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Sintilimab combined with bevacizumab in relapsed/persistent ovarian clear cell carcinoma (INOVA): an investigator-initiated, multicentre clinical trial—a study protocol of clinical trial

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ABSTRACT

Background Ovarian clear cell carcinoma (OCCC) has an abysmal prognosis with a median overall survival (OS) of 25.3 months because of a low response to chemotherapy. The 5-year disease-specific survival rate after recurrence is 13.2%, with more than two-thirds of the patients dying within a year. Therefore, it is urgent to explore new therapeutic options for OCCC. Based on the characteristic immune-suppressive tumour microenvironment derived from the gene expression profile of OCCC, the combination of immunoantiangiogenesis therapy might have certain efficacy in recurrent/persistent OCCC. This trial aims to evaluate the efficacy and safety of sintilimab and bevacizumab in patients who have failed platinum-containing chemotherapy with recurrent or persistent OCCC.

Method and analysis In this multicentre, single-arm, open-label, investigator-initiated clinical trial, 38 patients will be assigned to receive sintilimab 200 mg plus bevacizumab 15 mg/kg every 3 weeks. The eligibility criteria include histologically diagnosed patients with recurrent or persistent OCCC who have been previously treated with at least one-line platinum-containing chemotherapy; patients with Eastern Cooperative Oncology Group (ECOG) performance status 0–2 with an expected survival greater than 12 weeks. The exclusion criteria include patients previously treated with immune checkpoint inhibitor and patients with contraindications of bevacizumab and sintilimab. The primary endpoint is the objective response rate. The secondary endpoints are progression-free survival, time to response, duration of response, disease control rate, OS, safety and quality of life. Statistical significance was defined as $p<0.05$.

Ethics and dissemination This trial was approved by the Research Ethics Commission of Tongji Medical College of Huazhong University of Science and Technology (2020-S337). The protocol of this study is registered at www.clinicaltrials.gov. The trial results will be published in peer-reviewed journals and at conferences.

Trial registration number NCT04735861; Clinicaltrials.gov.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first clinical trial investigating programmed cell death protein 1 (PD-1) inhibitor and bevacizumab in ovarian clear cell carcinoma.
⇒ It is a multicentre study with patients recruited from 13 institutions, allowing benchmarking among patients.
⇒ The relatively small sample size of this phase II study will restrict the analysis of subgroup outcomes.
⇒ This is an open-label, single-arm study without outcome comparisons between groups and randomisation, blinding design.

INTRODUCTION

Gynaecological tumours seriously threaten the health of women all over the world and have become a global health concern. As the third most common gynaecological malignancy, ovarian cancer is the most common cause of death from gynaecological cancer, resulting in approximately twenty-one thousand deaths in 2020.[1–5] Ovarian clear cell carcinoma (OCCC) is one of the rare subtypes of which the prognosis is extremely poor. It is reported that the median OS of OCCC is merely 25.3 months.[6]

The 5-year disease-specific survival rate after recurrence is 13.2%, with more than two-thirds of the patients dying within a year, and 93.1% within 2 years.[6] In comparison with high-grade serous ovarian cancer, OCCC has a relatively lower objective response rate (ORR) in first-line platinum-containing chemotherapy (11% vs 72.5%).[7] Furthermore, the ORR in chemotherapy after recurrence is between 6% and 8%.[8] Researchers and clinicians have made great efforts in using chemotherapy to improve the response

of OCCC in the past decades. However, the results are below expectation.[9] At this stage, National Comprehensive Cancer Network (NCCN) guidelines have no recommendation specifically for OCCC. All these prompt us to further explore the new treatment for the intractable disease.

