Sintilimab combined with bevacizumab in recurrent/persistent ovarian clear cell carcinoma after platinum-based chemotherapy: a multicenter, open-label, single-arm, exploratory study

informed consent

Study name: INOVA

Protocol version: 3.0, March 3, 2021

Informed consent version: 3.0, March 3, 2021

Study center name:

Researcher:

Main research unit: Tongji Hospital, Tongji Medical College, University of Science and Technology

Subject initials: __ __ __ __  Subject number: [__________]
Informed consent
main body

Dear ____________ Subject:

Hello!

You will be invited to participate in a "Sintilimab Combined with Bevacizumab in Recurrent/Persistent Ovarian Clear Cell Carcinoma After Platinum-Based Chemotherapy". This study was sponsored by the main research unit: Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology. This study has been reviewed and approved by the main research unit: Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, and by the ethics committee of this hospital. This study plans to enroll 38 patients with ovarian clear cell carcinoma after first-line platinum-containing chemotherapy.

Please read this informed consent form carefully before you decide whether to participate. It can help you understand the study and why it is being done, the procedure and duration of the study, and the possible benefits, risks and discomforts that may come to you if you take part in the study. You can also discuss it with your relatives, friends, or ask your doctor to explain. Please voluntarily decide whether to sign this informed consent form after understanding all the following information.

This informed consent form is in duplicate. If you participate in this study, you can consult your study doctor about relevant issues. After full understanding, you and your study doctor will sign this informed consent form, and you will obtain a portion.

1. Study background and purpose

The main purpose of this study is to observe the efficacy and safety of sintilimab combined with bevacizumab in patients with recurrent or persistent ovarian clear cell carcinoma after selecting recurrent or persistent ovarian clear cell carcinoma patients who have failed platinum-containing chemotherapy by histological confirmation (for tumors with mixed histology, at least 70% of the component is composed of clear cell carcinoma), thereby to provide a theoretical basis for more effective and precise treatment for this type of patients.
The traditional platinum-based chemotherapy is the main treatment for postoperative chemotherapy and post-recurrence treatment of epithelial ovarian cancer, which can improve the survival and prognosis of patients. However, patients with ovarian clear cell carcinoma have a poor prognosis due to the low response rate to traditional regimens. This might be due to the significant differences between ovarian clear cell carcinoma and other epithelial ovarian cancers. Therefore, we need to explore new targeted treatment options for these patients, and immune checkpoint inhibitors might have great potential. Previous studies have shown that immune checkpoint inhibitors could improve the survival of patients with ovarian clear cell carcinoma: (1) In the Keynote100 study, the response rate of pembrolizumab in the clear cell carcinoma population was 15.8% (the response rate of the overall ovarian cancer population was only 8%). (2) In the NRG GY003 study, the response rate of nivolumab combined with ipilimumab in patients with ovarian clear cell carcinoma was approximately 5 times that of other patients; (3) In the UMIN000005714 study, a patient with clear cell carcinoma was treated with nivolumab and achieved a complete remission (CR). In addition, anti-angiogenesis therapy is also a class of ovarian cancer targeted drugs with clinical potential. Bevacizumab is a recombinant anti-vascular endothelial growth factor (VEGF) humanized monoclonal antibody injection developed by Roche. It inhibits the proliferation and metastasis of tumour cells by inhibiting the growth of blood vessels of tumour tissue, thereby producing an antitumor effect. Previous large-scale clinical trials have confirmed that bevacizumab can prolong the progression-free survival (PFS) of ovarian cancer patients; at the same time, clinical studies have suggested that bevacizumab might have a better effect on patients with ovarian clear cell carcinoma. Therefore, the combination of anti-angiogenesis therapy and immunotherapy is the hope for patients with ovarian clear cell carcinoma. Given the mechanism of the two drugs and the clinical needs of patients with ovarian clear cell carcinoma, further clinical study is worthwhile to verify whether the combined therapy could benefit patients with ovarian clear cell carcinoma.

