【Informed Consent Form Template (Version V1.0; Version Date 2022-01-01) Instructions】: This template is developed by researchers from our institution for clinical research purposes. This template is for reference only. Researchers should draft the informed consent form based on the specific circumstances of the project, not limited to this template. Please fill in the version number, version date, underlined sections, and blank spaces in the template according to the actual project situation. **【Informed Consent Form Template (Version V1.0; Version Date 2022-01-01) Instructions】: This template is developed by researchers from our institution for clinical research purposes. This template is for reference only. Researchers should draft the informed consent form based on the specific circumstances of the project, not limited to this template. Please fill in the version number, version date, underlined sections, and blank spaces in the template according to the actual project situation.**

Informed Consent Form for Participants

Study Title: Efficacy and Safety of PD-1 Inhibitor Combined with Chemotherapy for Locally Advanced (III-IVB), Poorly Differentiated Head and Neck Squamous Cell Carcinoma: A Multicohort, Prospective Phase II Study

Research Institution: Beijing Tongren Hospital, Affiliated to Capital Medical University

Dear Patient:

We are conducting a clinical research study, and your condition may meet the inclusion criteria for this study. Therefore, we invite you to participate in this study. This informed consent form will introduce the purpose, procedures, benefits, risks, etc. of this study to you. Please read it carefully and make a decision whether to participate in the study.

When the researcher explains the content of this informed consent form to you, you can ask questions at any time and ask him/her to explain any parts that you do not understand. After discussing with your family, friends, and your treating physician, you can make a decision.

The principal investigator of this study is Dr. Xiaohong Chen at Beijing Tongren Hospital, affiliated with Capital Medical University.

This study has no project support.

1. Why is this study being conducted?

Surgery is the main treatment for head and neck squamous cell carcinoma. Early cases can be cured by surgery alone or radiation therapy. For intermediate and advanced cases, surgery combined with radiation or chemotherapy can achieve better results. However, most patients with head and neck tumors are already in the advanced stage (stage III-IVB) or late stage when they seek medical attention, and they may have lost the opportunity for surgery. They can only choose comprehensive treatment mainly based on radiation and chemotherapy. Currently, data shows that the 5-year survival rates for patients with early-stage, locally advanced, and metastatic head and neck squamous cell carcinoma using standard treatment are 80%, 50%, and 25% respectively. 50% to 60% of newly diagnosed participants cannot be cured and experience recurrence or metastasis within 3 years. For recurrent or metastatic patients who have failed first-line treatment, the median survival period with chemotherapy is only 6 to 9 months, with a 1-year survival rate of 5% to 33% and a 5-year survival rate of only 3.6%.

The prognosis of tumors is closely related to pathological grading. At present, histological grading is also an important indicator for evaluating prognosis. As a pathological subtype of HNSCC, poorly/undifferentiated squamous cell carcinoma has strong invasiveness, high rates of distant metastasis and regional metastasis, and shows completely different characteristics from well-differentiated squamous cell carcinoma in terms of biological behavior. It has poor treatment efficacy and prognosis. Studies have shown that there is a 30% difference in the 5-year overall survival rate between patients with well-differentiated and poorly-differentiated laryngeal squamous cell carcinoma. Currently, the molecular mechanism of poorly/undifferentiated squamous cell carcinoma is still unclear, and there is no consensus on diagnosis and treatment recommendations based on the degree of differentiation. There is also a lack of large-scale, multicenter prospective clinical research on the treatment of poorly/undifferentiated squamous cell carcinoma of the head and neck, both domestically and internationally.

Neoadjuvant chemotherapy, also known as induction chemotherapy, refers to chemotherapy used before surgery or radiation therapy. It has the advantages of good

patient compliance, reducing tumor burden, increasing radiation sensitivity, improving organ preservation rate in surgical patients, eliminating potential metastatic lesions, and reducing the risk of distant metastasis. The most commonly used induction chemotherapy regimen is the PF regimen. With the application of docetaxel (T), it is also being explored whether docetaxel can be added to the induction chemotherapy regimen.

