Informed Consent Form for a Study on the Efficacy and Safety of Low-Dose Radiation Combined with Neoadjuvant Chemotherapy and Immunotherapy in Locally Advanced Esophageal Squamous Cell Carcinoma

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Dear Research Participant,

We invite you to participate in the study titled "Effectiveness and Safety of Low-Dose Radiotherapy Combined with Neoadjuvant Chemotherapy and Immunotherapy in Locally Advanced Esophageal Squamous Cell Carcinoma," approved by West China Hospital of Sichuan University. This study will be conducted at West China Hospital of Sichuan University, and it is estimated that 30 voluntary participants will be enrolled. This study has been reviewed and approved by the Biomedical Ethics Review Committee of West China Hospital of Sichuan University.

Why is this study being conducted?
Esophageal cancer ranks fifth among all malignant tumors in China, with as many as 324,000 new cases and 301,000 deaths annually. Immunotherapy has shown significant survival benefits in advanced esophageal cancer patients. Immunotherapy combined with chemotherapy has become the standard first-line treatment for advanced esophageal cancer. The use of PD-L1 antibodies for immunotherapy and surgery has shown comparable long-term survival outcomes to traditional radiotherapy and chemotherapy. This further demonstrates the potential of neoadjuvant immunotherapy compared to traditional neoadjuvant radiotherapy and chemotherapy. However, the local control effect of immunotherapy alone or in combination with chemotherapy is still unsatisfactory, which may affect the curative effect of surgery and long-term survival of patients. Therefore, combining low-dose radiotherapy with immunotherapy is undoubtedly a more promising treatment option. The purpose of this study is to use neoadjuvant low-dose radiotherapy combined with chemotherapy and immunotherapy (chemoimmunotherapy) to improve local control efficacy and reduce adverse reactions caused by combined treatment modalities by reducing the radiotherapy dose.

What will you need to do if you participate in the study?
Participants will be enrolled in the study from the time of diagnosis of esophageal squamous cell carcinoma in the outpatient clinic until 3 years after surgery, ending with the final follow-up. There will be a total of 7 follow-up visits. Additional low-dose radiotherapy will be administered during the neoadjuvant stage, with no additional examinations or procedures required.
Participants will receive neoadjuvant low-dose radiotherapy combined with chemoimmunotherapy. During the neoadjuvant treatment stage, patients will receive two cycles of low-dose radiotherapy combined with chemotherapy and immunotherapy, with each cycle lasting 21 days. The specific treatment plan is as follows: Day 1 and Day 2: Low-dose radiotherapy (4 Gy/2f); Day 3: Toripalimab, fixed dose of 200mg; Albumin-bound paclitaxel 260mg/m2; Cisplatin 75mg/m2 or Carboplatin AUC = 5. The interval between radiotherapy and chemotherapy should not exceed 3

days. Drug infusion will be administered in the order of toripalimab → albumin-bound paclitaxel → cisplatin/carboplatin, with a minimum interval of 30 minutes between each infusion. At the end of neoadjuvant treatment, patients will undergo surgical treatment 6-8 weeks after the last treatment.

What are the alternative treatment options available?
Participants have other alternative treatment options, such as neoadjuvant concurrent chemoradiotherapy or neoadjuvant chemotherapy.

Who should not participate in the study?
You should not participate in the study if you: (1) are not suitable for the immunotherapy and chemotherapy regimen specified in the protocol; (2) have received treatment for esophageal squamous cell carcinoma, including investigational drugs, chemotherapy, radiotherapy, or treatment with anti-PD-1, anti-PD-L1, anti-PD-L2 antibodies, or drugs targeting specific T-cell co-stimulatory checkpoint pathways; (3) have a history of primary tumor infiltration causing fistulas; (4) are assessed by the investigator as having a high risk of fistulas or signs of perforation; (5) have any symptoms requiring systemic corticosteroid therapy (prednisone > 10 mg/day or equivalent) or other immunosuppressive therapy within 14 days before the first dose; use of adrenocorticosteroids as replacement therapy (prednisone ≤ 10mg/day or equivalent) and locally, ocularly, intra-articularly, intranasally, and inhalationally administered corticosteroids with minimal systemic absorption, and short-term (≤ 7 days) use of corticosteroids for the prevention or treatment of non-autoimmune diseases; dexamethasone can be used for paclitaxel premedication; (6) have active autoimmune diseases or a history of autoimmune diseases that may recur; participants with controlled type I diabetes, hypothyroidism requiring only hormone replacement therapy, controlled celiac disease, skin diseases that do not require systemic treatment (such as vitiligo, psoriasis, or alopecia), or diseases that will not recur without external triggering factors can be enrolled in the study; (7) have a history of interstitial lung disease, non-infectious pneumonia, or poorly controlled pulmonary disease (including pulmonary fibrosis, acute pulmonary disease, etc.); (8) require systemic antibacterial, antifungal, or antiviral therapy for infections, including pulmonary tuberculosis infection. Severe infections occurring within 4 weeks before the first dose, including but not limited to infections with complications requiring hospitalization, sepsis, or severe infectious pneumonia occurring within 2 weeks before the first dose of therapeutic oral or intravenous antibiotics; (9) have known allogeneic organ transplantation (except corneal transplantation) or allogeneic hematopoietic stem cell transplantation; (10) have known allergies to the study drug toripalimab or the active ingredients or excipients of the combined chemotherapy drugs; (11) have significant and uncontrollable abnormalities in rhythm, conduction, or morphology on resting electrocardiography, such as complete left bundle branch block, second-degree or higher heart block, ventricular arrhythmia, or atrial fibrillation; unstable angina pectoris, congestive heart failure, chronic heart failure with New York Heart Association (NYHA) class ≥ 2.