Sintilimab is a recombinant fully human anti-PD-1 monoclonal antibody injection independently developed by Innovent Biopharmaceutical (Suzhou) Co., Ltd. It was officially approved by the National Medical Products Administration (NMPA) on December 24, 2018. Bevacizumab (trade name: Dayutong®) is a biosimilar drug developed by Innovent with reference to the original research drug bevacizumab injection (trade name: Avastin®/Avastin®; Roche Pharmaceuticals). The recombinant anti-VEGF humanized monoclonal antibody was approved for marketing on June 19, 2020.
2. The main inclusion criteria of this study

1. Before the start of any procedure of the trial, informed consent must be provided, and the informed consent must be recorded in the study center;

2. Female patients aged ≥ 18 years and < 75 years old;

3. Histologically confirmed diagnosis of ovarian clear cell carcinoma. For tumors with mixed histology, at least 70% or more is composed of clear cell carcinoma;

4. Patients with recurrent/persistent ovarian clear cell carcinoma who have received first-line platinum-containing chemotherapy;

5. Patients must have measurable disease as defined by Response Evaluation Criteria in Solid Tumors 1.1 (RECIST1.1). Measurable lesions were defined as:
   - Presence of at least one lesion that can be accurately measured in at least one dimension;
   - Each lesion must be ≥ 10 mm when measured by CT or MRI or caliper on clinical examination; or ≥ 20 mm when measured by chest X-ray;
   - When lymph nodes are measured by CT or MRI, the short axis of the lymph node must be ≥ 15 mm;

6. The patient should be at least 4 weeks away from the last antitumor treatment before starting the trial treatment;

7. No history of immune checkpoint inhibitor use;

8. Provide archived tumor tissue blocks (or at least 15 freshly excised unstained slides) in which such samples are present in sufficient quantities for analysis;

9. ECOG score ≤ 2;

10. Understand the trial procedure and have the ability to comply with the trial protocol for the trial for the duration of the trial, including cooperating with any treatment, examination, testing, follow-up and questionnaires required to complete the trial;

11. The patients are willing to cooperate with the completion of the questionnaire on the quality of life during the trial treatment and follow-up, and agree that the results of these questionnaires will be used in clinical research;

   Patients currently participating in other clinical trials or having other inappropriate reasons suggested by investigators should not participate in this study.

3. Do I have to participate?

   It is up to you to decide whether to participate in this study. Even if you decide not to participate in this study, the treatment and medical attention you deserve will not be affected in
any way. Your study doctor will explain to you the treatment options in this clinical study, as well as the potential clinical benefits and risks of participating in this study.

Your participation in this study is entirely voluntary. Your decision to participate in the study will not have any effect on you or your medical care. If you wish to participate in this study, you will need to sign this informed consent form to indicate your consent to the use and sharing of your personal health information and clinical data by your study doctor for the purpose of checking information related to this study. Your personal information and corresponding privacy will be protected in accordance with relevant laws and regulations.

After signing this informed consent form, you may discontinue your study participation at any time without affecting your right to receive further treatment. Your study doctor may also decide to stop your study treatment if he or she believes that you should not continue your study treatment (eg, if your condition worsens or develops other medical conditions, which means you cannot continue your study treatment). After you stop this study treatment, you will still need follow-up until the end of the study.

4. Do I have other treatment options?

Your study doctor will discuss other options for treating your disease with you. If you decide not to participate in this study, please ask your study doctor about other treatment options.

5. What will happen if I participate in the study?

If you are willing to participate in this study, you will be required to visit the hospital regularly for clinical follow-up on dates requested by your doctor over the next few months so that we can gather information to ensure your safety and treatment efficacy. Thereafter, we will collect information about your research for as long as possible. The longer we stay in touch, the more information we have about you, which will help us learn more about the efficacy and safety of this investigational drug, and help us learn more about the fight against cancer in patients with the same condition as you.

**Examination to be done before starting treatment (screening):**

During the screening period before you receive study treatment, your study doctor will explain the study to you. If you agree to participate in this study, please sign this informed consent form. After signing this informed consent form, you need to cooperate with the study doctor or researcher to complete the following examinations:
• You will be asked for demographic information such as date of birth and ethnicity.

• You will be asked about your past medical history and information on any medications you have used in the past.

• Take your resting temperature, pulse, respiratory rate and blood pressure as well as your height and weight.

• ECOG PS Score: This is an overall status assessment that your doctor will rate your overall status.

• Have a full physical examination.

• A 12-lead electrocardiogram (ECG) will be performed. This is a test that measures the electrical activity of your heart.

