Study Protocol

Efficacy, safety and pharmacokinetics of apatinib plus etoposide versus apatinib alone for platinum-resistant recurrent ovarian cancer: protocol of a multicenter, open-label, randomized phase 2 trial

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Background: Currently preferred single-agent nonplatinum chemotherapy or its combination with bevacizumab results in a low response rate and modest survival benefit for platinum-resistant recurrent ovarian cancer, and thus more effective regimens are needed. In our previous phase 2 trial, apatinib plus etoposide showed promising efficacy and an acceptable safety profile in platinum-resistant recurrent ovarian cancer patients. Due to the single-arm design, the role of apatinib still needs to be determined.

Methods: In this phase 2 trial, 54 adult patients with platinum-resistant current ovarian cancer will be recruited at 15 sites in China. Patients with prior administration of small-molecule tyrosine kinase inhibitors or etoposide will be excluded. Patients will be randomized (1:1) to receive apatinib (375 mg, orally, once daily) alone or in combination with etoposide (50 mg, orally on days 1–14 of each 21-day cycle) until disease progression or intolerable toxicity. Randomization will be performed using a computerized central randomization system, stratified by platinum resistance for the first time (yes or no). Imaging examinations will be conducted every 6 weeks. The primary endpoint is the objective response rate (ORR) according to the Response Evaluation Criteria In Solid Tumors (version 1.1), which will be compared between groups using the Cochran-Mantel-Haenszel test.

Discussion: This study will provide prospective data of 2 experimental regimens using a randomized design. It will help determine whether apatinib monotherapy can provide favorable clinical benefits or needs to be combined with chemotherapy to be effective.

Trial Registration: ClinicalTrials.gov Identifier: NCT04383977. It was registered on May 12, 2020.

Keywords: Apatinib; etoposide; ovarian cancer; platinum; protocol

Submitted Aug 23, 2023. Accepted for publication Oct 24, 2023. Published online Oct 26, 2023.
doi: 10.21037/tcr-23-1924
View this article at: https://dx.doi.org/10.21037/tcr-23-1924

Introduction

Ovarian cancer is a serious global health issue, ranking eighth in both incidence and mortality among all cancers in women worldwide (1). In 2020, there were over 300,000 new cases of ovarian cancer and over 200,000 deaths across 185 countries (1). Unfortunately, most patients have advanced disease at diagnosis, making treatment challenging. The standard initial treatment for newly diagnosed advanced ovarian cancer is cytoreductive surgery followed by adjuvant platinum-based chemotherapy with or without bevacizumab (2). However, disease relapse is almost inevitable, and patients will eventually develop platinum resistance (3-5). It is suggested that the number of tumor infiltrating lymphocytes, homologous recombination repair functional score, presence or absence of *BRCA* mutation, cancer antigen (CA)-125 elimination rate, and defined gene signatures are associated with platinum-resistant relapse (6). Currently, the preferred single-agent nonplatinum chemotherapy [including docetaxel (7), etoposide (8), gemcitabine (9,10), liposomal doxorubicin (9,10), paclitaxel (11), or topotecan (12,13)] for patients with platinum-resistant recurrent ovarian cancer only results in an objective response rate (ORR) of 6–29% (7-12), making more effective regimens necessary.

Antiangiogenetic agents are being increasingly used in treating platinum-resistant current ovarian cancer, as angiogenesis is an essential process for tumor development and metastasis (3,14-17). A meta-analysis of 13 studies showed that applying antiangiogenetic agents could improve the treatment response and survival in patients with recurrent ovarian cancer (18). The phase 3 AURELIA trial proved that bevacizumab plus chemotherapy could result in a significantly longer median progression-free survival [PFS; 6.7 *vs.* 3.4 months; hazard ratio (HR) 0.48, 95% confidence interval (CI): 0.38–0.60] and a higher ORR (27.3% *vs.* 11.8%; P=0.001) compared with chemotherapy alone in patients with platinum-resistant current ovarian cancer (19). However, another preferred regimen mentioned in the current guideline (2), bevacizumab plus single-agent nonplatinum chemotherapy, still has unsatisfactory efficacy.

