

Clinical trial protocol information

Study Title: Neoadjuvant PD-1 Blockade in Resectable Oral Squamous Cell Carcinoma

Official Title: A Randomized Phase II Study of Neoadjuvant PD-1 Blockade Alone or Plus TPF Induction Chemotherapy for Resectable Local Advanced Oral Squamous Cell Carcinoma

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1. Background and rational

1.1Background

Oral squamous cell carcinoma (OSCC) is the most common malignant tumor in the oral and maxillofacial region, with a high incidence and a poor prognosis. The 5-year survival rate of patients with OSCC is about 50%. Among them, local advanced patients have a lower 5-year survival rate, only about 30%, due to high tumor burden, recurrence and metastasis. Currently, radical surgery combined with postoperative radiotherapy or chemoradiotherapy is the main treatment for local advanced OSCC, but its effect is not ideal. In recent years, researchers have tried the treatment of TPF induction chemotherapy (Docetaxel-cisplatin-5-fluorouracil) for patients with local advanced OSCC, but these results failed to increase the 5-year overall survival rate. Therefore, how to improve the treatment effect for patients with local advanced OSCC is a major challenge currently faced by oral and maxillofacial-head and neck tumor surgeons.

In recent years, the rapid rise of immunotherapy that won the 2018 Nobel Prize has brought hope to patients with advanced cancer. Among them, PD-L1/PD-1 blockade is currently a representative drug for tumor immunotherapy. It has been proven to have a significant and long-lasting effect in the treatment of patients with recurrent or metastatic malignant melanoma, lung cancer and head and neck squamous cell carcinoma who have lost the opportunity for surgery. What's more, the results of two clinical trials recently completed also suggest that the effect is much surprising if PD-1 monoclonal antibody is used as neoadjuvant immunotherapy for operable malignant tumors. Forde et al. performed two cycles of PD-1 monoclonal antibody neoadjuvant immunotherapy on patients with operable non-small cell lung cancer before surgery, and found that 45% (9/20) of the patients had pathological remission, and 3 of them had complete Pathological remission, and only 15% of patients have recurrence or metastasis 1 year after surgery, and the overall survival rate is as high as 90%. At the same time, Huang et al. treated patients with stage III/IV operable malignant melanoma with one PD-1 monoclonal antibody treatment before surgery, which resulted in 30% (8/27) patients with complete or overall pathological remission. The annual progression-free survival rate was 63%, and the overall two-year survival rate reached 93%. Taken together, PD-1 blockade is very promising as a neoadjuvant treatment to improve the efficacy of operable local advanced OSCC patients.

Of note, immunotherapy is not effective for every patient, less than 30% of patients can benefit from PD-1 blockade, whether it is used for the treatment of inoperable recurrent or metastatic tumors or for the preoperative adjuvant treatment of operable tumors. Therefore, further elucidating the precise regulation mechanism of tumor immune escape, exploring the molecular mechanism of immunotherapy tolerance, and finding biomarkers that can predict the efficacy in an early stage are important for achieving precise tumor immunotherapy and effectively prolonging the survival time and improving the quality of life of patients with malignant tumors. Our research has found that tumor cells can exert immunosuppressive effects by secreting PD-L1⁺ extracellular vesicles. More importantly, the concentration level of PD-L1⁺ extracellular vesicles in the peripheral blood of patients with metastatic malignant melanoma and its change trend and amplitude in the early stage of immunotherapy can effectively evaluate the patient's treatment effect. Based on the above research, we propose a liquid biopsy strategy based on the level of circulating PD-L1⁺ extracellular vesicles in the peripheral blood of tumor patients to predict the effectiveness of immunotherapy, which provides a fast and accurate method for early prediction of the efficacy of tumor immunotherapy. It has obvious advantages when compared with traditional tissue biopsy. At present, the research results have applied for international invention patents. However, whether this liquid biopsy strategy based on extracellular vesicles can be used to predict the efficacy of neoadjuvant immunotherapy, especially when used in the treatment of patients with local advanced OSCC, remains to be studied.

