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STUDY PROTOCOL

Efficacy and Safety of Low-Dose Lenvatinib and Toripalimab in Patients With Recurrent Platinum-Resistant Ovarian Cancer: Study Protocol of a Multicenter, Open-Label, Single-Arm, Phase II Clinical Trial

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Purpose: Therapeutic options for patients with platinum-resistant ovarian cancer (PROC) remain a major unmet need. PROC patients with multiple recurrences are unable to continue highly toxic treatment after prior multiple lines of systemic therapy. Chemotherapy-free option lenvatinib plus anti-programmed cell death protein-1 (PD-1) combination therapy has shown promising results in several malignancies including ovarian cancer, but the toxicity of a high starting dose of lenvatinib is also notable and needs to be improved. Our previous pilot study indicated that a reduced starting dose of lenvatinib may maintain comparable anti-tumor activity with favorable safety in heavily pre-treated ovarian cancer. This study is designed to further validate the efficacy and safety of the combination therapy of low-dose lenvatinib and PD-1 inhibitor toripalimab in patients with recurrent PROC.

Study Design and Methods: The study is designed as a multicenter, open-label, single-arm, prospective phase II study. Patients with recurrent epithelial ovarian cancer who have disease progression either during or within 6 months after completion of platinum-based therapy will be included. A total of 69 participants will receive low-dose lenvatinib (8 mg or 12 mg, daily, orally, based on patient's body weight) and toripalimab (240 mg, every 21 days, intravenously). Treatment will continue until the development of unacceptable toxicity or disease progression. The primary endpoint is the progression-free survival. The secondary endpoints include objective response rate, duration of response, disease control rate, overall survival, toxicity and patients' quality of life. Exploratory objectives aim to identify biomarkers and molecular signatures for predicting response or prognosis.

Keywords: ovarian cancer, platinum-resistant, immune checkpoint inhibitor, lenvatinib, dose adjustment

Introduction

Following an initial diagnosis and treatment with platinum-based chemotherapy, over 70% of patients with ovarian cancer will experience recurrence and eventual treatment resistance[1]. Patients with a platinum-free interval less than 6 months are considered to have platinum-resistant ovarian cancer (PROC). The mainstay of treatment for PROC has been the sequential use of non-platinum cytotoxic agents with monotherapy activity. In general, the reported response rates

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have been 10–15%, with short progression-free survival (PFS; <4 months) and overall survival (OS; <12 months)[2]. The AURELIA study established the addition of bevacizumab to chemotherapy as a standard of care in PROC, although it only improved PFS (median 6.7 months with bevacizumab-containing therapy vs 3.4 months with chemotherapy alone) instead of OS[3].

For patients with recurrent PROC who have undergone multiple lines of non-platinum chemotherapy, therapeutic options have been a significant challenge. Due to the cumulative toxicity of chemotherapy, including neutropenia, alopecia and neuropathy, patients are unable to continue receiving related treatments[4]. In light of these considerations, treatment paradigms are evolving to encompass non-chemotherapy options. Several emerging therapies, including anti-angiogenic agents, immune checkpoint inhibitors, human epidermal growth factor receptor 2 inhibitors, and agents targeting DNA damage response and cell-cycle pathways have shown mild to moderate activity in the platinum-resistant setting with response rates of 10–30%[5]. Most recently, an antibody–drug conjugate targeting folate receptor α mirvetuximab soravtansine has shown a significant benefit over chemotherapy with respect to PFS (median 5.62 vs 3.98 months) and OS (median 16.46 vs 12.75 months) among PROC patients[6], but only in those with high folate receptor α tumor expression (approximately 35–40%)[7].

Over the past several years, the combination of lenvatinib and pembrolizumab has demonstrated satisfactory anti-tumor activity in multiple types of solid tumors[8]. In the case of gynecological malignancies, the Study 309/KEYNOTE-775, which investigated the combination of lenvatinib and pembrolizumab in advanced/recurrent endometrial cancer, demonstrated significant improvements in both PFS and OS compared with chemotherapy, leading to the approval[9]. The related data concerning this combination therapy in ovarian cancer is rarely reported, with only case reports[10,11] and small-scale studies[12]. The preliminary efficacy data indicate that this combination therapy shows promise for treating recurrent or platinum-resistant ovarian cancer, warranting further investigation in larger clinical studies. Several prospective clinical trials are currently ongoing, including NCT04519151 for platinum-sensitive recurrent disease, NCT05114421 for platinum-resistant serous carcinoma, and NCT05296512 for recurrent and persistent clear cell ovarian cancer, though their results are pending[13].