Apatinib, an oral small-molecule tyrosine kinase inhibitor that selectively targets vascular endothelial growth factor receptor 2, has shown promising antitumor activity in several randomized controlled trials involving different types of cancer (20-23). In the randomized APPROVE trial, apatinib plus pegylated liposomal doxorubicin yielded a significantly longer median PFS (5.8 *vs.* 3.3 months; HR 0.44, 95% CI: 0.28–0.71) and overall survival (OS; 23.0 *vs.* 14.4 months; HR 0.66, 95% CI: 0.40–1.09) than did pegylated liposomal doxorubicin alone in patients with platinum-resistant current ovarian cancer (24). In our previous single-arm phase 2 trial, the combination of apatinib plus etoposide yielded a promising ORR (54.3%) and median PFS (8.1 months) in this population (25). The toxicities were also manageable, with the most common grade 3 or 4 adverse events (AEs) being neutropenia (50%), fatigue (32%), anemia (29%), and mucositis (24%) (25). This combination also showed feasibility in small cell lung cancer and breast cancer (26-28).

Therefore, a study has been devised to evaluate the efficacy and safety of apatinib plus etoposide or apatinib alone in patients with platinum-resistant current ovarian cancer. This may offer a more effective treatment option for this patient population. We present this article in accordance with the SPIRIT reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1924/rc).

Methods

Study design

This is a multicenter, open-label, randomized phase 2 trial that will be conducted at 15 tertiary hospitals with annual inpatient visits of 70,000–180,000 (Sun Yat-sen University Cancer Center; Qilu Hospital of Shandong University; The First Affiliated Hospital of Guangzhou Medical University; Peking University First Hospital; Jiangsu Province Hospital; Shanghai Tenth People's Hospital; Hunan Cancer Hospital; Nanfang Hospital; Liuzhou People's Hospital; Xiangya Hospital Central South University; The Second Norman Bethune Hospital of Jilin University; The Second Hospital of Hebei Medical University; Harbin Medical University Cancer Hospital; Meizhou People's Hospital; Dongying People's Hospital) in China. The study design is shown in *Figure 1*. The study will be conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki (as revised in 2013). The study protocol and its amendments (version 4.0; version date: September 30, 2021) have been approved by the ethics committee of the leading hospital (Sun Yat-sen University Cancer Center; No. SL-A2020-015-19) and all other participating centers. Each participant will sign the informed consent before enrollment. The study is registered at ClinicalTrials.gov (NCT04383977). The first patient was recruited on July 23, 2020. The study is expected to be completed in December 2024.

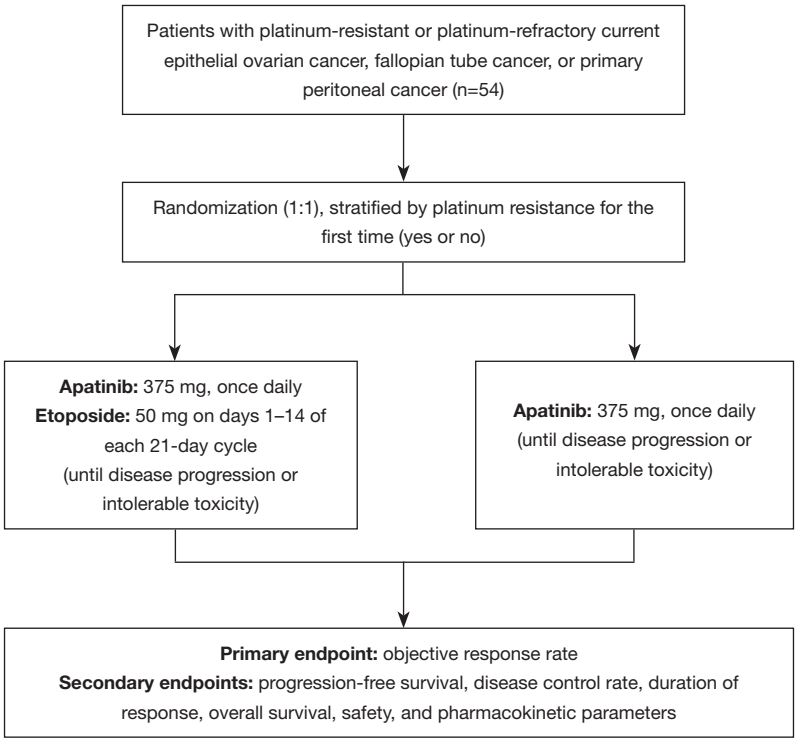

Figure 1 Study design.