1.2 Cancer immunotherapy

Cancer immunotherapy is to restore the body's normal tumor immune response by reinvigorating the tumor-immune cycle, so as to achieve the purpose of eliminating tumors. Cancer immunotherapy mainly include monoclonal antibody immune checkpoint inhibitors (CTLA-4 inhibitors, PD-1/PD-L1 inhibitors, etc.), therapeutic antibodies (anti-CD20 monoclonal antibodies, anti-CD30 monoclonal antibodies, anti-Her2 monoclonal antibodies, etc.), cancer vaccines, cell therapy (CAR-T therapy, etc.) and small molecule inhibitors, etc. Among them, PD-1/PD-L1 inhibitors are currently the most studied and fastest-growing immunotherapy. Immune checkpoint inhibitors. Since the US FDA approved the first PD-1 inhibitor Keytruda (Pembrolizumab) for the treatment of malignant melanoma in 2014, there have been many PD-1/PD-L1 inhibitors in the

market. The indications involve non-small cell lung cancer, melanoma, renal cell carcinoma, urothelial carcinoma, Hodgkin's lymphoma, hepatocellular carcinoma, advanced head and neck squamous cell carcinoma, etc. At present, the FDA has approved Pembrolizumab, Nivolumab, Atezolizumab, Duralumab, Avelumab, etc. for clinical treatment, and domestic PD-1/PD-L1 inhibitors such as Camrelizumab, Sintilimab, Toripalimab, etc.

In the current clinical trials, PD-1/PD-L1 inhibitors show obvious effects in patients with advanced unresectable malignant tumors, and many studies have confirmed that they are used as neoadjuvant immunotherapy in the local advanced stages.

1.3 Expressions of PD-L1 in human

Constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be generally expressed in cells of the macrophage cell line. When malignant tumors appear, PD-L1 is expressed in most malignant tumor cells. The expression of PD-L1 in patients with OSCC is related to the depth of tumor invasion, which further suggests that the expression of PD-L1 is related to tumor invasion and metastasis. Although there is still some controversy as to whether the expression of PD-L1 can evaluate the prognosis of OSCC, it has been confirmed that PD-L1 is related to poor prognosis in other tumor models.

1.4 Research of recurrent or metastatic head and neck squamous cell carcinoma

Nivolumab and Pembrolizumab have been approved for the treatment of recurrent or metastatic head and neck squamous cell carcinoma (R/MHNSCC). The clinical trial of Pembrolizumab (NCT01848834) confirmed that the overall response rate of imaging examination was 18%, and the patients could well tolerate the side effects. In another phase 3 clinical trial of R/MHNSCC (NCT02105636), the overall survival of patients treated with Nivolumab was longer than those with standard of care (7.5 months versus 5.5 months), and the one-year survival rate was also significantly improved (36.0% versus 16.6%), the incidence of serious side effects of grade 3 to 4 is relatively low (13.1% versus 35.1%).

1.5 Treatment of local advanced OSCC

At present, surgical resection combined with postoperative adjuvant treatment is still the main treatment for local advanced OSCC. Though surgical skills and radiotherapy and chemotherapy techniques have made great progress in the past 2 decades, the five-year survival rate of patients

with OSCC remains between 50% and 60%. In view of the high recurrence rate and metastasis rate, TPF inductive chemotherapy had been applied for local advanced OSCC, but the results show that it cannot effectively improve the survival rate of patients. The NCCN guidelines point out that for patients with local advanced OSCC, in addition to conventional treatment, it is recommended to conduct clinical trials to explore better treatment options.

1.6 Rational for preoperative neoadjuvant immunotherapy in OSCC

The main purpose of preoperative neoadjuvant immunotherapy for OSCC is to eliminate residual imaging and invisible lesions after surgical resection, and to prevent recurrence or metastasis caused by deep infiltration or scattered micro-metastasis. However, after a major surgical trauma, the patient's general condition is more difficult to tolerate the side effects of adjuvant therapy. On the other hand, it is difficult for chemotherapy drugs to enter the tumor microenvironment through the blood supply. Neoadjuvant immunotherapy can solve these problems. What's more, there are literature reports confirming that PD-1/PD- L1 inhibitors can reduce the pathological stage of tumors and bring better prognostic effects to patients.