However, it is noteworthy that the most commonly utilized dosage of lenvatinib in the context of gynecological tumors is 20 mg, including both completed and ongoing trials in ovarian cancer. This initial dosage has been associated with a high incidence of adverse events, causing drug interruption or discontinuation. In the KEYNOTE-775 trial, 66.5% of enrolled patients experienced dose reductions of lenvatinib, and 30.8% of patients discontinued lenvatinib due to adverse events[9]. A systematic review indicates that the increased toxicity associated with this combination primarily stems from lenvatinib[8]. How et al[14] reviewed the toxicity and efficacy of pembrolizumab in combination with lenvatinib in recurrent endometrial cancer between the recommended dose (20 mg) and reduced dose (<20 mg) of lenvatinib. There were no significant differences between the two dose cohorts with respect to response rates, PFS, or OS. Consequently, it is imperative to investigate the feasibility of low-dose lenvatinib.

Based on the aforementioned observations, this prospective, phase II study is primarily designed to determine the efficacy and safety outcomes of low-dose lenvatinib in combination with toripalimab in patients with recurrent PROC, who have limited therapeutic options. The goal is to provide an effective, chemotherapy-free treatment option with low toxicity for such patients.

Methods

Trial Design and Setting

This is a multicenter, open-label, single-arm, prospective phase II trial of lenvatinib combined with China-made PD-1 inhibitor toripalimab in recurrent PROC. The eligible patients will receive combination treatment with low-dose lenvatinib (8 or 12 mg, based on patient's body weight) orally once daily plus toripalimab intravenously 240 mg every 3 weeks. We will use the PFS as the primary endpoint and objective response rate (ORR), duration of response (DoR), disease control rate (DCR), overall survival (OS), AEs and patients' quality of life (QoL) as secondary endpoints. The study design is illustrated in Figure 1.