PD-1/PD-L1 monoclonal antibodies restore the function of tumor-specific T cells by blocking the binding of PD-1 and PD-L1, thereby enhancing anti-tumor immunity. They have been used to treat various types of tumors. The FDA approved pembrolizumab for the treatment of platinum-resistant recurrent or metastatic head and neck squamous cell carcinoma in 2016. In 2020, pembrolizumab combined with chemotherapy can be used as a first-line treatment for recurrent/metastatic head and neck squamous cell carcinoma. Additionally, pembrolizumab can also be used as a second-line treatment for platinum-resistant recurrent/metastatic head and neck squamous cell carcinoma. The efficacy of PD-1 monoclonal antibodies as a neoadjuvant therapy for head and neck squamous cell carcinoma is not yet clear. However, considering the favorable effects of immunotherapy in head and neck squamous cell carcinoma, the use of PD-1 monoclonal antibodies for induction therapy in poorly differentiated squamous cell carcinoma holds promising clinical prospects. In recent years, multiple studies have suggested that neoadjuvant therapy using nivolumab in combination with cisplatin and paclitaxel has good tolerability and satisfactory efficacy.

In summary, we anticipate that comprehensive genomic testing and analysis will be conducted on patients with poorly differentiated squamous cell carcinoma of the head and neck (non-nasopharyngeal cancer), in order to provide personalized guidance for treatment plans and to explore the safety and efficacy of PD-1/PD-L1 inhibitors combined with dual chemotherapy regimens, which may be more suitable for clinical application. By combining tumor tissue CPS expression, TMB, gene expression profiles, and peripheral blood lymphocyte immune characteristics, we aim to identify treatment options that are more effective and safe for poorly differentiated squamous cell carcinoma.

2. Who will be invited to participate in this study?

You are treated at the Department of Otolaryngology-Head and Neck Surgery of Beijing Tongren Hospital or you are an inpatient at our hospital. You need to meet the following inclusion criteria:

[1]. Patients with locally advanced (III-IVB) poorly differentiated head and neck tumors (hypopharyngeal cancer, laryngeal cancer, oropharyngeal cancer, nasal cavity and sinus cancer, excluding nasopharyngeal cancer) with a confirmed diagnosis by histology and/or cytology;

[2]. Patients who can receive systemic treatment or PD-1/L1 monotherapy before treatment;

[3]. Patients in arm2 must be evaluated as having resectable tumors before treatment;

[4]. The investigator believes that the patient can safely receive PD-1 combined with platinum-based and albumin-bound paclitaxel treatment;

[5]. Age ≥ 18 years;

[6]. ECOG 0-1；

[7]. Measurable disease defined by RECIST v1.1;

[8]. Adequate bone marrow reserve and organ function: absolute neutrophil count (ANC) ≥ 1,000/μL, platelets ≥ 75,000/μL, hemoglobin ≥ 8g/dL, no transfusion or erythropoietin (EPO) dependence (within 7 days of assessment);

[9]. Renal function: serum creatinine ≤ 1.5X upper limit of normal (ULN) OR measured or calculated creatinine clearance ≥ 60mL/min, creatinine level > 1.5X institutional ULN. (GFR can also be used instead of creatinine or CrCl). Creatinine clearance should be calculated according to institutional standards;

[10]. Liver function: For subjects with total bilirubin levels >1.5 ULN, serum total bilirubin ≤1.5X ULN or direct bilirubin ≤ULN; For patients with liver metastasis, aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≤2.5X ULN or ≤5X ULN; Albumin > 2.5 mg/dL;

[11]. Coagulation function: International normalized ratio (INR) or prothrombin time (PT)

≤1.5X ULN, if subjects require anticoagulant therapy, PT or PTT should be within the allowable range of anticoagulant use;

[12]. Women should agree to use contraception during the study and for 6 months after the end of the study (such as intrauterine devices (IUDs), contraceptive pills, or condoms); Within 7 days before study enrollment, serum or urine pregnancy test should be negative, and patients must be non-lactating; Men should agree to use contraception during the study and for 6 months after the end of the study.

A total of 100 subjects will be enrolled in this study.

