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Reviewer A

The paper titled "Apatinib plus etoposide versus apatinib alone for platinum-resistant recurrent ovarian cancer: protocol of a multicenter, open-label, randomized phase 2 trial" is interesting. This study will provide prospective data of 2 experimental regimens using a randomized design. It will aim to determine whether apatinib monotherapy can provide favorable clinical benefits or needs to be combined with chemotherapy to be effective. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) In the introduction of the manuscript, it is necessary to clearly indicate the the current treatment strategy for platinum-resistant recurrent ovarian cancer patients and the factors that affect the prognosis and recurrence.

Reply: Thanks for your comment. The current standard treatment for patients with platinum-resistant recurrent ovarian cancer is single-agent nonplatinum chemotherapy with or without bevacizumab, which has already been mentioned in the Introduction section (Page 3, Line 75-77; Page 3, Line 89-90; clean version). At this revision, we have added the factors associated with platinum-resistant relapse in the Introduction section (Page 3, Line 71-74; clean version).

Changes in the text: "It is suggested that the number of tumor infiltrating lymphocytes, homologous recombination repair functional score, presence or absence of *BRCA* mutation, cancer antigen-125 elimination rate, and defined gene signatures are associated with platinum-resistant relapse (1)." (Page 3, Line 71-74; clean version)

2) Compared with other chemotherapy regimens, what are the advantages of the treatment methods in this study? What is the most likely problem? It is recommended to add relevant content.

Reply: Thanks for your comment. Our previous phase 2 study showed an ORR of 54.3% with apatinib plus etoposide (2), higher than that of 6–29% with current standard single-agent nonplatinum chemotherapy (3-8). 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. These have been stated in the Discussion section (Page 9-10, Line 303-313; clean version).

Changes in the text: "Our previous phase 2 study showed an ORR of 54.3% with apatinib plus etoposide (2), higher than that of 6–29% with current standard single-agent nonplatinum chemotherapy (3-8). 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." (Page 9-10, Line 303-313; clean version)

3) What is the difference between this study and published study [Efficacy and Safety of Apatinib Combined with Etoposide in Patients with Recurrent Platinum-resistant Epithelial Ovarian Cancer: A Retrospective Study, J Cancer, PMID: 32742481]? What is the innovation? These should be described in the discussion.

Reply: Thanks for your comment. Yourmentioned observational study used the same regimen to treat platinum-resistant current ovarian cancer as our previous single-arm phase 2 clinical trial (2). However, it was a retrospective study with inevitable bias. We consider that it may be more appropriate to indicate the promising value of apatinib plus etoposide by citing our previous phase 2 clinical trial. Thus, we are sorry that we did not cite yourmentioned reference in the Discussion section. Compared with our previous study (2), the innovation of the present randomized phase 2 study is that we can further determine the role of apatinib in the treatment of patients with platinum-resistant current ovarian cancer. Whether apatinib monotherapy can also provide favorable clinical benefit or a combination with chemotherapy is necessary may be answered

Changes in the text: None.

4) The description of the results section is missing in this study, and the entire manuscript is not complete enough.

Reply: Thanks for your comment. The article type of this manuscript is Study Protocol. We actually described the design of this study rather than analyzing the study results. Thus, the manuscript does not have the Results section.

Changes in the text: None.

5) What are the characteristics and evaluation criteria of apatinib? What are the effects of apatinib on tumor micrometastasis? It is recommended to add relevant content.
Reply: Thanks for your comment. Apatinib is an oral small-molecule tyrosine kinase inhibitor that selectively targets vascular endothelial growth factor receptor 2. Several randomized controlled trials have proved the effect of apatinib on delaying tumor progression (9-12). All these have already been mentioned in the Introduction section. However, the effect of apatinib on tumor micrometastasis remains unclear, and we are sorry that we cannot find any references to discuss this effect.
Changes in the text: None.

6) It is recommended to increase the detection of predictive indicators for efficacy, which may make the entire study more complete.
Reply: Thanks for your valuable suggestion. This study started in July 2020, and the enrollment was almost done. We are sorry that we cannot revise the prespecified prototol to collect baseline tumor samples at this timepoint. However, we will consider to perform some post-hoc analyses on predictive indicators (such as radiographic indicators) for efficacy when we perform the formal analysis.
Changes in the text: None.

7) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "Apatinib with etoposide capsules as a third- or further-line therapy for extensive-stage small cell lung cancer: an open-label, multicenter, single-arm phase II trial, Transl Lung Cancer Res, PMID: 33718030". It is recommended to quote this article.
Reply: Thanks for your comment. This refence has been cited in the Introduction section (Page 4, Line 103-104; clean version).
Changes in the text: "This combination also showed feasibility in small cell lung cancer and breast cancer (13-15)." (Page 4, Line 103-104; clean version).

