# Informed Consent Form

**Dear patient:**

We invite you to participate in a prospective randomized single blind controlled study on maintenance therapy with Xindilizumab for locally advanced head and neck tumors after radiotherapy and chemotherapy based on peripheral blood CD8TEX detection. Before deciding whether to participate in this study, please carefully read the following content, which can help you understand the study, why it is necessary to conduct this study, the procedure and duration of the study, The benefits, risks, and inconveniences that may arise from participating in research.

The following is an introduction to this study:

**1、 Research background and purpose**

**1.1 Research background**

Head and neck squamous cell carcinoma (HNSCC) includes cancers of the mouth, oropharynx, larynx and hypopharynx. The incidence rate ranks the sixth with a mortality rate of 40-50%. It is a serious disability and life-threatening disease. Due to the unique anatomical location, the surgical disability rate of HNSCC is high, which seriously affects the quality of life of patients. Radiation therapy is a very important local treatment for malignant tumors. Radiation therapy not only protects organ function and has cosmetic effects, but also has a long-term survival comparable to surgical treatment for early HNSCC patients receiving radiation therapy. However, over 60% of HNSCC patients are initially diagnosed as locally advanced. For patients with locally advanced stage who cannot undergo surgery, the current standard treatment regimen is synchronous radiotherapy and chemotherapy (CRT) or synchronous targeted treatment with cetuximab, followed by clinical follow-up. However, there are still relatively high rates of local recurrence or distant metastasis in patients with locally advanced head and neck tumors after radiotherapy and chemotherapy. The 3-year PFS rate is about 60%, 50% of relapses occur within 2 years after radiotherapy and chemotherapy, 20% to 30% of patients experience distant metastasis, and the overall 5-year survival rate is less than 50%. Therefore, it is necessary to further optimize the maintenance treatment plan after radiotherapy and chemotherapy, in order to improve the clinical cure rate of patients with locally advanced head and neck tumors.

Immunotherapy has achieved significant breakthroughs in recurrent and metastatic head and

neck tumors. Studies on various tumor models have shown that tumor infiltration of PD-1+CD8+depleted T cells (CD8+TEX) is an important mechanism for the reduction of anti-tumor function and tumor progression in the body. Immunotherapy can reactivate T cell responses by blocking the PD-1 pathway. A clinical study by Checkmate 141 showed that anti PD-1 monoclonal antibodies showed long-lasting efficacy in treating recurrent and metastatic HNSCC, with a nearly three fold increase in OS rate at 2 years (16.9% vs 6.0%). Therefore, in 2016, the first anti PD-1 antibody was approved by the FDA for recurrent or metastatic HNSCC that failed platinum chemotherapy. Radiation therapy can directly kill tumor cells while also reshaping the local immune microenvironment of the tumor, including the release of pro-inflammatory molecules and infiltration of immune cells. The subgroup analysis of KEYNOTE-001 and PEMBRO-RT studies found that patients who had previously undergone radiotherapy had better immunotherapy efficacy after recurrence and metastasis. However, studies on immunotherapy in locally advanced HNSCC have all failed, including the JAVELIN HEAD AND NECK 100 study comparing the efficacy of Avelumab combined with CRT treatment and Avelumab maintenance therapy with CRT standard treatment, and the GORTEC REACH study comparing the efficacy of Avelumab combined with cetuximab combined with radiotherapy and Avelumab maintenance therapy with standard treatment. Both studies used immunosynchronous therapy at the beginning of radiotherapy without adaptive screening, and the PFS of both studies showed a trend of numerical benefits but no statistical significance. Therefore, can better biomarkers be selected to screen suitable HNSCC patients for maintenance therapy after synchronous radiotherapy and chemotherapy?