3. How is this study conducted?

First, we need to conduct a thorough physical examination and focused specialty examinations to exclude contraindications, collect your basic and clinical data, and if necessary, supplement with relevant imaging or cytological examinations based on your condition. Before treatment, undergo FoundationOne CDx comprehensive genomic sequencing analysis and CPS testing, and adjust the treatment plan based on the results. The study is divided into 2 groups, Arm1 group: PD-1 combined with platinum-based combined albumin paclitaxel (dose according to the drug instructions) for 2 to 3 cycles (determined by the investigator based on the tumor shrinkage of the patient), if the imaging reaches CR/PR, suitable patients will undergo surgical treatment, and patients who are not suitable for surgery or have SD/PD will receive synchronous radiochemotherapy or synchronous radiochemotherapy combined with PD-1 treatment (a total of no more than 17 cycles); Arm2 group: PD-1 combined with platinum-based combined albumin paclitaxel (dose according to the drug instructions) for 2 cycles in patients with stage III, IVA (T3NxM0, T4aNxM0) poorly differentiated head and neck squamous cell carcinoma (hypopharyngeal cancer, laryngeal cancer, oropharyngeal cancer, nasal cavity and sinus cancer, excluding nasopharyngeal cancer). Patients who undergo surgery will undergo surgery within 2 weeks. According to the pathological results, patients with pCR will receive PD-1 monotherapy maintenance treatment or low-dose radiotherapy followed by PD-1 monotherapy maintenance treatment. Patients

without pCR and positive surgical margins or extracapsular invasion after surgery will receive synchronous radiochemotherapy followed by PD-1 maintenance treatment (a total of no more than 17 cycles), and patients without high-risk factors will receive PD-1 maintenance treatment after radiotherapy (a total of no more than 17 cycles). All patients will be followed up every 3 months for 1 year after the end of treatment; Then, they will be followed up every 6 months for 3 years; Afterwards, they will be followed up once a year; Record patient recurrence and survival data. The main evaluation of the study is the objective response rate (ORR) after PD-1 combined with platinum-based and albumin paclitaxel treatment in Arm1, and the pathological complete response rate (pCR) after PD-1 combined with platinum-based and albumin paclitaxel neoadjuvant treatment in Arm2. Secondary endpoints include tumor TNM downstaging rate; Progression-free survival (PFS), quality of life (QoL), safety, etc., and study the correlation between tumor tissue CPS expression, TMB, gene expression profile, and peripheral blood lymphocyte immune repertoire characteristics and the efficacy of the pembrolizumab combined chemotherapy regimen, providing a basis for the rational clinical application of PD-1 treatment. Analyze the effectiveness, safety, and prospects of immunotherapy in the application of poorly differentiated squamous cell carcinoma in the head and neck.

4. Would you like to participate in this study and its potential benefits?

Patients who meet the eligibility criteria for this study may experience the following potential benefits:

- Reduced risk of tumor metastasis
- Improved disease survival rate
- Enhanced quality of life

Additionally, you will not receive any direct financial benefits from participating in this study.

5. What are the potential risks and inconveniences of participating in this study?

Head and neck poorly differentiated squamous cell carcinoma has a high rate of distant metastasis and poor prognosis. Due to insufficient clinical data on immunotherapy combined with chemotherapy, there is a possibility of poor treatment efficacy and disease

progression. We will closely monitor and evaluate relevant indicators, make timely adjustments to the treatment plan, and strictly select appropriate treatment indications and drug usage indications to minimize risks.

This study collects postoperative tumor tissue, or paraffin tissue and peripheral blood provided by you, which will not affect your normal diagnosis and treatment process and will not bring you additional risks. This study requires the collection of blood specimens, and during the blood collection process, there may be local skin discoloration, pain, and extremely rare local infections. This study will not disclose your personal information and will not have adverse effects on your life and work.

The drugs used in this study may cause allergic reactions, liver and kidney damage, immune-related pneumonia, endocrine disorders, and other immune-related adverse reactions. During the treatment process, relevant indicators will be monitored in a timely manner to avoid serious adverse reactions.

6. How does participating in this study affect your daily life?

This study may require the collection of blood and tissue samples, which can be done during your clinic visit or hospital stay, or by borrowing your case slides from an external hospital. Immunotherapy and chemotherapy require intravenous administration of medication.

Follow-up mainly consists of phone calls and necessary postoperative or follow-up visits, which should not significantly impact your daily work and family life, except for medical appointments. If there are any special circumstances, we will contact you in advance. If you have any questions about the tests and procedures involved in the trial, you can consult with us.

7. If you choose not to participate in this study, are there any alternative treatment options available?

You can choose not to participate in this study, which will not have any adverse effects on your access to routine treatment. Currently, there are no preventive treatment methods for patients with distant metastasis, and the main approach is close monitoring. Targeted therapy, chemotherapy, and other approaches can be considered.

8. Who is responsible for the cost of your participation in this study?

(1) You will need to pay for routine and necessary treatment and examination expenses. The specimens required for this study are patient blood and postoperative tissue specimens, which will not result in additional treatment expenses or require you to bear any experimental costs.