Inclusion criteria

The inclusion criteria are the following: (I) aged ≥18 years; (II) pathologically confirmed primary peritoneal cancer, epithelial ovarian cancer, or fallopian tube cancer; (III) prior use of platinum-based chemotherapy after cytoreductive surgery; (IV) platinum-resistant disease, defined as recurrence or progression within 6 months after the last platinum-based chemotherapy (treatment must have been for ≥4 weeks) or during platinum-based chemotherapy; (V) Eastern Cooperative Oncology Group performance status 0–2; (VI) at least 1 measurable lesion as per the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (29); (VII) expected survival ≥12 weeks; (VIII) adequate organ function defined as neutrophil count ≥1.5×10^9/L, platelet count ≥90×10^9/L, hemoglobin ≥90 g/L, total bilirubin ≤1.5 × upper limit of normal (ULN), serum albumin ≥30 g/L, alanine aminotransferase and aspartate aminotransferase ≤3 × ULN (≤5 × ULN for patients with liver metastases), and serum creatinine ≤1.5×ULN; (IX) willingness to use highly effective contraception starting from signing informed consent to a specific time after the last dose of the study drug (8 weeks for apatinib or 6 months for etoposide, whichever is longer), a negative human chorionic gonadotropin test result within 72 hours before randomization and nonlactation for patients who still have fertility after cytoreductive surgery; (X) ability to swallow tablets; and (XI) written informed consent.

Exclusion criteria

The exclusion criteria are the following: (I) other cancers within 5 years, except for cured skin basal cell cancer and cervical or breast cancer *in situ*; (II) untreated central nervous system metastases (patients with stable brain or meningeal metastases for ≥1 month after local radiotherapy or surgery who have no clinical symptoms and have discontinued systemic steroid therapy for >2 weeks can be enrolled); (III) symptomatic pleural effusion, pericardial effusion, or ascites that require drainage; (IV) history of gastrointestinal perforation or abdominal abscess or previous intestinal obstruction within 3 months before randomization or current intestinal obstruction indicated by imaging examination and clinical symptoms; (V) uncontrolled hypertension (diastolic blood pressure ≥90 mmHg and/or systolic blood pressure ≥140 mmHg); (VI) uncontrolled cardiac disease or symptoms, such as

unstable angina, heart failure (New York Heart Association class II or higher), atrial fibrillation, myocardial infarction (within 1 year), clinically meaningful supraventricular or ventricular arrhythmia that requires treatment, PR interval >250 ms, and corrected QT interval >470 ms; (VII) abnormal coagulation function (prothrombin time >16 s or international normalized ratio >2.0), with bleeding tendency or receiving thrombolytic or anticoagulant therapy (prophylactic use of low-molecular weight heparin and low-dose aspirin is permitted); (VIII) definite bleeding tendency or clinically meaningful hemorrhage symptoms, such as gastrointestinal hemorrhage, hemorrhagic stomach ulcer, and vasculitis within 3 months before randomization (for patients with positive fecal occult blood which is confirmed after retest, gastroscopy can be performed if needed); (IX) arterial/venous thrombosis, such as deep venous thrombosis, cerebral infarction, cerebral hemorrhage, transient ischemic attack, and pulmonary embolism, within 6 months before randomization (patients with superficial vein thrombosis can be enrolled after judgement by investigator); (X) existence of hereditary or acquired hemorrhage or bleeding tendency, such as hemophilia, thrombocytopenia, and coagulation disorder; (XI) unhealed wound, fracture, or active ulcer; (XII) urine protein ≥++, with 24-hour urine protein quantitation >1.0 g; (XIII) prior radiotherapy, chemotherapy, or targeted therapy within 4 weeks (within 5 half-lives for oral targeted drugs) before randomization and for patients with AEs (except for alopecia) after prior therapy, AEs recovered to grade ≤1 before enrollment as per the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0; (XIV) baseline white blood cell >15×10^9/L, active infection, or fever of unknown origin (≥38.5 ℃) within 7 days before randomization; (XV) congenital or acquired immune deficiency, such as human immunodeficiency virus infection; (XVI) active hepatitis (positive hepatitis B surface antigen with hepatitis B virus DNA ≥500 IU/mL; or positive hepatitis C virus antibody with hepatitis C virus copy number > ULN); (XVII) prior palliative radiotherapy area >5% of the bone marrow region within 4 weeks before randomization for patients with bone metastases; (XVIII) receiving moderate-to-strong CYP3A inducers within 4 weeks before randomization or receiving moderate-to-strong CYP3A or P-gp inhibitors; (XIX) receiving drugs that affect secretion of stomach acid within 2 weeks before randomization; (XX) prior use of apatinib or other small-molecule tyrosine kinase inhibitors; (XXI) prior use of etoposide; (XXII) allergy to any study drugs or ingredients; (XXIII) heavy smoker (≥5 cigarettes per day) or drinker (≥14 units of alcohol every week; 1 unit = 25 mL for spirits, 100 mL for wine, or 285 mL for beer) who cannot quit smoking or drinking during the study period; (XXIV) ingestion of grapefruit or grapefruit-containing products or food or beverages containing caffeine, xanthine, or alcohol within 48 hours before randomization or during the study period, as well as strenuous exercise or other factors affecting drug absorption, distribution, metabolism, or excretion; and (XXV) other factors possibly affecting the study results or leading to forced study termination, such as drug abuse, other severe diseases (including mental disorders) requiring combination therapy, severe abnormal laboratory tests, and social or family factors that may affect patient safety, as judged by the investigator.