At present, there are no research reports on the changes of CD8+TEX cells in the tumor immune microenvironment after radiotherapy. In our preliminary research, we found in the HNSCC mouse tumor model that the proportion and quantity of PD-1+CD8+TEX cells in the tumor and peripheral blood significantly increased with the prolongation of time after radiotherapy, and the best therapeutic effect was achieved by combining immunotherapy at the end of radiotherapy or 7 days after radiotherapy. We further tested the proportion of TEX in human peripheral blood and the expression level of PD1 during and after synchronous radiotherapy and chemotherapy, and found a similar trend as in the mouse model. So we speculate whether the proportion of peripheral blood CD8+TEX cells and the expression level of PD1 can be used as a

suitable screening for immunotherapy. In the early stage, we retrospectively analyzed three patients who underwent immune maintenance therapy after synchronous radiotherapy and chemotherapy, and found that they have been followed up for three years, and no PFS time has been obtained. This study aims to ensure that patients receive standard treatment. By screening the proportion of CD8+TEX cells in peripheral blood and the expression level of PD1, patients with upregulation of CD8TEX in peripheral blood after radiotherapy or patients with PD1 expression levels higher than normal were randomly divided into two groups: one group received maintenance therapy for immunity, and the other group received placebo comparison to evaluate PFS time.

**2. Research objectives**

**2.1 Research Purpose:**

A prospective randomized single blind controlled study on maintenance therapy with Xindilizumab after radiotherapy and chemotherapy for locally advanced head and neck tumors

**2.2 Main study endpoints:**

Evaluation of progression free survival (PFS) and 1-year progression free survival (PFS) in two groups of patients with locally advanced head and neck tumors after radiotherapy and chemotherapy (using RECIST 1.1 criteria)

**2.3 Secondary study endpoints:**

Evaluation of overall survival (OS), safety and tolerability, changes in quality of life relative to baseline, and time to deterioration in maintenance therapy with Xindilimab in patients with locally advanced head and neck tumors after radiotherapy and chemotherapy (EORTC QLQ-C30 and H&N-35)

The primary safety analysis will be conducted based on subjects who experience toxicity (as defined by CTCAE standards). CTCAE version 5.0 will be used to evaluate safety through reported adverse events. The relationship between adverse events and drugs, onset time, duration of events, their resolution, and any concomitant medication will be recorded. Adverse events (AEs) will be analyzed, including but not limited to all AEs, SAEs, lethal AEs, and laboratory changes.

**2.4 Exploratory study endpoint:**

Exploring biomarkers for predicting therapeutic efficacy and adverse reactions, in order to obtain better guidance for the combination therapy of immunotumor drugs

Information on treatment and safety. In order to identify novel biomarkers, we collected biological samples such as 10-20ml of blood (before treatment and during efficacy evaluation) to support the analysis of cellular components (such as DNA, proteins, etc.), such as whole exome gene detection, TMB, PD-L1, MRD, etc.

**3、 Specific procedures and processes**

This study is a prospective single blind randomized controlled clinical trial of maintenance therapy with Xindilimab based on peripheral CD8TEX screening after standard radiotherapy and chemotherapy for locally advanced head and neck tumors. Synchronous radiotherapy and chemotherapy are routine standard treatments and do not require the use of immunotherapy drugs in this study. Blood samples were collected before and after radiotherapy, and participants were screened and evaluated according to the inclusion and exclusion criteria of the protocol within 28 days before randomization. Patients who agree to participate in this study will sign an informed consent form (ICF) prior to the screening process. After completing all screening activities, eligible participants can start receiving study treatment. According to the estimated sample size, a total of 104 participants are planned to be randomly assigned equally to the experimental group and control group. The treatment cycle for the study is 21 days. The experimental group starts treatment within one month after the end of radiotherapy and chemotherapy. On the first day of each cycle, intravenous treatment with Xindilizumab is given, with a cycle of 21 days. It is expected to be administered for a total of 18 cycles, or until the disease progresses; The control group received placebo treatment. The experimental group underwent routine blood tests, liver and kidney function, myocardial enzyme spectrum, thyroid function, electrocardiogram every 2 cycles, and CT scans every 4 cycles to evaluate toxic side effects; The control group underwent the same frequency of follow-up and observation. The study started on January 1, 2024 and ended on January 1, 2027, to explore the efficacy of maintenance therapy with Xindilimab after radiotherapy and chemotherapy for locally advanced head and neck tumors.

**4、 What do you need to do if you participate in the research**

You will conduct screening and evaluation according to the inclusion criteria of this plan. If you agree to participate, you will sign an informed consent form

(ICF). After completing all screening activities, if you meet the criteria for enrollment, you can start receiving research treatment. The treatment starts within one month after the end of

radiotherapy and chemotherapy, and medication is administered intravenously on the first day of each cycle, with 21 days as a cycle. Review blood routine, liver and kidney function, myocardial enzyme spectrum, thyroid function, electrocardiogram, PD1 protein expression every 2 cycles, and evaluate toxic side effects and recurrence through CT scans every 4 cycles.