Participants with the following conditions should not participate in the study:

What are the risks of participating in the study?

During radiotherapy, patients may experience more or less radiation-related toxic side effects. However, preliminary diagnosis and corresponding examinations are needed to confirm the diagnosis and treat it promptly. Common radiation therapy-related toxic reactions in clinical practice include radiation pneumonitis, radiation esophagitis, and radiation dermatitis.

Paclitaxel (albumin-bound) and toripalimab are used off-label in this study. Participants may experience chemotherapy and/or immunotherapy-related toxic side effects.

Treatment-related severe adverse events of low-dose radiotherapy: During the low-dose radiotherapy stage, if grade 2 radiation pneumonitis occurs, immunotherapy can be discontinued without stopping radiotherapy, and local radiotherapy can continue while symptomatic treatment with steroids is given, but the risk and benefit need to be judged by the treating physician, and close monitoring for development of grade 3 or higher radiation pneumonitis is needed. If grade 3 or 4 radiation pneumonitis/pulmonary infiltration related to radiotherapy occurs, it is recommended to suspend radiotherapy and toripalimab treatment. If symptoms improve to ≤ grade 1 or are controlled with a prednisolone dose ≤ 10 mg/d (or equivalent corticosteroid dose), radiotherapy and toripalimab treatment can be resumed. If symptoms persist after corticosteroid therapy, study treatment should be discontinued.

Rescue plan for severe adverse events related to toripalimab treatment: If a hypersensitivity reaction is observed, the patient will receive epinephrine injection and dexamethasone infusion, and then be immediately monitored and, if necessary, transferred to the intensive care unit.

Rescue plan for severe adverse events related to paclitaxel (albumin-bound) treatment: Discontinue the drug immediately, monitor the patient, and, if necessary, notify the intensive care unit for possible transfer.

Each patient in this study will be covered by clinical trial insurance, providing security for the patient's treatment. When a patient suffers harm related to the study, doctors will provide timely treatment and rescue according to clinical diagnosis and treatment procedures and norms. In case of harm during the study, including death, if it is determined by medical-related departments to be related to the study, compensation can be made to the patient according to relevant insurance regulations.

Claim details: Each patient in this study will be covered by clinical trial insurance with a compensation of 500 yuan per case. When a research participant experiences a severe adverse event (SAE) related to toripalimab treatment during the clinical trial process, the investigator will judge the relationship between SAE and the investigational drug. If the determination results indicate a possible or definite relationship, the subject can apply to the insurance company for compensation for the losses caused by treating SAE. After obtaining the responsibility determination from the authoritative department of the insurance company, compensation will be made according to the terms and scope of liability and the agreement of the policy. The cumulative compensation limit is RMB 1 million (¥2,000,000.00), and the compensation limit for each accident is RMB 1 million (¥2,000,000.00).

What are the potential benefits of participating in the study?

Participants in this study will receive corresponding compensation, including two cycles of free toripalimab infusion provided by Suzhou Shengdiya Biopharmaceutical Co., Ltd., a transportation subsidy of 100 yuan per trip, and clinical trial insurance purchased at 500 yuan per case. Blood collection will be reimbursed at 200 yuan per instance from the project leader's research funds.

Participation in this study may improve your condition, and the study will also help determine which treatment method can safely and effectively treat other patients with similar conditions to yours. However, participants are explicitly informed that "you may not benefit from the treatment in this study."

Do I need to pay any fees to participate in the study?
Participants will be fairly and reasonably selected for the study, and no fees will be charged to participants for participating in the study. Reasonable expenses incurred by participants during the trial process will be appropriately compensated.
Participants will receive active and free treatment and reasonable compensation in case of harm related to the study.
Insurance will be purchased for each study participant. When a participant experiences a severe adverse event related to the study drug, expenses for the treatment of the severe adverse event will be covered by the insurance company.

Is personal information kept confidential?
Your research data will be kept confidential at West China Hospital of Sichuan University, accessible to the researchers, supervising department, and ethics review committee. Any public reports on the results of this study will not disclose your personal identity. We will make every effort to protect the privacy and personal information of your medical records within the limits permitted by law.

Am I required to participate in the study?
Participation in this study is entirely voluntary. You have the right to refuse to participate in the study or to withdraw from the study at any stage without discrimination or retaliation, and your medical treatment and rights will not be affected. If you decide to withdraw from the study, please contact your doctor for appropriate diagnosis and treatment of your condition.

Research Participant Declaration: I have read the above introduction to this study, and my research personnel have fully explained and clarified the purpose, procedures, potential risks, and benefits of participating in this study, and have answered all my relevant questions. I voluntarily agree to participate in this study.

I agree☐ or I decline☐ to the use of my research data and biological specimens for other studies besides this research.

Name of Participation：_____

Participant Signature：_____Date：_ _ _ _ Year _ _ month _ _ day

Phone number：_____

Doctor's Declaration: I have explained the relevant details of the study to the volunteer

participating in this research and provided them with a signed original copy of the informed consent form. I confirm that I have thoroughly explained the details of this study to the research participant, especially the ethical principles and requirements regarding risks and benefits, free and compensated participation, harm and compensation, voluntariness, and confidentiality.

Researcher Signature：_____Date：_ _ _ _ Year _ _ month _ _ day

Phone number：_____