1.7 Clinical trials of immunotherapy in OSCC

Oral squamous cell carcinoma has been shown to be an immunosuppressive disease. Studies have found that there is a decrease in infiltrating lymphocytes in oral squamous cell carcinoma, while inhibitory regulatory T-cell proliferation promotes tumor immune escape. Disruption of the function and antigen presentation capacity of natural killer cells is a manifestation of impaired immune cell function. The expression of PD-L1 in tumor tissues has a close relationship with the depth of tumor invasion and lymph node metastasis, and the depth of tumor infiltration and lymph node metastasis are closely related to the patient's poor prognosis.

Ferris et al, studied PD-1 inhibitors for recurrent head and neck squamous cell carcinoma. The result showed that PD-1 inhibitors achieved satisfactory results compared with cisplatin chemotherapy. PD-1 inhibitors significantly improved overall survival and one-year survival, and the incidence of serious adverse events was also found to be lower in patients treated with PD-1 inhibitors than in patients treated with cisplatin chemotherapy.

1.8 Development of Camrelizumab

Camrelizumab is a high-affinity IgG4 (kappa) anti-programmed cell death 1 (PD-1)

monoclonal antibody. By competing with PD-L1 or PD-L2 to bind PD-1 molecules to block the PD-1/PD-L1 axis signaling pathway to increase tumor antigen-specific T cells and restart the tumor-immune cycle. After a single injection of different doses of Camrelizumab, the T cell receptor binding rates of subjects at 60, 200, and 400 mg doses were 81%, 85%, and 88%, respectively.

Since the first phase I clinical trial in Australia in 2015, the research of Camrelizumab on Hodgkin's lymphoma, B cell lymphoma, esophageal squamous cell carcinoma, gastric-esophageal junction cancer, liver cancer has been launched in the Cancer Hospital of the Chinese Academy of Medical Sciences, the Cancer Center of Sun Yat-sen University, and Peking University Cancer Hospital.

1.9 Clinical experience with Camrelizumab

The results of 9 clinical trials published by Jiangsu HengRui Medicine Co., Ltd show that the immune-related adverse event (irAE) rate is 97%, most of the irAEs are mild to moderate including skin reactions, fever, hypothyroidism, fatigue, cough, and decreased appetite. 24% of subjects have irAEs \geq grade 3. The overall adverse reaction is slighter than conventional chemotherapy. In a phase II clinical trial of patients with relapsed/refractory classic Hodgkin's lymphoma who failed of two or more systemic treatments, the subjects are scheduled to be injected with Camrelizumab every two weeks. The response rate is 31.8%. In another study of nasopharyngeal carcinoma treated with Camrelizumab alone or plus gemcitabine and cisplatin, both treatments show satisfactory results. In Camrelizumab group, the overall progression rate is 34%, and the half-year progression-free survival rate is 48.2%. In Camrelizumab plus gemcitabine and cisplatin group, in which the subjects are treated with 6 courses of 200 mg of Camrelizumab, 1 g/m² of gemcitabine, and 80 mg/m² of cisplatin and followed by 200 mg of Camrelizumab, the overall progression rate is 91% and half-year progression-free survival rate is 86.4%. The above results indicate that Camrelizumab is safe as well as feasible.

2. Purpose

The purpose of this study is to investigate the safety and feasibility of neoadjuvant PD-1 blockade alone or neoadjuvant PD-1 blockade plus TPF induction chemotherapy in subjects with resectable local advanced OSCC. And on this basis, we will explore the changes of the profiles and functions of immune cells within tumors, lymph nodes and peripheral blood after the experimental

interventions, as well as their correlation with the patients' response and prognosis.

3. Objective

3.1 Primary endpoint

To investigate the pathologic response of resected tumors and lymph nodes to neoadjuvant PD-1 blockade alone or neoadjuvant PD-1 blockade plus TPF induction chemotherapy.