Randomization and treatment

After signing the informed consent, patients who meet the eligibility criteria will be randomized in a 1:1 ratio to receive apatinib (375 mg, orally, once daily) alone or in combination with etoposide (50 mg, orally on days 1–14 of each 21-day cycle) until intolerable toxicity, disease progression, death, withdrawal of consent, or other reasons judged by the investigator. Stratified randomization will be performed using a computerized central randomization system, and the stratified factor will be platinum resistance for the first time (yes or no). Patients and investigators will be aware of the treatment allocation.

Dose reductions, interruptions, or discontinuation of apatinib and/or etoposide will be permitted to manage AEs, as detailed in *Table 1*. Dose reductions of apatinib will be permitted to be reduced stepwise from 375 mg once daily to 250 mg once daily and then to 250 mg once every other day. Dose reductions of etoposide will be permitted to be reduced stepwise from 50 mg on days 1–14 of each cycle to 50 mg on days 1–10 of each cycle and then to 50 mg once every other day on days 1–14 of each cycle. Dose escalation is not permitted upon resolution of toxicity.

Endpoints

The primary endpoint is ORR. Secondary endpoints include PFS, disease control rate (DCR), duration of response (DoR), OS, safety, and pharmacokinetic (PK) parameters. ORR is defined as the proportion of patients with complete or partial response. PFS is defined as the time from randomization to disease progression or any-

Table 1 Dose adjustment criteria

CTCAE 5.0	Criteria for resuming treatment	Dose adjustment of apatinib and/or etoposide after resuming treatment	Permanent dose discontinuation criteria for apatinib and/or etoposide
Treatment-related hematological toxicities			
ANC <1,000/mm^3 without fever or PLT <50,000/mm^3 without hemorrhage event	ANC >1,000/mm^3, PLT ≥75,000/mm^3, and hemoglobin >80 g/L	Interrupt apatinib and/or etoposide and resume at initial dose level after the first occurrence of an AE and resume at a reduced dose level after reoccurrence of the same AE	Consecutive interruption of apatinib for >14 days or reoccurrence of the same AE after 2 dose reductions of apatinib and/or etoposide
ANC <1,000/mm^3 with fever (≥38.5 ℃); PLT <50,000/mm^3 with grade ≥2 hemorrhage event, regardless of ANC; or hemoglobin ≤80 g/L or requiring blood transfusion	ANC >1,000/mm^3, PLT ≥75,000/mm^3, and hemoglobin >80 g/L	Interrupt apatinib and/or etoposide and resume at a reduced dose level	Consecutive interruption of apatinib for >14 days or reoccurrence of the same AE after 2 dose reductions of apatinib and/or etoposide
Treatment-related nonhematological toxicities			
Grade ≥3 hypertension	Systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg	Interrupt apatinib and resume at initial dose level after the first occurrence of an AE and resume at a reduced dose level after reoccurrence of the same AE. Interrupt etoposide and resume at a reduced dose level	Consecutive interruption of apatinib for >14 days or reoccurrence of the same AE after 2 dose reductions of apatinib and/or etoposide
Grade ≥3 proteinuria without significantly increased creatinine	24-hour urine protein quantitation ≤2 g	Interrupt apatinib and/or etoposide and resume at a reduced dose level	Consecutive interruption of apatinib for >21 days or reoccurrence of the same AE after 2 dose reductions of apatinib and/or etoposide
Grade ≥3 palmar-plantar erythrodysesthesia syndrome	Recovery to grade ≤1	Interrupt apatinib and/or etoposide and resume at a reduced dose level	Consecutive interruption of apatinib for >21 days or reoccurrence of the same AE after 2 dose reductions of apatinib and/or etoposide
Grade ≥3 AST and/or ALT increased for ≥7 days or grade ≥3 total bilirubin increased	Recovery to grade ≤1 (AST and ALT ≤5 × ULN for patients with liver metastases)	Interrupt apatinib and/or etoposide and resume at a reduced dose level	Consecutive interruption of apatinib for >14 days or reoccurrence of the same AE after 2 dose reductions of apatinib and/or etoposide
Grade ≥3 nausea/vomiting	Recovery to grade ≤1	Interrupt apatinib and/or etoposide and resume at initial dose level after the first occurrence of an AE and resume at a reduced dose level after reoccurrence of the same AE	Consecutive interruption of apatinib for >14 days or reoccurrence of the same AE after 2 dose reductions of apatinib and/or etoposide
Other grade ≥3 nonhematological toxicities	Recovery to grade ≤1 or baseline level	Interrupt apatinib and/or etoposide and resume at a reduced dose level	Consecutive interruption of apatinib for >14 days or reoccurrence of the same AE after 2 dose reductions of apatinib and/or etoposide