8) With the discovery of new drug targets and the continuous emergence of new combination treatment options, what breakthroughs will there be in the treatment of platinum-resistant recurrent ovarian cancer with peritoneal metastasis in the future? It is recommended to add relevant content.
Reply: Thanks for your comment. With the development of antibody-drug conjugates, replication stress inhibitors, and immune checkpoint inhibitors, antiangiogenic agents, PARP inhibitors, and their combinations with backbone chemotherapy, we believe that the prognosis of platinum-resistant recurrent ovarian cancer patients with peritoneal metastasis will be improved a lot in the future. However, the evidence focused on

patients with peritoneal metastasis is lacking. Previously published phase 3 studies also did not perform subgroup analysis on patients with peritoneal metastasis. Thus, we are sorry that we cannot add relevant contents on this.

Changes in the text: None.

Reviewer B

1) First, the title needs to indicate the outcomes of this study such as efficacy and safety outcomes.

Reply: Thanks for your comment. The title has been revised accordingly (Page 1, Line 3-5; clean version).

Changes in the text: "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" (Page 1, Line 3-5; clean version)

2) Second, the abstract needs some revisions. The background need to indicate the clinical question to be answered by this study. The methods need to describe the inclusion of subjects, the randomization method, follow up procedures, and main statistical analysis. The conclusion needs to have comments on the clinical contribution of this potential study.

Reply: Thanks for your comment. The abstract has been revised accordingly (Page 2, Line 36-58; clean version).

Changes in the text: "**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 17 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 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." (Page 2, Line 36-58; clean version)

3) Third, in the introduction of the main text, the authors need to review the single-arm clinical trial by the authors and analyze its limitations to indicate the clinical needs for this RCT. It is also necessary to review the safety data of Apatinib plus etoposide.

Reply: Thanks for your comment. Our previous phase 2 study showed an ORR of 54.3% with apatinib plus etoposide (2), higher than that of 6–29% with current standard single-agent nonplatinum chemotherapy (3-8). 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. All these were added in the Discussion section (Page 9-10, Line 303-313; clean version) rather than the Introduction section.

The safety data of apatinib plus etoposide in our previous phase 2 study were reviewed and added in the Introduction section (Page 3-4, Line 101-103; clean version).

Changes in the text: "Our previous phase 2 study showed an ORR of 54.3% with apatinib plus etoposide (2), higher than that of 6–29% with current standard single-agent nonplatinum chemotherapy (3-8). 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." (Page 9-10, Line 303-313; clean version) & "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%) (22)." (Page 3-4, Line 101-103; clean version)

4) Fourth, in the methodology of the main text, please briefly describe the participating centers of this RCT, to explain their clinical settings and annual inpatient visits. The inclusion and exclusion criteria are strict but my concern is that this reduce the external generalizability of the findings from this proposed study. Please use a separate part to describe the quality control measures of this study such as the adherence of treatment of patients, data quality check, data management, and training of researchers. In statistics, please describe the statistical software and P value for statistical significance.

Reply: Thanks for your comment. The 17 sites in our study are all tertiary hospitals with annual inpatient visits of 70,000–180,000. This has been added in the Methods section (Page 4, Line 113; clean version).

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. All these have been described in the Quality control measures sub-section (Page 8-9, Line 259-274; clean version).

Statistical analyses will be performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). P<0.05 will be considered statistically significant. This has been added in the Statistical analysis sub-section (Page 9, Line 298-300; clean version).

Changes in the text: "This is a multicenter, open-label, randomized phase 2 trial that will be conducted at 17 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." (Page 4, Line 113; clean version) & "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." (Page 8-9, Line 259-274; clean version) & "Statistical analyses will be performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). P<0.05 will be considered statistically significant." (Page 9, Line 298-300; clean version)

5) Finally. Please consider to review and cite some related papers: 1. Li S, Zhang J, Du W, Ren X, Zhang X. Pathologic complete response to immune checkpoint inhibitor in a stage IIIB ovarian clear cell carcinoma patient with POLE mutation resistant to platinum-based chemotherapy: a case report. Gland Surg 2022;11(9):1562-1567. doi: 10.21037/gs-22-420. 2. Greening S, Sood N, Nicum S. The challenges and opportunities in ovarian cancer relapse—the role of second and third-line chemotherapy: literature review. Gynecol Pelvic Med 2022;5:15. 3. Romanchik D,

Albukhari A, Artibani M, Ahmed AA. Role of immunotherapy in ovarian cancer: a narrative review. Gynecol Pelvic Med 2022;5:33. 4. EL-Tawab S, Soleymani majd H. Evolutions in the management of advanced ovarian cancer. Gynecol Pelvic Med 2023;6:1.

Reply: Thanks for your comment. After review, the papers by Greening et al. and EL-Tawab et al. have been cited in the Introduction section of our manuscript (Page 3, Line 71; clean version). The papers by Li et al. and Romanchik et al. are less relevant to our manuscript, thus we are sorry that we cannot cite those two references.

Changes in the text: "However, disease relapse is almost inevitable, and patients will eventually develop platinum resistance (16-18)." (Page 3, Line 71; clean version)

References

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10. Qin S, Li Q, Gu S, et al. Apatinib as second-line or later therapy in patients with advanced hepatocellular carcinoma (AHELP): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol 2021;6:559-68.
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