3.2 Secondary endpoint

To investigate the clinical response of tumors and lymph nodes to neoadjuvant PD-1 blockade alone or neoadjuvant PD-1 blockade plus TPF induction chemotherapy, as evaluated by radiographic examinations and defined by RECIST 1.1.

To investigate the two-year event-free survival (EFS) on each treatment group. EFS is the time from the date of randomization to the date of first record of disease progression as defined by RECIST 1.1.

To investigate the two-year overall survival on each treatment group.

To investigate the irAE rate. Number of participants experiencing any sign, symptom, disease, or worsening of preexisting conditions temporally associated with the experimental interventions or irrespective of the experimental interventions.

3.3 Exploratory endpoint

3.3.1 To explore the changes of the profiles and functions of immune cells within tumors, lymph nodes and peripheral blood after the experimental interventions, as well as their correlation with the patients' response and prognosis.

3.3.2 To evaluate the changes of the profiles and functions of extracellular vesicles within tumors, saliva and peripheral blood after the experimental interventions, as well as their correlation with the patients' response and prognosis.

3.3.3 To investigate the sensitivity and specificity of specific subsets of extracellular vesicles in saliva or peripheral blood of patients and their key biomolecules as liquid biopsy markers to predict the efficacy of neoadjuvant therapy or to dynamically monitor its efficacy.

4. Study design and treatment plan

4.1 Recruitment

Subjects will be recruited through the Department of Oncology, Wuhan University

Stomatological Hospital after being approved by the Ethics Committee of Wuhan University Stomatological Hospital and completing the procedures of clinical trial platform registration and Hubei Provincial Health Commission registration. Each subject will be assigned an ordered trial number (A-001, A-002, etc.) randomized into two groups by the electronic data acquisition system.

4.2 Determination of Eligibility

After eligibility is established, the study staff will register participants. The following are required to be submitted for successful registration:

- a) Registration form;
- b) Copy of informed consent;
- c) Copy of pathological diagnosis report;
- d) CT or PET/CT report, copies of chest CT and ECT;
- e) Copy of clinical data:

- Routine blood examination including hemoglobin, red blood cell count, white blood cell count, granulocyte count, lymphocyte count, platelet count;

- Blood biochemistry including alkaline phosphatase, urea nitrogen, creatinine, fasting blood glucose, potassium, sodium, and chlorine;

- Hepatitis B virus surface antigen, hepatitis B surface antibody, hepatitis B e antigen, hepatitis B e antibody, hepatitis B core antibody;

- Serum thyroid hormone determination: Thyroid-stimulating hormone (TSH), patients with endocrine abnormalities should receive care or additional examinations according to the normal program.

4.3 Study design and toxicity assessments

4.3.1 Study design and sample collection

This study is a single-center, dual-arm, randomized open clinical trial, which will be conducted in the Department of Oral and Maxillofacial-Head and Neck Tumor Surgery, Wuhan University Stomatological Hospital. 68 people will be enrolled in this trial, and the subjects included are mainly from the oral and maxillofacial-head and neck tumor surgery. 68 Subjects will be randomly and averagely divided into two groups, Camrelizumab alone group (hereinafter referred to as the single group) and Camrelizumab plus TPF chemotherapy group (hereinafter referred to as the combined

group):

Single group: Camrelizumab injection, surgical resection, radiotherapy/chemoradiotherapy.

Combined group: Camrelizumab injection plus TPF induction chemotherapy, surgical resection, radiotherapy/chemoradiotherapy.

For Camrelizumab injection, subjects will receive 200 mg Camrelizumab each 2-week cycle for 3 cycles prior to surgery. And for TPF induction chemotherapy, subjects will receive 75 mg/m² docetaxel (T), 75 mg/m² cisplatin (P) and 750 mg/m² 5-Fluorouracil (F) each 3-week cycle for 2 cycles.

Serial blood and saliva collection of the subjects will be performed prior to each Camrelizumab injection, once prior to surgery, once prior to radiotherapy, and each follow-up. Preoperative tumor biopsy and postoperative tumor lesion will be obtained for further study. The tissue biopsy specimens should be of a certain size to meet the volume requirements of rapid frozen examination and genomic analysis. The surgically resected specimen should contain tumor tissue and normal mucosa adjacent to the tumor. If there is cervical lymph node metastasis, it should contain cervical lymph nodes. The tissue should be embedded and fixed as soon as possible, or frozen in liquid nitrogen for subsequent analysis.