CTCAE, Common Terminology Criteria for Adverse Events; ANC, absolute neutrophil count; PLT, platelet count; AE, adverse event; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal.

cause death, whichever comes first. DCR is defined as the proportion of patients with complete response, partial response, or stable disease. DoR is defined as the time from the first complete or partial response to disease progression or death, whichever comes first. OS is defined as the time from randomization to any-cause death. PK parameters include maximum concentration (C_{max}), time to maximum concentration (T_{max}), half-life ($T_{1/2}$), area under the concentration-time curve from time zero to time of the last measurable concentration (AUC_{0-t}), apparent oral clearance at steady state (CL_{ss}/F), apparent volume of distribution (Vz/F), and elimination rate constant (λz).

Follow-up and assessments

Imaging examinations (computed tomography or magnetic resonance imaging) and CA-125 tests will be conducted every 6 weeks. Tumor response will be assessed by investigator as per RECIST 1.1 (23). For patients who discontinue the study treatment due to reasons other than progression, subsequent imaging examinations will be performed every 3 months until disease progression, death, or initiation of other anticancer therapies. Survival status will be followed every 2 months until loss to follow-up, death, or study termination. AEs will be evaluated and recorded before each treatment cycle and within 30 days after the last treatment and will be graded as per CTCAE 5.0.

Blood samples (4 mL) will be collected at the following time points on day 7 of cycle 1 for PK analysis: 1 hour before administration, and 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours after administration. If patients require treatment interruption due to AEs, the blood samples will be collected at steady state (consecutive combination therapy for 7 days in the apatinib plus etoposide group or consecutive monotherapy for 7 days in the apatinib group) after resuming treatment. Blood samples will not be collected after dose reduction. The plasma concentration of apatinib and etoposide will be determined using the validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. PK parameters will be analyzed using Phoenix WinNolin software (Pharsight Corporation, Mountain View, CA, USA).

Quality control measures

Before the conduct of the study, protocol training will be done for all the investigators and medical staffs participating in this study.

Both apatinib plus etoposide can be administered orally, and patients can receive the study treatment anywhere. To enhance the patient compliance to follow-up, all the examinations will be free of charge for all patients. Each patient will also receive transportation fee compensation for each follow-up visit.

All the results and abnormal findings observed during the study period should be verified and recorded in time using the electronic case report form (eCRF). The appointed investigators and clinical research coordinators (CRCs) will be allowed to login the electronic data capture (EDC) system after training and input the raw data into the EDC system. Clinical research associate (CRA) will regularly inspect and confirm the recording and report of all data. When CRA has a question about the data, investigators or CRCs must respond with tracked changes or explanations. Investigators should be responsible for the attributability, readability, timeliness, originality, accuracy, persistence, integrity and consistency of all the raw data in the source documents and eCRF. All the data and documents should be stored for 5 years after the end of the study.

