismal response to subsequent therapy. Given the expanded clinical use of PARPi and the fact that platinum resistance is the primary contributor to mortality in patients with EOC, effective subsequent therapeutic options are urgently needed for patients who are PARPi/platinum-resistant and ineligible for bevacizumab treatment.

Accordingly, we designed a phase II, multicenter, investigator-initiated, two-cohort study, OPERA/KGOG 3065/APGOT-OV6 (NCT05407584) to assess oregovomab plus non-platinum-based chemotherapy in patients with PARPi/platinum-resistant EOC. The results of this study will provide novel insights into the antitumor efficacy and safety profile of oregovomab plus non-platinum chemotherapy in recurrent patients with PARPi/platinum-resistant EOC.

Article highlights

- Subsequent therapeutic strategies for patients with platinum- and poly (ADP-ribose) polymerase inhibitor (PARPi)-resistant ovarian cancer are to be established.
- Oregovomab, a murine monoclonal antibody specifically targeting cancer antigen (CA)-125, has shown promising efficacy in patients with recurrent ovarian cancer, achieving a median progression-free interval of 11 weeks and median overall survival of 70.4 weeks.
- The efficacy of oregovomab in combination with non-platinum chemotherapy for patients with PARPi/platinum-resistant epithelial ovarian cancer (EOC) remains unexplored.
- The OPERA/KGOG 3065/APGOT-OV6 is designed to investigate the efficacy of oregovomab plus non-platinum-based chemotherapy in patients with PARPi-resistant EOC unsuitable for platinum-based therapy.
- The findings of this trial will afford novel insights into the antitumor efficacy and safety profile of oregovomab plus non-platinum chemotherapy in patients with PARPi-resistant EOC.

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Author contributions

J-Y Lee is the principal investigator. The study was designed by J-Y Lee. J-Y Lee and J Park acquired the funding. HW Cho, MC Lim, CH Choi and J-Y Lee recruited study participants and aided in data collection. J Park wrote original draft. All other authors contributed to the writing and review of the manuscript. The corresponding author had final responsibility for the decision to submit for publication on behalf of the collaborative authors' group. All authors were not precluded from accessing data in the study, and they accept responsibility to submit for publication. All authors have read and approved the final manuscript.

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Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that the protocol has been approved by each participating institutional review board (IRB) before initiating patient accrual at each institution: IRB of Yonsei University (No. 4-2022-0430), IRB of Korea University Guro Hospital (No. 2023GR0068), IRB of National Cancer Center (No. NCC2023-0162) and IRB of Samsung Medical Center (No. 2022-04-006). The study will be performed in accordance with the ethical principles of the Declaration of Helsinki and conducted in adherence to the study protocol, applicable Good Clinical Practices and applicable laws and country-specific regulations in which the study is being conducted. Written informed consent will be obtained from all patients before any study-related procedures are conducted.

Data availability statement

The raw clinical and imaging data are protected by patient privacy laws. The datasets generated and/or analyzed during the study are available from the corresponding author, J-Y Lee,

on request, and de-identified clinical data and experimental data are available on request sharing, which will require the approval of the institutional ethical committees. De-identified data will then be transferred to the investigator via secure file transfer.

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