You can voluntarily withdraw from the study at any time, or the participant or sponsor may withdraw due to safety or behavior reasons

Request for withdrawal due to reasons such as failure to comply with the research visit time or steps required by the protocol

Research.

**5、 Possible benefits of participating in this study**

1. Personal benefits: For locally advanced head and neck tumors, the current standard treatment plan is synchronous radiotherapy and chemotherapy, but

If the patient still has a higher incidence of local recurrence or distant metastasis after treatment. The main purpose of this study is to improve the objective response rate and survival benefits of participants, and further enhance their quality of life; At the same time, the entire

The treatment process can receive close follow-up and attention from researchers. But it is also possible that they will not benefit.

2. Social benefits: such as acquiring new knowledge: further revealing the relationship between radiotherapy and T cell expression of PD1,

Promoting further development of scientific research, facilitating the development of more effective drugs, changing standard treatment plans, and promoting

People's health.

**6、 Possible adverse reactions, risks, and risk prevention measures for participating in this study**

Common adverse reactions of Xindilizumab: pneumonia; Diarrhea/colitis; Hepatitis; Nephritis; Gastritis; Endocrine diseases such as hypothyroidism/hyperparathyroidism/hypophysitis/adrenal insufficiency/hyperglycemia or type I diabetes; Skin related adverse reactions, including Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN); Thrombocytopenia; Other immune related adverse reactions such as pancreatitis/myocardium

Inflammation/encephalitis.

In order to prevent the occurrence of risks, researchers will closely observe and follow up throughout the entire treatment period for timely treatment. If serious adverse events related to the study occur, we will promptly contact your agent, and the hospital will respond accordingly

The relevant laws and regulations will strive for compensation for you.

**7、 Explanation of cost situation**

At present, conventional treatment does not require the use of the immunotherapy drugs in this study, but it is an indication for the use of Xindilizumab in this study, and a buy one get one free plan is implemented.

**8、 Compensation for participation in research, including compensation for damages**

Blood collection compensation: 100 yuan/time

Transportation fee: 100 yuan/trip

There was no special reduction in imaging examination between the experimental group and the control group.

If the research causes damage, we will provide active treatment and all related costs will be waived.

**9、 Alternative solutions**

If the subjects do not participate in this study or withdraw from the study, they can continue to receive treatment according to the standard diagnosis and treatment plan, or participate in other studies, etc.

**10、 Confidentiality of your personal information**

Your medical records (including research medical records and physical and chemical examination reports, etc.) will be kept in the hospital according to regulations. Except for researchers, ethics committees, monitoring, auditing, pharmaceutical management departments, and other relevant personnel who will be allowed to access your medical records, other personnel unrelated to the study have no right to access your medical records without permission. The public report of the results of this study will not disclose your personal identity. We will be within the allowed range

Internally, make every effort to protect the privacy of your personal medical information.

**11、 Termination of research participation**

Whether to participate in this study depends entirely on your voluntary choice. You may refuse to

participate in this study, or withdraw from the study without reason at any time during the study process, which will not affect your relationship with the doctor, nor will it affect the loss of your medical or other benefits. In addition, your participation may be terminated due to the following reasons

Related to this study:

1. You did not follow the instructions of the research doctor.

2. You have encountered a serious situation that may require treatment.

3. The research doctor believes that terminating the study is most beneficial for your health and well-being.

**12、 Ethics Committee**

his study has been reported to the Human Research Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine. After comprehensive review by the committee and risk assessment of the subjects, it has been approved. During the research process, ethical and rights issues can be addressed by contacting the Human Research Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine.

Phone: daytime 0571-87783759; Evening (total shift): 13757118366;

Email address: HREC2013@126.com

**I confirm that I have read and understood the informed consent form for this study, and voluntarily accept the treatment methods in this study, and I agree to use my medical data for the publication of this study.**

Subject's signature:

Contact information:

Date:

Agent's signature:

Contact information regarding the relationship with the subject

Date(If needed)

Witness (if required):

Contact information:

Date:

**I confirm that I have explained the detailed information of this study to the patient, including their rights, potential benefits, and risks, and provided them with a signed copy of the informed consent form.**

Researcher's signature:

Contact information:

mobile phone：

Date: