Informed Consent for Efficacy and safety of NeoAdjuvant chemotherapy with or without tIslelizumab followed by debulking surgery for oVarian cancEr (NAIVE study) in China: an open-label, phase II, randomized controlled trial

Distinguished Subjects,

We invite you to participate in the research project titled "Efficacy and safety of NeoAdjuvant chemotherapy with or without tIslelizumab followed by debulking surgery for oVarian cancEr (NAIVE study) in China: an open-label, phase II, randomized controlled trial" which has been approved by the Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang University. This study will be conducted at The Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang University, with an estimated 40 participants voluntarily taking part. The study has been reviewed and approved by the Institutional Ethics Committee of the Second Affiliated Hospital of the Medical College of Zhejiang University.

The following is an introduction to this study:

Background and purpose of the study?

Ovarian cancer is among the most prevalent malignant neoplasms of the female reproductive system, with an incidence rate that places it in the top ten worldwide and a mortality rate that positions it in the top five among female neoplasms. Annually, 52,100 new cases of ovarian cancer and 22,500 deaths are reported in China, designating it as a major health concern for women. The insidious onset of the disease, in addition to the absence of effective screening methods, results in the majority of patients being diagnosed only when they present with pelvic masses, ascites and distant metastases. By the time a diagnosis is made, approximately two-thirds of patients are in the advanced stage (Stage III/IV). The standard initial treatment for advanced ovarian cancer currently consists of tumour reduction surgery and individualised platinum-based adjuvant chemotherapy. The overall prognosis of ovarian cancer is poor, with approximately 80% of patients experiencing recurrence following initial treatment, with a median time to recurrence of only 14 months. Achieving R0 status during tumor cytoreduction

has been demonstrated to significantly improve survival outcomes in advanced ovarian cancer cases. However, the wide scope of the initial tumour reduction surgery, which often includes the resection of multiple organs in the pelvic and abdominal cavities, is not feasible for all patients. Furthermore, some patients are unable to tolerate the surgery due to the large initial tumour load or the limited level of treatment available at their medical institutions. In such cases, some patients with advanced stage ovarian cancer elect to undergo a combination of neoadjuvant chemotherapy and tumour cytoreduction following a definitive diagnosis. Research studies, including the EORTC55971 study, have indicated that a greater proportion of tumour cytoreduction following neoadjuvant chemotherapy achieves R0 resection. Nevertheless, the impact of neoadjuvant chemotherapy on long-term prognosis remains controversial, and it is not clear whether all patients will benefit from this treatment. Consequently, for patients who are unable to undergo initial tumor reduction surgery or who do not achieve adequate tumor reduction with a substantial tumor load, neoadjuvant chemotherapy may be a viable option. There is an urgent need to explore new effective therapies to control the disease preoperatively and provide R0 chance of surgery and overall survival.

Tumor immunotherapy represents a major focus of research in the field of tumor therapy, with considerable clinical benefits being achieved in the treatment of tumors. Programmed death receptor-1 (PD-1) is an immunosuppressive molecule that is the focus of considerable attention at present, which is primarily expressed in activated T cells and B cells. The binding of PD-1 to programmed death molecule ligand-1 (PD-L1), which is predominantly expressed in tumor cells, activates the PD-1 signaling pathway, thereby resulting in the impaired function of T cells. The use of PD-1 inhibitors that target this signaling pathway has the capacity to impede the binding between PD-1 and PD-L1, thus preventing the negative regulatory signaling pathway from being blocked and, consequently, restoring the functional activity of T cells. This, in turn, enhances the body's immune response ability. A plethora of clinical trials have been conducted on PD-1/PD-L1 inhibitors, and the results have confirmed the significant therapeutic efficacy of these inhibitors on various tumours. The NCCN guideline recommends the utilisation of PD-1 inhibitors in the second-line treatment of recurrent ovarian cancer.

Nevertheless, the role of PD-1 inhibitors in neoadjuvant therapy for advanced ovarian cancer is yet to be fully elucidated. The mechanism of immunotherapy involves the production of anti-tumour effects in response to the presence of tumours, which can significantly stimulate infiltrating T cells within the tumour by inhibiting the immune checkpoint pathway. This results in the exertion of immune killing and surveillance.

This phase II study was thus designed to explore the safety and efficacy of neoadjuvant chemotherapy with or without tIslelizumab in patients with advanced ovarian cancer. The study also sought to collect information, including patients' tumour samples, with a view to further exploring the predictive biomarkers of this treatment.

What do you need to do if you participate in the study?

The study comprises three phases: screening/baseline, treatment, and follow-up. Subjects who meet the eligibility criteria will receive neoadjuvant chemotherapy with or without tIslelizumab at 21-day intervals for a total of three cycles.

The following regimens are to be administered to patients enrolled in the neoadjuvant chemotherapy with tislelizumab cohort: nab-paclitaxel 260 mg/m², carboplatin AUC=5, and tislelizumab 200 mg, to be administered intravenously. The regimen for patients in the neoadjuvant chemotherapy cohort comprises nab-paclitaxel 260 mg/m² and carboplatin AUC=5, administered intravenously. Neoadjuvant therapy is administered every three weeks, with a total of three cycles. Computed tomography (CT) or magnetic resonance imaging (MRI) scans will be conducted at the baseline and prior to interval cytoreductive surgery (IDS), with the objective of evaluating the tumour response in accordance with the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Following IDS, participants will be required to attend regular follow-up assessments at three-month intervals until the conclusion of the study.

Should consent be provided for participation in this study, the treating physician will perform a screening examination and meticulously document the subject's general health in order to ascertain their suitability for participation in this treatment study. The aforementioned tests include a physical examination, blood draws for routine blood and blood biochemistry tests,

urine tests, an electrocardiogram, and an enhanced CT or PET-CT. These evaluations are essential for the study's objective of understanding the patient's ovarian cancer and ruling out any comorbidities. Following the successful completion of the screening process, participants will be randomly assigned (1:1) to either the carboplatin + nab-paclitaxel treatment group or the carboplatin + nab-paclitaxel + tislelizumab treatment group. Throughout the course of the study, scheduled check-ups will be conducted, and comprehensive observations and records of the subject's condition will be maintained. It is imperative to note that the evaluation tests constitute indispensable components of the standard treatment regimen. The purpose of these evaluations is threefold: firstly, to ascertain the efficacy of the treatment; secondly, to ascertain the suitability of the patient for continued participation in the study; and thirdly, to guarantee the safety of the patient.

It is imperative that patients provide exhaustive details to their study doctor or nurse regarding any medications they are currently taking and any ongoing treatments. The physician will inquire as to whether the patient is experiencing any adverse effects associated with the medications and whether the patient is adhering to the instructions provided by the physician. Upon completion of the study or premature termination thereof, the administration of immune-neoadjuvant therapy will be discontinued. Furthermore, a physical examination and laboratory tests must be scheduled for the patient's safety.

Who are not suitable to participate in this study?

1) Individuals between the ages of 18 and 75 years.

2) Pathologically confirmed as epithelial ovarian cancer, fallopian tube cancer, or peritoneal cancer (exclusive of mucinous adenocarcinoma).

3) International Federation of Gynecology and Obstetrics (FIGO) stage IIIc with a Suidan computed tomography (CT) score of 3 or greater or a Fagotti laparoscopic score of 8 or greater; or FIGO stage IV.

4) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, with the ability to

tolerate chemotherapy.

5) No previous immunotherapy for malignant tumors.

6) The subject must demonstrate an ability to comprehend the nature of the study and must have signed the informed consent form.

What are the risks of participating in study?

Potential complications and adverse effects:

1. Infection: Respiratory tract infection, urinary tract infection. Reactions affecting the blood and lymphatic systems may manifest as anaemia, leukopenia or neutropenia. Reactions affecting the endocrine system may manifest as hypothyroidism or hyperthyroidism.

4. Gastrointestinal reactions may manifest as diarrhea, nausea, vomiting, abdominal discomfort, constipation, and dry mouth.

5. Dermatological reactions: rash Skeletal muscle reactions: arthralgia, skeletal muscle pain.

9. Liver Function AbnormalitiesThe following adverse effects are frequently observed. In the event of any of the aforementioned adverse effects manifesting, it is imperative that the study physician be informed without delay.

In order to mitigate the risks associated with PD-1 inhibitors, training and studies are conducted in accordance with the guidelines for the management of immunotherapy-related adverse reactions. This ensures that medical personnel involved in clinical research are equipped with the knowledge and skills to recognise and manage adverse reactions.

What are the possible benefits of participating in this study?

Despite the existence of evidence that substantiates the efficacy of neoadjuvant chemotherapy for advanced ovarian cancer, it cannot be guaranteed that this treatment will be effective for the individual patient. Those who participate in this trial will receive the following

benefits: Firstly, participants will receive comprehensive anti-tumour treatment and assistance in the timely completion of all treatments within the treatment cycle.Secondly, the study will contribute to the determination of the most efficacious and safe treatment method for other patients with similar conditions.

Do you need to pay any relevant fees to participate in the study?

All ovarian cancer-related genetic tests that can be used to guide the full course of treatment, including those for BRCA1/2 and HRD, will be made available to patients. Moreover, patients will be provided with complimentary PD-1 inhibitors. During the study, participants will be responsible for covering the costs of routine examinations, including blood routine, biochemistry, coagulation, stool routine, urine routine, myocardial markers, thyroid function, T cell count, electrocardiogram, and imaging, as well as for the costs of hospitalization and outpatient diagnosis and treatment.

Is your personal information confidential?

The materials in question are to be stored at the Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang University. Access to these medical records will be granted to researchers, research authorities, and ethics review committees. Any public reports related to the results of this research will not include any information that could identify you personally. The confidentiality and personal data of your medical records will be safeguarded in accordance with the legal framework.

Do you have to participate in research?

Participation in this study is entirely voluntary, and participants are free to refuse to participate or withdraw from the study at any stage of the trial.

Subject Statement: I have read the above introduction about this study, and my researchers have explained to me the purpose, operational process, potential risks and benefits of participating in this study, and answered all my relevant questions. I voluntarily participate in this study.

Subject signature: _____ Date: _____(Y)_____(M)_____(D)

Subject's contact phone number: _____

Signature of legal representative: _____ Date: _____(Y)_____(M)_____(D)

Relationship with subjects: _____

Doctor's statement: I have explained the relevant details of the study to the volunteer mentioned above, and provided him/her with an original signed informed consent form. I confirm that I have provided the participants with a detailed explanation of the situation of this study, especially the ethical principles and requirements that may arise from participating in this study, such as risks and benefits, free and compensation, damages and compensation, voluntary and confidentiality.

Doctor's signature: _____ Date:_____(Y)_____(M)_____(D)

Doctor's contact phone number: _____

Institutional Ethics Committee of the Second Affiliated Hospital of the Medical College of Zhejiang University

Contact phone number: 0571-87783759