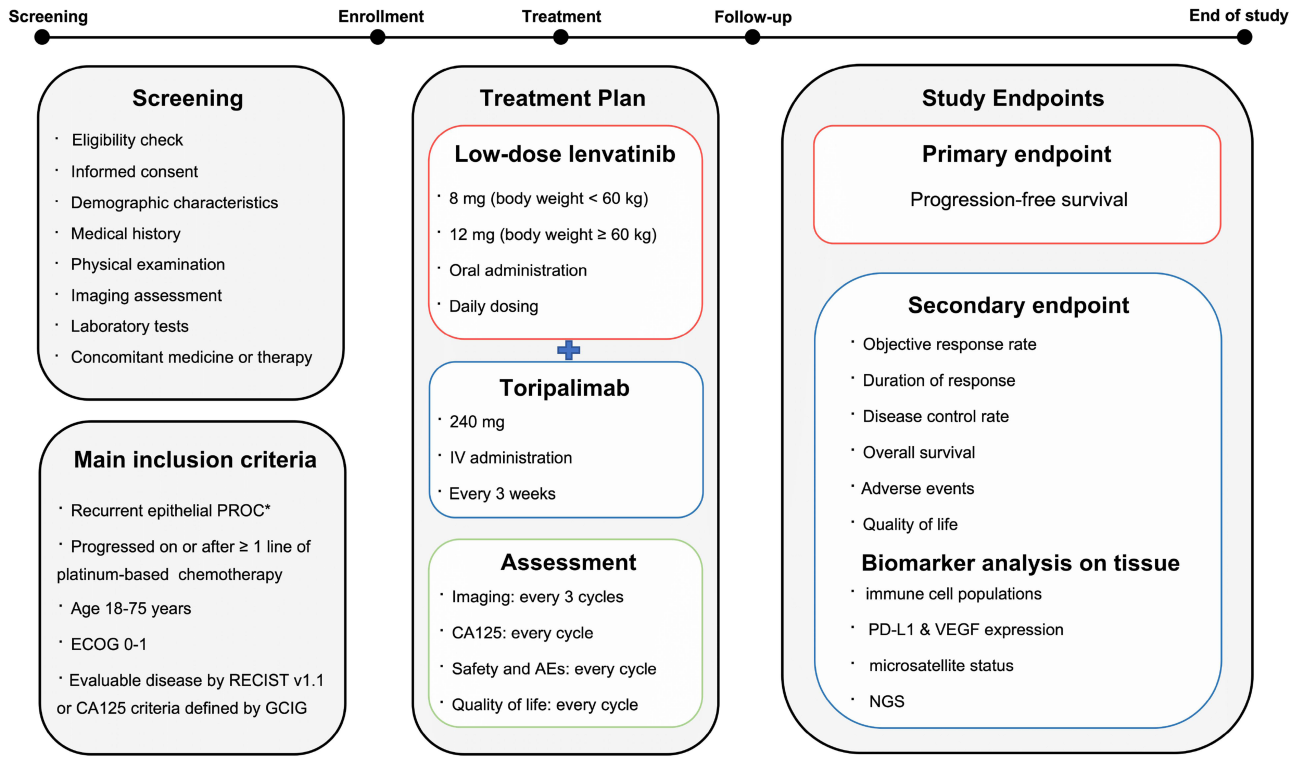

Figure 1 Study design. *Recurrent primary peritoneal cancer and fallopian tube cancer resistant to platinum-based chemotherapy will also be included and collectively referred to as platinum-resistant ovarian cancer.
Abbreviations: PROC, platinum-resistant ovarian cancer; ECOG, Eastern Cooperative Oncology Group; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; GCIG, Gynecological Cancer Intergroup; IV, intravenous; AE, adverse event; PD-L1, programmed cell death ligand 1; VEGF, vascular endothelial growth factor; NGS, next-generation sequencing.

The protocol has been registered on the NIH Clinical Trials database (www.clinicaltrials.gov/, NCT06241105. Registered on 2024/02/05). The trial is investigator initiated by the Department of Obstetrics and Gynecology, Peking Union Medical College Hospital. Three other major medical centers in China are involved in the study. This study will be conducted in compliance with Declaration of Helsinki principles. Before enrolment of the first patient, the study protocol has been approved by the Ethics Committee of all these research centers and all patients provided written informed consent before enrolment. Recruitment is ongoing and is expected to continue until December 2025.

Patient and Public Involvement

Neither patients nor public will be involved in the design, recruitment, outcome measures, and conduct of the study. The findings from the analysis of the trial will be disseminated through scientific and professional conferences, and published in peer-reviewed journals.

Patient Selection

Inclusion in the trial requires that certain tumor and patient criteria are met. The key inclusion and exclusion criteria are as follows.

Inclusion Criteria

- Female 18–75 years of age;
- Histologically confirmed recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer resistant to platinum-based chemotherapy; disease progression during platinum-based therapy or have disease recurrence within 6 months from the date of the last dose of platinum, are defined as platinum-resistant; the assessment of disease progression or recurrence before trial enrollment is based on imaging criteria Response

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Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) or CA125 progression criteria defined by the Gynecological Cancer Intergroup (GCIG)[15];

- Have received at least one line of platinum-based chemotherapy and shown evidence of disease recurrence;
- To have at least one measurable lesion according to RECIST v1.1, or measurable CA125 level (≥70 IU/L) in accordance with GCIG definitions for response in ovarian cancer trials using CA125;
- Eastern Cooperative Oncology Group performance status from 0 to 1;
- Expected survival time > 3 months;
- Willing to participate in this study and signed the informed consent.

Exclusion Criteria

- Poor blood pressure control despite medication: systolic > 140 mmHg or diastolic > 90 mmHg;
- Radiographic evidence of major blood vessel invasion or infiltration;
- Clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug;
- Serious nonhealing wound, ulcer, fistula, or bone fracture;
- The active autoimmune disease requires a systemic treatment or patients requiring treatment with systemic corticosteroids;
- Baseline blood and biochemical indicators do not meet the following criteria: hemoglobin ≥ 80 g/L; absolute neutrophil count ≥ 1.5×10^9/L; platelets ≥ 100×10^9/L; alanine aminotransferase and aspartate aminotransferase ≤ 2.5 × the upper limit of normal (ULN); serum total bilirubin ≤ 1.5 × ULN; serum creatinine ≤ 1.5 × ULN;
- Serious medical illness, such as severe mental disorders, cardiac disease, uncontrolled infection;
- Pregnancy or breastfeeding women;
- Allergic to any component of the therapy.