4.3.2 Toxicity assessments

Researchers will evaluate the safety of the subjects' toxicity from the start of the injection to 90 days following the last dose of Camrelizumab. No dose delays due to toxicity will be permitted for patients enrolled on this study. If toxic side effects occur after the first injection of the drug and the patient cannot receive the second injection on time, the patient will begin to undergo surgical evaluation and begin subsequent treatment. Before surgery, make sure that the patient is in a irAE grade \leq 1.

4.4 Diagnostic and surgical evaluation

4.4.1 Diagnostic evaluation and pre-surgical workup

Subjects should obtain tissue biopsy to determine the nature of the disease before receiving drug treatment, and the specimen for tissue biopsy should be of a certain size to meet the volume requirements for rapid freezing examination and genomic analysis at the same time.

The surgically resected specimen should include tumor tissue and normal mucosa adjacent to

the tumor. If there is cervical lymph node metastasis, the cervical lymph node should be included. Tissue should be embedded and fixed as soon as possible, or frozen in a liquid nitrogen tank for subsequent analysis.

4.4.2 Diagnostic evaluation and pre-surgical workup

All subjects included in the experimental study must be patients with clinical stage III to IVb OSCC. The patient will undergo imaging tests before surgery to assess the progression of the disease and the possibility of surgical resection. The surgeon or anesthesiologist evaluates the risk of surgery based on the patient's examination report within 7 days before surgery. Surgery for patients enrolled on this protocol will be according to generally accepted standards of care.

4.4.3 Principle of surgery

Tumor resection should strictly follow the NCCN Head and Neck Cancer Guidelines (Second Edition, 2018) for the resection of the primary oral squamous cell carcinoma and neck lymph node dissection, and follow-up treatment based on the results of surgery and pathological examination (Figure 1).

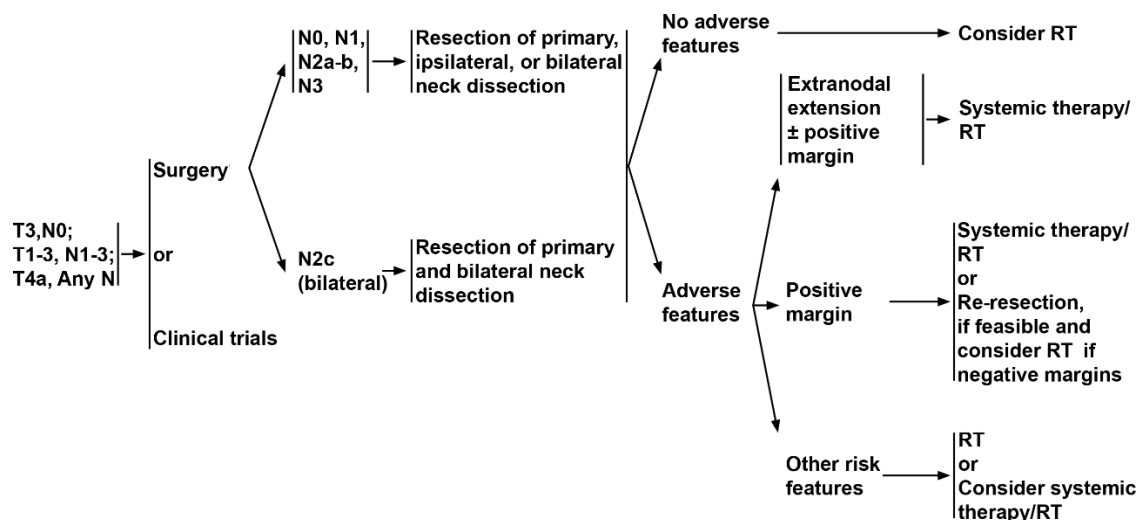


Fig 1. NCCN guideline, version 2, 2018. Cancer of the oral cavity.