Unlike other epithelial ovarian cancers, OCCC is unique in epidemiology, clinicopathological characteristics, gene expression profile and immune microenvironment. OCCCs are usually positive in PIK3CA mutation, and ARID1A mutation with high microsatellite instability (MSI) and mismatch repair (MMR) defects accompanied by upregulation of hepatocyte nuclear factor-1β.[10 11] The expressions of PD-L1 and B7-H1 are usually enhanced.[12–16] The factors above resulted in a distinctive immunosuppressive microenvironment of OCCC, which provides the theoretical basis for the application of immunotherapy. Previous clinical trials in epithelial ovarian cancer have shown that anti-programmed cell death protein 1 (PD-1)/PD-L1 immune checkpoint inhibitors (ICIs) may be effective in OCCC. In a phase II study of nivolumab in patients with platinum-resistant recurrent ovarian cancer, the ORR was 23%, while the disease control rate (DCR) was 54%. Two patients showed durable partial response (PR).[17] It is worth noting that one of these two long-term responders is an OCCC patient. Another phase II, open-label, multicentre clinical trial of pembrolizumab in recurrent epithelial ovarian cancer (KEYNOTE-100) also supports this finding. The ORR of patients with clear cell histology was 15.8%, while that of the total population was only 8%.[18] Recently, arandomised controlled trial (RCT) investigating nivolumab combined with ipilimumab versus nivolumab in the treatment of platinum resistant or refractory ovarian cancer also obtained valuable conclusions. It was observed that the response rate of OCCC was five times as much as that of non-OCCC patients.[19] In summary, immunotherapy may be a promising treatment for OCCC.

On the other hand, some clinical studies of antiangiogenic therapy in OCCC showed limited efficacy with a single antiangiogenic agent. GOG-254, a phase II trial, demonstrated limited antitumor activity of sunitinib in 35 patients with relapsed OCCC, with an ORR of 6.7%.[20] In a phase II trial (NRG-GY001), patients with relapsed OCCC received single cabozantinib, a Vascular Endothelial Growth Factor Receptor (VEGFR), mesenchymal-epithelial transition factor (MET), and Ret Proto-Oncogene (RET) kinase inhibitor, with a median progression-free survival (PFS) of 3.6 months and OS of 8.1 months. However, one patient received 23 cycles of cabozantinib and was still on treatment at the time of data cut-off.[21] Surprisingly, in the phase II clinical trial of OCCC, it was found that in a subgroup analysis of the efficacy of ENMD-2076 (an oral multitarget kinase inhibitor targeting both Aurora kinase A and VEGFR), patients with ARID1A deletion had better PFS than ARID1A-positive patients.[22] This indicates that OCCC patients may potentially benefit from antiangiogenesis therapy.

Some preclinical studies of antiangiogenic agents have also revealed antitumour activity in OCCC. In vivo experiments using patient-derived tissues demonstrated that clear cell tumour xenografts were exquisitely sensitive to antiangiogenesis therapy (sunitinib) compared with serous tumors.[23] Another study elucidated that sunitinib might exert an antitumour effect by targeting interleukin 6-signal transducer and activator of transcription 3-hypoxia induced factor (IL6-STAT3-HIF) signalling.[16] These results might suggest that, though single-agent antiangiogenic therapy did not exhibit expected efficacy, they may still stand a chance in OCCC. In this regard, a combination with immune therapy is a reasonable choice.

The similarities of gene profiles shared between OCCC and renal clear cell carcinoma (RCCC) also inspired us. RCCC is also characterised by frequent somatic mutations in ARID1A, overexpression of MDM2 and upregulation of the PI3K/AKT pathway.[12 24–27] Hierarchical clustering by microarray data sets of pan-cancer cell lines also discriminates a specific cluster within OCCC cell lines and NCI6 cell lines.[28] These common characteristics might give us a clue in breaking through the predicament of OCCC treatment. In RCCC, antiangiogenesis therapy has been approved for clinical use, and the combination of bevacizumab and PD-1 inhibitor has shown safety and clinical activity,[29 30] which suggests that the combination of antiangiogenesis therapy and immunotherapy may have a certain efficacy in treating OCCC.

Sintilimab is a recombinant humanised monoclonal antibody (mAb) of PD-1, while bevacizumab is a mAb targeting vascular endothelial growth factor (VEGF). In this clinical trial, we aim to evaluate the safety and efficacy of sintilimab combined with bevacizumab for relapsed/persistent OCCC that failed platinum-containing chemotherapy and find a more specific therapy for patients with OCCC.