Interventions

Eligible patients will receive treatment with lenvatinib mesilate capsule (Geruite®, CSPC Ouyi Pharmaceutical Cooperation, China) orally 8 mg once daily (21 days as a cycle) at the beginning of enrollment. Following a 7-to-14-day interval, they will receive toripalimab intravenously 240 mg in a 3-week cycle. Throughout the course of treatment, adjustments should be made exclusively to the dosage of lenvatinib. The starting dosage for lenvatinib is 8 mg, which can be escalated to 12 mg for patients weighing over 60 kg if no adverse reactions are observed in the first four weeks. For individuals weighing less than 60 kg, the maximum dosage of lenvatinib is 8 mg once daily. If AEs occur and cannot be relieved by supportive care, the dosage of lenvatinib is permitted to be reduced to a minimum dose of 4 mg per day. If the toxicity is still intolerable at the lowest dose level, lenvatinib is discontinued permanently. Toripalimab can be administered for up to two years, with a total of 35 cycles. If AEs, abnormalities in laboratory tests or other comorbidities occur during treatment, toripalimab will be delayed or suspended. For patients who respond to treatment for two years, treatment will be discontinued for those who achieve complete response, while those who achieve partial response will continue to receive lenvatinib monotherapy.

The treatment termination criteria will be as follows: (1) disease progression during treatment; (2) encounter intolerable toxicity; (3) request to withdraw from the cohort of this study due to various reasons; (4) accompanied by other non-tumor diseases make the patient unable to accept this treatment plan; (5) investigator decision to terminate treatment. The reasons for discontinuing treatment will be documented in the patient's medical records.

Endpoints and Measurements

The primary endpoint is investigator-assessed PFS, defined as the time from the treatment initiation to disease progression or death. This will be assessed either by radiographic imaging according to RECIST v1.1 for patients with at least one measurable lesion, or by tumor marker CA125 response agreed by the GCIG for patients without measurable lesions. The changes in CA125 will be evaluated every cycle, and radiologic assessment will be performed every three cycles.

The secondary endpoints include ORR (the portion of patients achieved complete or partial response) by RECIST v1.1, DoR (time from the first evidence of response to disease progression or death, whichever occurred firstly), DCR (the rate of

patients who had best response of complete or partial response or stable disease lasting for at least 4 weeks), OS (time from the treatment initiation to the date of death or the last follow-up), AEs and patients' QoL. The following assessments are performed before each cycle: a complete blood cell count, measurement of liver and renal function, myocardial enzymogram, thyroid-related hormones, 12-lead electrocardiogram. AEs will be recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 after the first dose of therapeutic drugs to 30 days after the last dose. During treatment, toxicity will be assessed every cycle through summaries of AEs, changes in laboratory test results, vital signs, and exposure to the study drugs. The QoL of patients will be evaluated before each cycle using the Europe Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-C30.

Follow-up

Patients who discontinue treatment for reasons other than progressive disease will be followed until documentation of progressive disease or the start of a new anticancer therapy. All patients who discontinue treatment will be followed for survival every three months until death, loss to follow-up, or the end of the study. The follow-up contents include the physical examination, tumor marker examination and radiologic examination.

Biomarker Analysis

This analysis aims to identify biomarkers and molecular signatures that can predict treatment response or prognosis. Previously archived tumor tissue specimens will be collected before treatment, which will be used to explore immune cell populations and the expression of selected tumor markers, including programmed cell death ligand 1 expression, microsatellite status, and vascular endothelial growth factor expression. Tumor samples will also undergo next-generation sequencing analysis to generate comprehensive genomic profiles, examining key molecular alterations that may predict treatment response and clinical outcomes, including tumor mutation burden, homologous recombination deficiency status, and other potential genomic biomarkers.

Sample Size Calculation

According to the AURELIA trial, patients with PROC receiving non-platinum chemotherapy alone in the control group demonstrated a median PFS of 3.4 months[3]. Furthermore, two key studies have since explored lenvatinib plus anti-PD-1 combination in ovarian cancer: the LEAP-005 study using standard-dose lenvatinib achieved a median PFS of 4.4 months[12], while our recent pilot study exploring low-dose lenvatinib demonstrated a comparable median PFS of 4.1 months[16]. Building upon these data, we anticipate achieving a median PFS of 5 months with our modified low-dose approach in the current trial, which would not only maintain efficacy comparable to standard-dose combinations but also represent a meaningful improvement over historical chemotherapy outcomes. The sample size was calculated using a single-arm survival design. With a null hypothesis of median PFS = 3.4 months (based on the AURELIA trial control group) and an alternative hypothesis of median PFS = 5 months, using a one-sample Log rank test with 80% power (β = 0.2) at a two-sided significance level of 0.05, and considering a 10% dropout rate, a total of 69 patients will be required.