(2) You can enjoy **free comprehensive genomic sequencing analysis** service once

(3) You can enjoy **free CPS** testing once

(Note: This study does not provide transportation subsidies)

9. Did you receive any compensation for participating in this study?

(1) You can enjoy a free comprehensive genomic sequencing analysis service once

(2) You can enjoy a free CPS test once

(3) PD-1 inhibitor cost discount program: self-pay

10. What should you do if you experience research-related injuries?

We will thoroughly evaluate patients who meet the study's inclusion criteria, and experts will assess the occurrence and management of risks and complications. If you are injured as a result of participating in this study, we will provide necessary medical measures. According to relevant regulations in our country, the research institution will bear the corresponding medical expenses and provide appropriate financial compensation.

11. Under what circumstances may this study be terminated prematurely?

If you experience significant adverse reactions related to this study, we will promptly terminate the study.

12. Are you required to participate in and complete this study?

Is your participation in this study completely voluntary? If you do not wish to participate, you can refuse without any negative impact on your current or future medical care. Even if you agree to participate, you can change your mind at any time and inform the researcher to withdraw from the study. Your withdrawal will not affect your access to regular medical services.

In principle, after your withdrawal, the researcher will securely preserve your relevant information until it is ultimately destroyed. During this period, the information will not be used or disclosed further. However, in very rare cases, the researcher may continue to use or disclose your relevant information, even if you have withdrawn from the study or the study has ended. These cases include: when removing your information would affect the scientific validity of the research or the evaluation of data security; Providing limited information for research, teaching, or other activities (this information will not include your name, ID number, or other personally identifiable information); If any information arises that may affect your decision to continue participating in this study, we will promptly inform you.

13. Will your personal information be kept confidential?

If you decide to participate in this study, your participation and personal information in the study will be kept confidential. Your specimens will be identified by research codes rather than your name. Any information that can identify your identity will not be disclosed to members outside the research team without your permission. All research members and stakeholders will keep your identity confidential as required. Your records will be kept in a locked file cabinet and only accessible to research personnel. To ensure that the research is conducted in accordance with regulations, government authorities, school authorities, or members of ethics committees may access your personal information at the research site as required. When the results of this study are published, no personal information about you will be disclosed.

Your participation in this study and your personal information in this study will be kept confidential. The research data will be stored in a locked filing cabinet and only accessible to relevant researchers. When necessary, government regulatory agencies and ethics committees may access your personal information according to regulations. When the results of this study are published, your identifiable information will not be disclosed.

The tissue or blood samples used for genetic testing will only be used in this research institution and third-party testing institutions. After the testing is completed and the test

report is confirmed to be accurate, it will be destroyed within 5 days. Only the principal investigator of this study and yourself have the right to access the test report.

14. If you have any questions or difficulties, you can contact whom?

If you have any questions related to this study or experience any harm related to this study, please contact (researcher) Chen Xiaohong, Kou Xiujuan, Ding Yiming, contact number: 18910371563.

If you have any questions related to your own rights and interests, you can contact the Ethics Committee of Beijing Tongren Hospital, Capital Medical University, contact number: 010-58268486 ext. 8004.

Informed Consent Form Signature Page

Subject's Statement

I am aware of the purpose, process, risks, and benefits of this study.

I have had enough time and opportunity to ask questions, and my questions have been satisfactorily answered.

I am aware of who to contact if I have any questions, concerns, suggestions, or if I want further information about this study.

I have carefully read this informed consent form and agree to participate in this study.

I understand that I can withdraw from this study at any time during the research period without providing any reasons.

I will receive a copy of this informed consent form, which includes the signatures of both myself and the researcher.

_____ _____

Participant's Signature (Print) Date

_____ _____

Legal Guardian's Signature (Print) Date

(If necessary, please indicate the relationship with the subject)

_____ _____

Signature of impartial witness (in regular script) Date

(If necessary)

Researcher's Statement

I have informed the subject of the purpose, process, risks, and benefits of this study, given the subject sufficient time to read this informed consent form or discuss with others, and provided detailed answers to questions regarding the study; I have informed the subject of the contact information when encountering research-related questions; I have informed the subject that they can withdraw from the study at any time; I have informed the subject that they will receive a copy of this informed consent form, which includes both my and his/her / her signature. "

_____ _____

Researcher's Signature for Obtaining Informed Consent (Regular Script)
Date

_____

Contact Number