4.5 Adjuvant therapy

4.5.1 Postoperative radiotherapy

All subjects will receive postoperative adjuvant radiotherapy within 4-6 weeks after surgery. Radiotherapy should be started as soon as possible for patients with high risk of recurrence, unless the patient's general condition is poor and cannot tolerate radiotherapy. Even if the wound is partially healed, the skin flap is poorly healed and the tracheal intubation or nasogastric tube is not removed,

the radiotherapy time should not be postponed, so as not to affect the prognosis. The dose of radiotherapy should be adjusted according to the site of cancer and lymph node metastasis.

4.5.2 Postoperative chemotherapy

After surgery, patients with the following high-risk and adverse prognostic factors should be supplemented with chemotherapy concurrently with radiotherapy: positive tumor margin (less than 5 mm or tumor cells are seen on the margin); extracapsular lymph node metastasis. Of note, postoperative chemotherapy should not be started until camrelizumab-related toxicity is less than grade 2.

4.6 Perioperative safety assessment

From the start of treatment to the last injection of camrelizumab within 90 days, or within 30 days after the completion of the operation, the patient's medical records should be reviewed once a week to evaluate the complications of the operation, guide whether to delay the operation and assess potential immune-related side effects. irAE will be discussed in regular meetings held every one to two weeks, and the discussion time and content of the meeting will be recorded. If the subject refuses to continue his or her perioperative treatment due to personal reasons, every attempt will be made to collect this information either by direct contact or through communication with the subjects outside physician.

5. Laboratory research

5.1 Tissue specimen

Specimens of subjects will be collected in unified standards. At least 0.5 cm³ of tissue biopsy should be incised to meet the requirements of frozen biopsy and other examinations. 10 mL of blood and 10 mL of saliva should be collected in the morning without eating. The time points of blood and saliva collection include: the day on each Camrelizumab injection, 3 days (+/-2 days) before surgery, 3 days (+/-2 days) before radiotherapy, every follow-up. The surgically resected specimens should retain at least 1 cm³ of fresh tumor tissue and 0.5 cm³ of adjacent mucosal tissues, and cryopreserved in -80°C refrigerator for subsequent research.

5.2 Handling of biopsy specimen

The tumor tissue biopsy specimen is divided into three pieces, one is used for frozen biopsy to diagnose the nature and pathological classification of the disease, one is used for

immunohistochemical to detect markers of cell and molecular, and the last one is stored in a liquid nitrogen tank for future RNA or DNA analysis.

The tumor tissue biopsy specimen should be fixed in 10% formalin or 4% paraformaldehyde solution within 30 minutes after being isolated for no less than 12 hours, and the tissue should be embedded within 24 hours. The slice thickness is 4 μ m, and at least 15 slices should be cut. The slice should be clearly marked with the patient's study number, date and time, and consecutive sample numbers.

5.3 Handling of surgical tumor specimen

The surgical tumor specimen should be processed within 30 minutes and be divided into two pieces of tissue not less than 0.5 cm*0.5 cm in size: one piece is immediately lysed into a single cell suspension, and stored frozen according to the corresponding experimental manual; the other part tissue directly frozen in liquid nitrogen tank for RNA sequencing. The remaining tissues and a part of the lymph nodes are embedded, sliced and labeled according to the method of fixing tissue biopsy specimens and sent to the tissue chip.

5.4 Handling of blood

Whole blood will be collected and processed per manufacturer's instructions of PMBC. Aliquot the upper plasma into 500 μ L/tube and store it at -80 °C for later ELISA or Western Blot analysis; Aliquot the middle PBMC into 500 μ L/tube and freeze it in liquid nitrogen for subsequent study.

5.5 Handling of saliva

Saliva will be collected and centrifugated at 2,600 g, for 15 min, the supernatant will be centrifugated at 2,600 g for 15 min. Aliquot the supernatant into 500 μ L/tube and store it in -80 °C nitrogen for subsequent study.

6. Screening and discontinued /withdrawal

This trial is open to all races and ethnicities, and this clinical trial does not discriminate against gender or race.

6.1 Inclusion criteria

1. Histologically documented oral squamous cell carcinoma (biopsy required).
2. Local advanced oral squamous cell carcinoma (clinical stage T1-2N1-3M0, T3-4aN0-3M0) with resection option for potential cure, as assessed by a faculty surgeon at Hospital of Stomatology, Wuhan University.
3. Distant metastasis was excluded by chest CT and emission computed tomograph.

4. Adequate organ function as follows:
 - 1) Leukocyte count $\geq 2,000/\text{mm}^3$
 - 2) Absolute neutrophil count $\geq 1,000/\text{mm}^3$
 - 3) Platelet count $\geq 100,000/\text{mm}^3$
 - 4) Hemoglobin $\geq 90 \text{ g/Ld}$
 - 5) Serum albumin $\geq 30 \text{ g/L}$
 - 6) Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN)
 - 7) AST (SGOT) and ALT (SGPT) $< 2.5 \times$ ULN
 - 8) ALP $\leq 2.5 \times$ ULN
 - 9) Prothrombin time-international normalized ratio ≤ 1.5
 - 10) Serum creatinine $\leq 1.5 \times$ ULN
 - 11) INR/PT ≤ 1.5
 - 12) TSH \leq ULN.
5. ECOG performance status 0-1.
6. Female patient tested HCG negative in serum or urine within 7 days prior to the start of investigational product. Both patient and partner must agree to use contraception prior to study entry and for the duration of study participation and for up to 120 days after the last dose of PD-1 blockade.

Patient understands the study regimen, its requirements, risks and discomforts and is able and willing to sign the informed consent form.

6.2 Exclusion Criteria

1. History of ≥ 3 grade immune related adverse events (irAEs) or have not recovered to ≤ 1 grade irAEs from previous treatment.
2. History of other treatments for cancer, including surgery, chemotherapy, radiotherapy or molecular targeted therapy within past 5 years.
3. Previous therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 or any other antibody targeting T cell co-regulatory pathways.
4. Active autoimmune disease or history of refractory autoimmune disease.
5. Active systemic infection requiring therapy.
6. Patients who are receiving psychotropic drug or alcohol/drug abuse.
7. Subjects with concurrent other active malignancies.
8. HIV or untreated active HBV or HCV infections, or vaccinated (HBV, flu, varicella, etc) within 4 weeks before recruitment.
9. Uncontrollable systemic diseases, including diabetes, hypertension, etc.
10. History of stroke or transient ischemic attack within past 6 months.

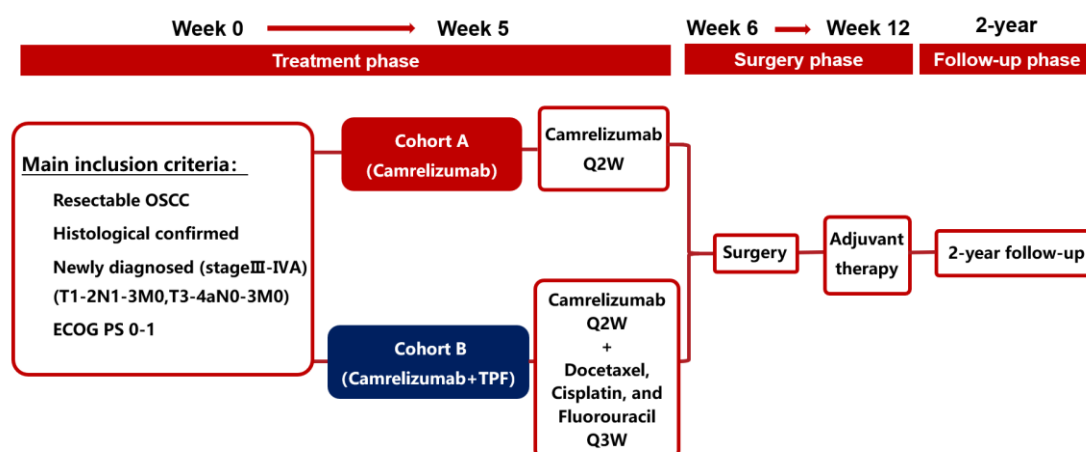
6.3 Withdrawal from study

1. The reasons for withdrawal from the study include:
2. The subject withdraws the informed consent and asks to withdraw;
3. Those who cannot tolerate the toxicity of TPF chemotherapy or Camrelizumab immunotherapy;