METHODS AND ANALYSIS

Trial design

This is a multicentre, single-arm, open-label, investigator-initiated clinical trial, which recruited from 13 institutions, including Tongji Hospital of Huazhong University of Science and Technology (detailed information is shown in online supplemental file 1). This study aims to evaluate the efficacy and safety of sintilimab and bevacizumab in patients who have failed platinum-containing chemotherapy with recurrent or persistent OCCC confirmed by histopathology. Approximately 38 patients (target enrolment) will be recruited to receive sintilimab 200 mg intravenously plus bevacizumab 15 mg/kg intravenously every 3 weeks. The recommended dose of sintilimab and bevacizumab is mainly based on the clinical trial ORIENT32.[31] The administration of bevacizumab is up to 22 cycles and sintilimab up to 2 years. The treatment will be given until confirmed progression, death, unacceptable toxicity or any other protocol-specified criterion for withdrawal, whichever occurs first. If patients discontinue

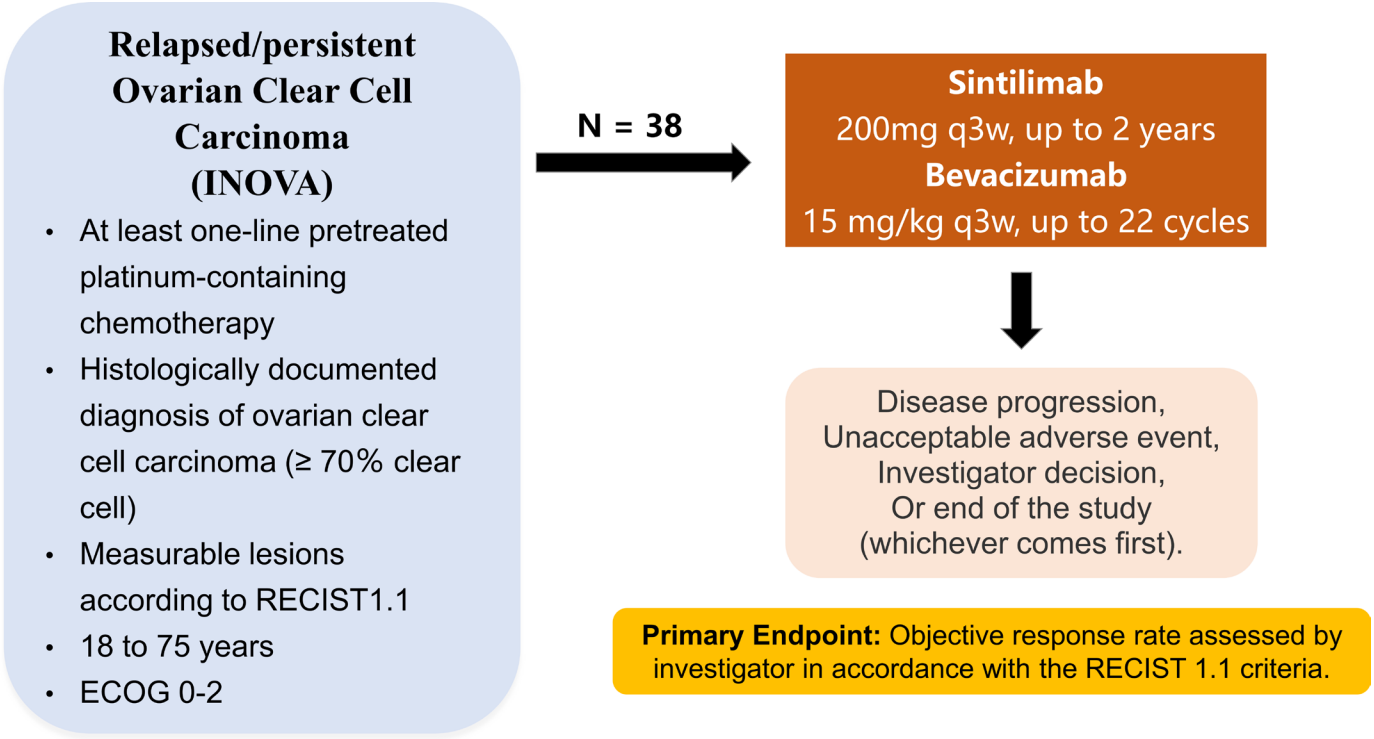

Figure 1 Approximately 38 patients who have failed platinum-containing chemotherapy with recurrent or persistent ovarian clear cell carcinoma will be assigned to receive sintilimab 200 mg plus bevacizumab 15 mg/kg every 3 weeks. The administration of bevacizumab is up to 22 cycles and sintilimab up to 2 years. Treatment is given until confirmed progression, death, unacceptable toxicity or any other protocol-specified criterion for withdrawal, whichever occurs first. The primary endpoint of this study is the objective response rate, which is defined as the proportion of patients with complete response (CR) and partial response (PR) assessed by the investigator in accordance with the RECIST 1.1 criteria. ECOG, Eastern Cooperative Oncology Group; RECIST1.1, Solid Tumor Response Assessment Standard 1.1.

one drug temporarily or permanently during combined therapy due to intolerable toxicity, they could continue receiving the other drug according to the physician's decision (figure 1). The first participant was enrolled on 7 April 2021, and the study is expected to be terminated by April 2024 with the anticipated inclusion of 38 study participants.

In the first 18 weeks of the trial, efficacy assessment will be performed every 6 weeks as well as evaluation of safety and health-related quality of life (QoL). After the first 18 weeks, all evaluations will be performed every 12 weeks. Response assessment is determined using Response Evaluation Criteria in Solid Tumors (RECIST V.1.1) by the investigator. Follow-up time for patients is up to 2 years. Multiple follow-up methods such as telephone follow-up and online follow-up are carried out in parallel. Even if the patient withdraws halfway, the follow-up will continue until the end of the study.

Patients

Patients who have histologically documented diagnosis of recurrent or persistent OCCC with at least one-line platinum-containing chemotherapy will be enrolled in this study. For tumours with mixed histology, at least 70% of the tumours must consist of clear cell carcinoma. Biopsy of recurrent foci is suggested for patients where passible, though it is not compulsively required. All patients must provide informed consent, aged ≥18 years and <75 years, and with one or more measurable lesions by RECIST V.1.1 criteria. Previous administration of ICIs, including anti-PD-1/PD-L1/PD-L2 drugs or anti stimulating/synergistic inhibition of T cell receptor (eg, CTLA-4, OX-40, CD137) drugs, is prohibited. Patients should have ECOG performance status 0–2 with expected survival of >12 weeks. Detailed criteria of inclusion and exclusion are shown in the supplementary file.

Patients who lack tumour samples (archived and/or recently obtained) will be excluded. Patients who have contraindications of sintilimab and bevacizumab will be excluded from this study. These contraindications include but are not limited to previous gastrointestinal perforation, receiving surgery, or having an incomplete-healing wound within 28 days before administration of combined therapy, severe bleeding or recent haemoptysis and other circumstances that are inappropriate for bevacizumab according to the physician's assessment. Patients diagnosed with other malignant diseases other than ovarian cancer within 5 years before the first administration or with an active autoimmune disease that requires systemic treatment within 2 years before the first administration will also be excluded.

Primary endpoint

The primary endpoint of this study is the ORR. ORR is defined as the proportion of patients with complete response (CR) and PR assessed by the investigator following the RECIST V.1.1 criteria.

Secondary endpoints

The secondary endpoints are PFS, time to response (TTR), duration of response (DOR), DCR, OS, safety and QoL. PFS is defined as the time from enrolment to the first imaging disease progression or death (whichever occurs first). TTR is defined as the time from the first administration to the first CR or PR recorded. DOR is defined as the time interval from the first record of disease response to disease progression or death (whichever occurs first). DCR is defined as the proportion of the patients with CR, PR and stable disease after treatment. PFS, TTR, DCR and DOR are evaluated by the investigator according to RECIST V.1.1. OS is defined as the time between enrolment and the patient's death due to any cause. Safety includes the adverse event (AE) profile of sintilimab and bevacizumab according to the Common Terminology Criteria for Adverse Events V.5.0. QoL will be assessed by Functional Assessment of Cancer Therapy-Ovarian,[32] Hospital Anxiety and Depression Scale,[33] Insomnia Severity Index,[34] International Physical Activity Questionnaire,[35] EuropQol Visual Analogue Scale,[36] EORTC Core Quality of Life Questionnaire.[37]

Exploratory endpoint

The exploratory endpoint of this study is to identify new predictive biomarkers for the response of ovarian OCCC to combination therapy, which includes but is not limited to PD-L1, tumour mutation burden (TMB), MMR-deficient, MSI-H and lymphocyte infiltration. Therefore, biological specimens for genetic analysis are scheduled. It is also scheduled to investigate the dynamic profiles of cancer/immune system biomarkers during the treatment and compare the changes before and after the therapy. Subgroup analyses will be applied according to these biomarker profiles of patients included.