• Your blood samples, urine samples, and stool samples will be collected to assess your general health, including blood routine, blood chemistry, coagulation, thyroid function, HIV antibody test, HBs antigen test, HCV antibody test, urine routine, pregnancy test, CA125 and fecal occult blood, etc.

• A pregnancy test will be performed (for women).

• Adverse events that occurred after you signed the informed consent form will be evaluated.

• You will be asked about concomitant medications you have used since you signed the informed consent.

• You will be scheduled for laparoscopy (preferred) or puncture of tumor tissue, and computed tomography (CT) and/or magnetic resonance (MRI) examinations of the chest, abdomen and brain for tumor assessment.

The above are routine procedures for tumor status assessment, which will be performed whether or not you are participating in this study. The frequency of assessments in this study was comparable to that of standard clinical practice. Be sure to tell your doctor promptly if you have any conditions that may be related to your treatment.
After all screening procedures are complete, your study doctor will conduct an evaluation to determine your eligibility to participate in this study.

**Treatment period**

If you meet all the requirements for this study, you will begin treatment with sintilimab in combination with bevacizumab with the following dose: sintilimab 200 mg intravenous infusion (over 30-60 minutes) every 3 weeks as a cycle, administered on the first day of each cycle; bevacizumab 15 mg/kg, intravenous infusion, every 3 weeks as a cycle, administered on the first day of each cycle.

During treatment, you will need to follow up on the cycle prescribed by the clinical trial for the following assessments:

- Take your temperature, pulse, respiratory rate, weight and blood pressure.
- Physical examination.
- ECOG PS score.
- 12-lead electrocardiogram (ECG).
- Blood routine, urine routine, blood biochemistry, CA125 and other tests.
- Thyroid function, coagulation function.
- There will be an evaluation of adverse events you have experienced.
- You will be asked about your concomitant medications used during the study.
- Tumor imaging evaluation: After randomization, for the first 18 weeks after starting treatment, tumor imaging evaluation is performed every 6 weeks (2 dosing cycles). After 18 weeks after starting treatment, tumor imaging evaluation is performed every 12 weeks (4 dosing cycles) until disease progression or study termination, whichever occurs first. Scans including CT (computed tomography) or MRI (magnetic resonance imaging) will be used to assess your disease status. These assessments will be performed according to routine clinical criteria whether or not you are participating in this study. If needed, follow your doctor's recommendation for additional imaging evaluations.
If you or your study doctor decide to stop treatment, we will ask you to continue with your study visit or stay in touch unless you decide to withdraw from the study entirely.

**Follow-up period**

You will have a safety follow-up visit about 30 days after your last treatment/monitoring, which includes tests to learn more about the efficacy and safety of this treatment regimen. After the safety follow-up, the study doctor will keep in touch with you to understand your disease status and subsequent antitumor treatment, which may be of great value to research in this disease area and may also be helpful for other patients in the future for providing better treatment options.

6. What do you need to do?

You agree to follow the following research procedures:

- You need to tell your doctor if you have any changes in your health, or if you may have any symptoms, whether or not you think they are related to your treatment.

- You will be required to attend certain visits to receive all the examinations and assessments described in "What will happen if I participate in the study".

- Make sure you are receiving study medication as required.

- It is also important that before and during the study, inform your healthcare provider about other medicines you are taking or plan to take, including vitamins, nutritional supplements, herbal or other folk remedies, immunomodulators, antibiotics, etc., which may affect your antitumor treatment. Also, live attenuated vaccines cannot be received during immunotherapy.

- Any time you have questions, please contact your study doctor.

7. What should female patients of reproductive potential and male partners with female patients of reproductive potential pay attention to?

If you or your partner were pregnant or your partner was planning to become pregnant during the study period, we need to inform you that the study drug may have unknown risks to the unborn baby for safety reasons and that it is not recommended for use during pregnancy and breastfeeding. Because of these risks, you should not participate in this study if you are pregnant, plan to become pregnant or breastfeeding during the study, or within 6 months of your last dose.
of study treatment. Tell your study doctor immediately if you or your partner become pregnant or if you think you or your partner may become pregnant.

You and your partner will need to agree to use effective contraception or you will need to abstain from sex during the entire study period or for 6 months after the last dose of study treatment.

8. What are the possible benefits of participating in research?

Participation in this study may result in remission, but we cannot guarantee this. This research also helps determine which treatments are safer and more effective for other patients with conditions similar to yours.