Sample size calculation

In this randomized, parallel-controlled trial, we assume that the ORR with apatinib monotherapy will be 21%, and the ORR with apatinib plus etoposide will be 54%. Forty-eight patients are required to provide 80% power at a 1-sided significance level of 0.05. With a dropout rate of 10%, a total of 54 patients (27 in each group) are needed.

Statistical analysis

Efficacy will be primarily analyzed in the intent-to-treat population (i.e., all randomized patients). Additional efficacy analyses will be performed in the per-protocol set (i.e., patients without major protocol deviation or those with protocol deviation that has no significant impact on the study results). Safety will be analyzed in the safety set (i.e., all patients with at least 1 dose of the study drug). PK parameters will be analyzed in the PK analysis set (i.e., all patients with at least 1 dose of the study drug who have at least 1 posttreatment PK observation).

Continuous variables will be expressed as mean ± standard deviation or median (range), where appropriate. Categorical variables will be expressed as frequency (percentage). The 95% CIs of ORR and DCR will be

estimated using Clopper-Pearson method. Comparisons of ORR and DCR between the 2 groups will be performed using the Cochran-Mantel-Haenszel test. PFS, DoR, and OS will be estimated using the Kaplan-Meier method, and their 95% CIs will be estimated using the Brookmeyer-Crowley method. Comparisons of PFS, DoR, and OS between the 2 groups will be performed using the log-rank test. The plasma concentration-time curve will be plotted for PK analysis. Individual $AUC_{0\text{-}t}$ and C_{max} will be drawn using the box plot. Statistical analyses will be performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). $P<0.05$ will be considered statistically significant.

Discussion

Our previous phase 2 study showed an ORR of 54.3% with apatinib plus etoposide (25), higher than that of 6–29% with current standard single-agent nonplatinum chemotherapy (7-12). Due to the single-arm design of our previous study and different settings across studies, the role of apatinib in the treatment of patients with platinum-resistant current ovarian cancer still needs to be determined. Thus, the present randomized, phase 2 trial was designed, which includes 2 experimental groups and no control group. With a randomized design, the baseline characteristics of the 2 experimental groups can be well-balanced, and we can explore 2 regimens (apatinib plus etoposide or apatinib monotherapy) in a similar population. Whether apatinib monotherapy can also provide favorable clinical benefit or a combination with chemotherapy is necessary may be answered in this study.

In our previous phase 2 trial, the initial dose of apatinib was 500 mg once daily when combined with etoposide (25). However, 28 (82.4%) of 34 patients had a dose reduction to 500 and 250 mg on alternate days, and 12 (42.9%) of these 28 patients had further dose reduction to 250 mg once daily (25). Moreover, 17 (60.7%) of these 28 patients had a dose reduction of apatinib during cycle 1 or before the initiation of cycle 2 (25). Notably, nearly all patients continued the study treatment after dose reductions. Taking these circumstances into consideration, we changed the initial dose of apatinib to 375 mg once daily during the design of this randomized clinical trial.

In conclusion, this study will provide multicenter prospective evidence concerning 2 experimental regimens using a randomized design, which can better reflect the potential of apatinib in the treatment of patients with platinum-resistant current ovarian cancer.

Acknowledgments

We thank all the investigators who have contributed to this study.

Funding: This study was funded by Jiangsu Hengrui Pharmaceuticals Co., Ltd. The funder contributed to the study design and will contribute to the collection, analysis, and interpretation of data.

Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1924/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1924/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1924/coif). ZH is an employee of Jiangsu Hengrui Pharmaceuticals Co., Ltd. All authors report that this study is funded by Jiangsu Hengrui Pharmaceuticals Co., Ltd. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study will be conducted in accordance with the principles of Good Clinical Practice and with the Declaration of Helsinki (as revised in 2013). The protocol and its amendments (version 4.0; version date: September 30, 2021) have been approved by the ethics committee of the leading hospital (Sun Yat-sen University Cancer Center; No. SL-A2020-015-19) and all other participating centers. Written informed consent will be obtained from each participant before enrollment.

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Cite this article as: Hou Z, Lan C, Huang X, Salcedo-Hernández RA, EL-Tawab S. Efficacy, safety and pharmacokinetics of apatinib plus etoposide versus apatinib alone for platinum-resistant recurrent ovarian cancer: protocol of a multicenter, open-label, randomized phase 2 trial. Transl Cancer Res 2023;12(10):2959-2967. doi: 10.21037/tcr-23-1924