Sample size

The sample size was estimated based on the primary endpoint of ORR. A retrospective study of recurrent or refractory OCCC reported a 6%–8% response rate for second-line treatment.[8] Therefore, the null hypothesis is postulated of an ORR of 8% (P_0), while 23% or more in the experimental in this study (P_1). Using the Simon two-stage (Optimum) design with unilateral α=0.05 and β=0.2, totally 38 patients will be enrolled in this trial. In the first stage of accrual, 17 patients were enrolled. The response rate will be determined, if the total number of patients responding to sintilimab and bevacizumab is less than or equal to one patient, then the trial should terminate early and declare no worth of further investigation for the combination therapy. On the contrary, 17 patients will be recruited in the second stage, with a total of 34 patients. If the total number of patients achieving complete or PR is less than or equal to five cases, then the null hypothesis is true, and the trial does not reach the effective endpoint. Otherwise, it is determined that the combination regimen is effective and worthy of further large-scale clinical trials. Considering a dropout rate of 10%, a total of 38 patients will be included in this study.

Statistical methods

All treated patients were included in the analysis. Continuous variables will be described as mean (SD) and median (IQR), and categorical variables will be described as percentages (%). Point estimates and corresponding CIs will be employed to analyse ORR and DCR. PFS, TTR, DOR and OS will be summarised using the Kaplan–Meier method to estimate the median and corresponding 95% CI. For subjects with objective response, calculate the DOR at the time of cut-off data analysis. The secondary endpoints of the DCR will be summarised by using DCR and its 95% CI. Statistical significance was defined as p value less than 0.05.

Patient and public involvement

Patients and the public were not involved in the design of our study.

ETHICS AND DISSEMINATION

This trial has been approved by the Research Ethics Commission of Tongji Medical College of Huazhong University of Science and Technology (2020-S337), and the protocol of this study is registered at www.clinicaltrials.gov. The project is under ongoing review by the Ethics Commission with a frequency of 1 year. All participants will give written informed consent prior to their participation in the study (model consent form as a online supplemental file 1). The informed consent form already states the consent to the collection and use of participant data and biological specimens in the study, so no additional consent is required. The trial results will be disseminated in a peer-reviewed journal and at conferences.

DISCUSSION

This is the first clinical trial of PD-1 inhibitor and bevacizumab combination therapy in OCCC. After an initial breakthrough in melanoma, PD-1/PD-L1 blockade therapy promptly became a hotspot in antitumour therapy. Nowadays, numerous clinical trials have been designed to investigate the clinical benefit of PD-1/PD-L1 inhibitors in various solid cancers, including ovarian cancer. Nevertheless, the results of PD-1/PD-L1 inhibitors in ovarian cancer were unsatisfactory. KEYNOTE-028 and KEYNOTE-100, two clinical trials of pembrolizumab single regiment in recurrent ovarian cancer demonstrated ORRs of 11.5% and 8.0%, respectively.[18 38] Another PD-1 inhibitor, nivolumab, showed an ORR of 15% in phase 2 clinical trial recruiting patients with advanced or relapsed

platinum-resistant ovarian cancer (UMIN00005714).[17] Two clinical trials of PD-L1 inhibitors (avelumab and atezolizumab) also revealed moderate ORRs.[39 40] The results above raised doubts about the applicability and efficacy of ICIs in ovarian cancer. Recently, McGrail *et al* pointed out that high TMB (also known as TMB-H and defined as ≥10 mutations/megabase of DNA), as an indication for PD-1 inhibitors across cancer types, might not be appropriate in all types of solid cancer as a response biomarker.[41] The abovementioned information suggests that the PD-1/PD-L1 inhibitors may not be so broadly applicable in pan-cancer treatment. Considering that ovarian cancer belongs to the category of cancer that TMB-H does not predict response to ICIs, selection of appropriate population is a vital question in the further exploration in ovarian cancer.[41] From this perceptive, OCCC is a proper candidate for ICIs owing to its distinct suppressive tumour microenvironment derived from genetic alteration, which makes immunotherapy a potential therapeutic in this chemotherapy-refractory disease.