9. What are the possible side effects, risks and discomforts of participating in the study?

The study drug can cause some side effects, which can be mild to severe or even life-threatening and can vary from person to person. We will take all feasible precautions and encourage you to report any concerns that bother you to us.

**Known related side effects of sintilimab**

In completed clinical studies, the most common (≥10%) adverse events after receiving sintilimab included anemia (27.4%), pyrexia (23.9%), increased aspartate aminotransferase (16.3%), increased alanine aminotransferase (15.7%), fatigue (13.9%), cough (13.0%), decreased white blood cell count (11.7%), decreased neutrophil count (11.7%), proteinuria (11.5%), constipation (10.9%) and decreased appetite (10.4%). Grade 3 and above TEAEs accounted for 36.5% (197/540), and the most common (≥1%) grade 3 or above TEAEs included pulmonary infection (4.8%), anemia (4.6%), neutrophil count Decreased (3.3%), increased lipase (2.6%), decreased platelet count (2.4%), pneumonia (1.9%), hypertension (1.9%), hyponatremia (1.9%), elevated gamma-glutamyl transferase (1.9%), decreased lymphocyte count (1.9%), infectious pneumonia (1.7%), upper gastrointestinal bleeding (1.5%), decreased white blood cell count (1.5%), leukopenia (1.3%), hypokalemia (1.3%), and upper respiratory tract infection (1.1%).

Immune-related adverse events included: immune-related pneumonitis (4.4%), immune-related colitis (1.9%), immune-related hepatitis (1.1%), immune-related nephritis (0.2%), immune-related endocrine disease (13.9%) %, and immune-related skin adverse reactions (3.3%).

**Known related side effects of bevacizumab**

Possible side effects of bevacizumab include:
Gastrointestinal perforation: gastrointestinal perforation may occur with bevacizumab, with an incidence of 0.3-3.2%.

Surgical and wound healing complications: the use of bevacizumab may increase the risk of wound healing and surgical complications.

Bleeding: patients receiving chemotherapy plus bevacizumab had increased rates of severe or fatal bleeding, including hemoptysis, gastrointestinal bleeding, central nervous system bleeding, epistaxis, and vaginal bleeding.

The other most common adverse events were hypertension, fatigue or asthenia, diarrhea and abdominal pain.

Bevacizumab biosimilars have a similar safety profile to bevacizumab and can be managed in accordance with the measures for bevacizumab safety management.

**Known related side effects the two-drug combination**

In the data released at the 2020 American Society of Clinical Oncology Annual Meeting, a total of 50 patients who received sintilimab combined with bevacizumab for the treatment of advanced liver cancer were included. The overall safety of sintilimab combined with bevacizumab is good, the vast majority of adverse events were mild to moderate, the most common being hypertension (28%) and pyrexia (26%).

**Other side effects (not related to study drug, but may be related to study participation):**

**To collect blood samples:**

There may be some discomfort when taking blood. There may be mild pain, light bleeding, discoloration, or bruising at the needle insertion site. There is also a risk of infection or phlebitis (inflammation of a vein caused by a small blood clot), but these side effects are rare.

Blood samples are drawn at various times throughout the study for safety assessment and to explore specific cancer markers present in your blood. A blood sample will be drawn at your visit.

To facilitate drawing a blood sample, a small tube (also called a cannula) may be placed into your vein, and the blood sample may be drawn from the cannula. You may experience discomfort from inserting the cannula.

**A CT or MRI procedure may involve some discomfort:**
Each scanning procedure may require you to lie flat on a platform that slides toward a large circular opening. Subjects with claustrophobia (fear of being in confined spaces) may experience discomfort during scans. Your study doctor may give you a drug to make you feel more comfortable.

During a CT scan, you will need an intravenous injection of contrast. As a result, you may experience a slight burning sensation at the injection site, a metallic taste in your mouth, and hot flashes. Rarely, the injection of contrast during a scan can cause an allergic reaction. This allergic reaction may include itching and rash or, in severe cases, difficulty breathing and a drop in blood pressure. You should tell your doctor or radiologist if you have any allergic reaction to imaging contrast media. Also, you are exposed to a small amount of radiation when you have a CT scan.

MRI scans do not involve radiation. When needed, a special type of contrast medium is injected into the vein to improve image quality. Reactions to MRI contrast agents are rare and usually do not exceed headache. MRI scanners are very noisy.