Statistical Analysis

The enrolled patients who receive at least one cycle of treatment drugs will be included in the efficacy and safety analysis. In general, patient characteristics will be reported as frequencies and percentages for categorical variables and medians and ranges for continuous variables. Time-to-event endpoints (PFS, OS, DoR) will be analyzed according to the Kaplan–Meier method, along with the two-sided 95% confidence interval (CI). The 95% CI of the ORR and DCR will be established using the Clopper–Pearson method. Cox univariate and multivariate analyses will be used to analyze the correlation between biomarker expression, clinical parameters and treatment prognosis. Given the known biological heterogeneity of different epithelial ovarian cancer subtypes, pre-planned subgroup analyses will be conducted to compare serous versus non-serous carcinomas with respect to treatment efficacy, safety profiles, and biomarker signatures. Outcomes with $p < 0.05$ are considered statistically significant. All related AEs will be described in a summary table.

All study-related information will be securely stored at the study site. Participants' information will be kept in locked file cabinets located in restricted-access areas. To maintain participant confidentiality, all laboratory specimens, reports, data collection, process, and administrative forms will be identified only by a coded identification number.

Data Management and Monitoring

The data collection and management will be achieved by researchers. The participants in the study and their personal data will be kept confidential. Although no formal futility interim analysis is planned given the previously demonstrated efficacy and safety of this combination, a comprehensive monitoring system will be implemented throughout the trial, including continuous safety assessment, regular efficacy evaluation, and quality control measures. The safety monitoring involves real-time review of AEs, with serious AEs being assessed within 24 hours. Efficacy will be evaluated through regular tumor response assessments and survival data monitoring. The study can be terminated early if unexpected severe toxicities occur, clear evidence of lack of efficacy emerges, or significant protocol violations are identified. The research-initiated institution Peking Union Medical College Hospital will periodically visit each participating center throughout the trial to ensure data submission, patient eligibility, and protocol compliance.

Discussion

This study represents the first prospective trial to gather evidence on the potential advantages of utilizing low-dose lenvatinib and anti-PD-1 combination therapy in recurrent PROC, reflecting a careful consideration of risks and benefits in the real-world clinical practice of this treatment combination.

In an in vivo model, lenvatinib substantially decreased tumor-associated macrophages and enhanced the activation of interferon-signaling pathway, leading to improved anti-tumor activity of PD-1 inhibitors[17]. Given the highly immunosuppressive tumor microenvironment characteristic of ovarian cancer, this combination therapy shows particular promise as a potential treatment strategy. Initial studies exploring the combination of lenvatinib, administered at a 20 mg starting dose, with PD-1 inhibitors have shown promising efficacy in ovarian cancer. Several case reports have documented durable responses to this combination in chemotherapy-resistant recurrent ovarian clear cell carcinoma[10,11]. In addition, the LEAP-005 study evaluated this combination in 31 patients with metastatic or unresectable ovarian cancer, demonstrating a median PFS of 4.4 months[12]. However, the study revealed significant safety concerns with the 20 mg starting dose of lenvatinib, as 68% of patients experienced grade 3–5 AEs, including treatment-related mortality. While lenvatinib has received regulatory approval for various solid tumors (including thyroid cancer, hepatocellular carcinoma, and renal cell cancer) with recommended starting doses ranging from 8 mg to 24 mg, anti-tumor activity has been observed across all dose levels[18–20]. Building on this knowledge, we have previously conducted a pilot study examining low-dose lenvatinib (8 or 12 mg daily) combined with PD-1 inhibitors in 15 patients with pre-treated recurrent ovarian cancer[16]. Our study achieved a comparable median PFS of 4.1 months while demonstrating an improved safety profile: all AEs were below grade 3, and only one patient discontinued both medications due to AEs, with no instances of lenvatinib-only discontinuation. Moreover, study has shown that patients with shorter dose interruptions of lenvatinib had longer PFS compared with those with longer dose interruption[21]. These results suggest that this low-dose approach may offer an optimal balance of efficacy and tolerability.

Furthermore, studies on thyroid cancer in Asian patients have demonstrated that a reasonable daily low-dose lenvatinib has compatible effective, with fewer dose interruptions[22,23]. Given that the standard protocol for lenvatinib treatment is based on data from Western populations, it is possible that dose adjustments may be necessary for Asian populations, who have smaller physiques. For this reason, the dose of lenvatinib in this study is designed to be adjusted according to the patient's body weight. Although the current study is one of the few reports to evaluate low-dose lenvatinib plus anti-PD-1 therapy in gynecological tumors, larger studies with control groups are still needed to determine the proper dose of lenvatinib in the area of gynecological tumors, especially for Asian populations.