Previous clinical studies of antiangiogenic drugs in patients with OCCC have exhibited limited efficacy. The single antiangiogenic drug seems not to be effective in treating patients with OCCC. Therefore, the combination of antiangiogenic drugs with other regimes might be a promising treatment strategy. A patient with refractory OCCC reached complete remission after nine cycles of pembrolizumab and bevacizumab combination therapy.[42] Moreover, a retrospective real-world study showed that adding bevacizumab to chemotherapy in recurrent OCCC resulted in a remarkable benefit compared with high-grade serous ovarian carcinoma (PFS: 20 m vs 14 m).[43] Overall, antiangiogenic drug-containing regimens tend to be more effective in recurrent OCCC.

On the other hand, combination strategy also plays a critical role in the treatment of ICIs. Proper combined therapy can improve the treatment response and prognosis of patients with cancer. In solid tumours, the combination of antiangiogenesis therapy and ICIs is one of the promising strategies with several ongoing clinical trials. It has been broadly investigated that VEGF is a critical immunosuppressive regulator in the tumour microenvironment. Despite its proangiogenesis function, VEGF can also inhibit the maturation of dendritic cells, suppress the proliferation and function of T cells and recruit immunosuppressive cells such as T regulatory cells (Treg cells) and myeloid-derived suppressor cells through various mechanisms.[44–47] Therefore, VEGF inhibitors, such as bevacizumab, are expected to reverse the suppressive tumour microenvironment and normalise tumour vasculature to enhance the efficacy of ICIs. In addition, immune therapy has also been demonstrated to hinder tumour angiogenesis by improving the tumour microenvironment.[48 49] Given the evidence above, it is reasonable to believe in the potent clinical benefit of ICI and bevacizumab combined therapy.

Double immunotherapy combination is another popular strategy in solid tumour treatment due to its possible robust drug efficacy; however, severe adverse effects might be a major concern. Although OCCC seems to have more benefit from the combination of ICIs than other types of ovarian cancer, the combination of CTLA-4 and PD-1 revealed a serious AE rate of 49% (compared with a single PD-1 inhibitor: 33%) in patients with ovarian cancer.[19] Another phase-three RCT of nivolumab and ipilimumab combination in renal cell carcinoma reported that 58% of patients received prednisone to manage treatment-related AEs.[50] In contrast, the combination of bevacizumab and atezolizumab is currently well tolerated in RCC with a 13% incidence of severe AE, and only 16% of the patients in the combination group received short-term prednisone for immune-related AE, which gives a promising signal of combination safety.[51 52] Although there are actual differences between the safeties of PD-1 and PD-L1 inhibitors, we believe in the considerable efficacy and safety of this combination based on previous data.

The study has some limitations. First, it is an open-label and single-arm trial without outcome comparisons between this combination therapy and the present therapy of relapsed OCCC, which may limit the generalisability of findings. Second, the absence of randomisation and blinding will augment the risk of bias in patient enrollment. Finally, the small sample size is a major obstacle for subgroup outcome analysis.

Protocol amendments and protocol version

Recruitment and manuscript writing are based on research protocol V.3.0 (30 March 2021). The revision of the protocol, the informed consent form and the patient recruitment materials must be submitted to the Research Ethics Commission for approval.

Ancillary and post-trial care

In the event of a study-related injury as a result of participation in this clinical study, the patient will receive necessary medical treatment. All enrolled patients have purchased AE insurance.

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Contributors Q-LG, JJ, GL and RL developed the study concept and protocol. XL, CS, WZ, JL, XJ and YY assisted in further development of the protocol. SZ, JC, YZ, GM, YH, ML and ZP assisted in literature searching and information collection. RL, XL, CS and WZ drafted the manuscript. Q-LG is responsible for the supervision of the clinical trial and has access to the final trial dataset. Q-LG revised this manuscript. All authors have read and approved the manuscript for publication.

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