10. Do I need to pay any fees for participating in this research? Are there remuneration and compensation?

To participate in this study, subjects will receive the study drugs sintilimab and bevacizumab free of charge throughout the course of the study. Other routine medical examination and treatment fees, such as registration fees, hospitalization fees, treatment fees, outpatient examination fees and other medicines you need to use, need to be paid by you.

11. What is the compensation for possible harm caused by participating in this research?

In the event of a study-related injury as a result of your participation in this clinical study, you will receive necessary medical treatment, provided that you are following the instructions of your study doctor.

The treatment and examination required for other diseases that you have concurrently will not be covered by the reimbursement.

12. How will my privacy be protected?

All medical records and research materials related to your identity will be kept confidential. Your name will not appear on the case report form, but will be recorded in English initials. Your medical records will be properly deposited with the investigator. Within the scope of relevant laws and regulations, these materials will not be disclosed. Even if the results of this study are
published in a medical journal, your profile will not be made public. If you drop out of the trial, your previously obtained data will continue to be used, but your information will not be made public.

Your original medical records may be reviewed by the State Food and Drug Administration, the government regulatory agency, sponsors, ethics committees, and doctors participating in the study.

By signing this informed consent form, you agree that the above-mentioned agencies or persons may review the relevant information.

13. How to obtain research consultation?

If you have any questions or concerns during the study, you can always contact the doctor(Name: _____) in charge of the study by phone(Tel: _____), and your doctor will promptly notify you of any new information related to the study, so that you can decide whether to continue participating in this study.

The protocol of this study has been reviewed and approved by the ethics committee. If you have questions about the rights and interests of subjects, you can consult the ethics committee of this hospital. Contact: _____ Tel: _____.

14. How can I get more information?

You can ask any questions about this study at any time. Your doctor will leave you his/her phone number so he can answer your questions.

Your doctor will promptly notify you of any important new information during the study, including but not limited to adverse events and major findings, which may affect your willingness to continue participating in the study. You will be asked to sign a new informed consent form to document your updated information.
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Informed consent signature page

I have carefully read this clinical study informed consent form or others have read the above to me. I confirm that I have fully understood the relevant information of this study, including possible risks and benefits, and have had sufficient time to consider whether to participate in this clinical study, and all questions have been satisfactorily answered. I still have the right to be consulted at any time and to decide to withdraw from this study at any time without penalty of any kind and without loss of any legal rights.

I volunteered to participate in this study and cooperated fully with the investigators.
I can obtain a signed copy of this informed consent form.
In the end, I decided to agree to participate in this study and follow my doctor's orders.

Subject's name (print)__________________

Subject's signature: _________________

Date of signature: _____(year-month-day)

Contact information: _________________

Legal representative (if applicable)

☐ Not applicable
When signed by a legal representative, please indicate the means by which you (as the legal representative) are authorized to provide consent on behalf of the subject.

(choose an item)

☐ Power of Attorney

☐ Health Care Attorney/Power of Attorney (explain in advance)

☐ Relationship to subject (spouse, siblings, etc., please specify below)

_________________________________________

☐ Other (please specify below)

_________________________________________

Legal representative name (print)______________
Signature of legal representative: _______________

Date of signature: _____ (year-month-day)

**Fair Witness (if applicable)**

☐ Not applicable

I certify that the information in this informed consent form has been accurately explained to the subject or his legal representative and that the subject or his legal representative has fully understood the information. I also certify that the subjects (or represented by their legal representatives) voluntarily agreed to participate in this research.

Fair Witness Name (Print)__________________

Fair Witness Signature: ____________

Date of signature: _______ (year-month-day)

Main contact information: ____________

Identification number: ____________

Address: ____________

**Investigator Statement**

I confirm that the nature, purpose, requirements and possible risks of this study have been explained and informed to the patient, and all relevant questions of the subject have been answered, and that the patient has voluntarily consented to participate in this study. This informed consent form is in duplicate, and the investigator and the subject each hold a signed informed consent form.

According to national laws and regulations and the program of this research, I will carry out the clinical study accurately and take necessary measures to protect the rights and safety of the above-mentioned subjects.

Investigator’s signature: ____________

Date: _________ (year-month-day)

Contact information: ____________