The study is also designed due to financial toxicity considerations, particularly for patients with a long disease course who have received multiple lines of previous therapies. The impact of the economic burden associated with lenvatinib and PD-1 inhibitors on these patients is also of paramount importance and should be addressed. Lenvatinib and toripalimab used in this study are both China-made drugs, which have lower costs compared to imported drugs. Since

the original lenvatinib LENVIMA® received approval in China, the China-made generic lenvatinib has developed rapidly and is widely used. The lenvatinib mesilate used in this study has obtained drug registration approval and passed the consistency of quality and efficacy evaluation of generic drugs. Additionally, as the first Chinese domestically manufactured anti-PD-1 monoclonal antibody approved by the China Medical Product Administration to commence clinical trials, toripalimab has displayed non-inferiority of clinical efficacy compared with pembrolizumab in other solid tumors[24]. The overall safety profile of toripalimab appears to be generally consistent with that reported for pembrolizumab and other PD-1 inhibitors[25]. General treatment-related AEs include fatigue, decreased appetite, pyrexia, nausea, and elevated transaminases, with a predictable spectrum of immune-related AEs, including thyroid dysfunction, pneumonitis, colitis, and dermatologic reactions. The majority of these events are manageable with established treatment algorithms incorporating temporary drug discontinuation and immunosuppressive therapy when indicated. Moreover, the efficacy and safety of lenvatinib plus toripalimab has been established in clinical trials for hepatobiliary malignancies[26,27], providing a rational foundation for exploring this combination approach in ovarian cancer. As discussed above, our previous pilot study of low-dose lenvatinib in ovarian cancer, where the majority of patients (86.7%, 13/15) received concurrent toripalimab, demonstrated both favorable efficacy and safety[16]. Furthermore, a study has reported the combination of toripalimab with another tyrosine kinase inhibitor, surufatinib, in treating ovarian clear cell carcinoma[28]. These data reinforce the feasibility of this combination strategy. However, it should be acknowledged that direct comparative data between these two domestic agents and the internationally approved ones in the field of gynecological tumors are currently lacking. Further, head-to-head clinical trials are still warranted to evaluate comparative efficacy, safety, and cost-effectiveness. To summarize, our phase II trial will provide crucial evidence to further optimize this combination therapy. The demonstrated feasibility of this approach, coupled with the low-dose strategy, has the potential to reduce both economic and physical burden on patients, making these potentially life-saving therapies more accessible, especially in resource-constrained healthcare systems.

The main limitation of this study was the single-arm trial. Due to the lack of a standard effective treatment, it is not possible to set up a randomized control group, which increases the uncertainty in assessing the benefits of treatment. However, phase II trials are more exploratory than confirmatory, and regression of malignant tumors by itself is almost impossible, the tumor response can be assumed to be almost entirely the effect of the drug. If the expected effect is achieved initially, further study will be conducted; otherwise, it will avoid more subjects with ineffective treatment and waste of resources.

In conclusion, this prospective phase II study will assess the efficacy of low-dose lenvatinib plus toripalimab in patients with recurrent PROC. If efficacy and safety can be demonstrated, this combination therapy may become an important chemotherapy-free treatment strategy in this patient population with limited therapeutic options and would be a significant improvement in the quality of life of these patients.

Abbreviations

PROC, platinum-resistant ovarian cancer; PFS, progression-free survival; OS, overall survival; PD-1, programmed cell death protein-1; ORR, objective response rate; DoR, duration of response; DCR, disease control rate; AE, adverse event; QoL, quality of life; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; GCIG, Gynecological Cancer Intergroup; ULN, upper limit of normal; CI, confidence interval.

Ethic Statement

This study is being conducted in accordance with the Good Clinical Practice guidelines and the guiding principles outlined in the Declaration of Helsinki. All prospective patients must provide written informed consent for participation in the study procedures. The trial is registered in ClinicalTrials.gov under registration number NCT06241105. The Medical Ethics Committee of Peking Union Medical College Hospital approved the study (approval number: I-23PJ434).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Hao Su and Xiao Shang are co-first authors for this study. Kui Jiang and Fengzhi Feng are co-correspondence authors for this study.

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Disclosure

The authors declare no potential conflicts of interest in this work.

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