4. The subjects have poor compliance;
5. The subject is lost to follow-up or lost contact;
6. The subject has a sudden illness or other situation during the experiment, and the situation will greatly affect the evaluation of the clinical state or the study treatment needs to be stopped;
7. Subjects are followed up for two years;
8. The researcher believes that it is necessary to withdraw the subject from the research.

Note: If subjects experience ultra-progressive imaging or serious immune-related adverse reactions after the first neoadjuvant immunotherapy, the second neoadjuvant immunotherapy should be stopped, and the patient's status should be adjusted directly before surgery and subsequent treatment. For subjects who are discontinued/withdrawn, the investigator must make every effort to complete the validity and safety inspections when launching the trial specified in the protocol, complete the safety follow-up, comprehensively record the adverse events and outcomes; complete the survival follow-up and record follow-up treatment plan and subject's survival status. The reason for treatment interruption should be carefully recorded in the medical record. Researchers can suggest or provide new or alternative therapies to subjects based on the patient's condition. If the subject interrupts or withdraws from the study, the researcher should collect blood, saliva and other specimens as much as possible with the consent of the subject.

7. Study procedures



7.1 Clinical operation schedule

7.1.1 Screening stage, 1-7 days prior to enrollment

1. Clinical examination and taking pictures to record the lesions, the lesion should meet T1-2N1-3M0, T3-4aN0-3M0;
2. Systemic examination to exclude the contraindications of surgery;
3. Take enhanced CT/MRI records of head and neck region to record the tumor status, and take emission computed tomography to exclude distant metastasis;
4. Tumor biopsy;
5. 10 ml of blood and saliva collection;
6. Subject should sign the informed consent form, then researcher submit the basic information to the electronic data collection system and divide the subject into a treatment group through the randomization system.

7.1.2 Neoadjuvant stage, day 1-40 (+/-7 days) after enrollment

1. Neoadjuvant immunotherapy

200 mg of Camrelizumab injection at the time points of day 1, day 15 and day 29.

2. TPF induction chemotherapy

Day 1: Deep venous catheterization (no chemotherapy drug injection on the same day, only for camrelizumab).

Day 2:

- a. 5% GNS 1000 ml + 10% KCl 10 ml iv gtt (6-8 h prior to CDDP);
- b. Normal saline 50 ml + 5-HT3 receptor antagonist (such as ondansetron 8 mg or glastron 3 mg or tropisetron 5 mg) iv gtt (30 minutes prior to chemotherapy, additional one administration is needed if severe nausea occurs);
- c. Dexamethasone 5 mg iv + Promethazine 25 mg im (docetaxel pretreatment);
- d. Normal saline 500 ml + docetaxel 75 mg/m² iv gtt for 2-3 hours;
- e. Normal saline or glucose solution 500 ml + 10% KCl 10 ml + dexamethasone 5 mg iv gtt for 3 hours;
- f. 20% mannitol 50 ml iv (before cisplatin use);
- g. 5% glucose solution 500 ml + CDDP 75 mg/m² iv gtt for 1-2h;
- h. 20% mannitol 50 ml iv q1h×5 times;
- i. Normal saline or glucose solution or Ringer's solution 1000 ml + 10% KCl 10 ml +

dexamethasone 5 mg iv gtt for 3 hours;

j. Normal saline 500 ml + 5-FU 750mg/m²/d×5 d iv gtt;

k. Ringer's solution 500 ml + vitamin C 2 g + vitamin B6 200 mg iv gtt;

l. Other auxiliary drugs such as heparin.

Day 3:

a. 1500 ml normal saline or glucose solution + 10% KCl 20 ml + dexamethasone 10 mg iv gtt;

b. 20% mannitol 50 ml iv q1h×3 times;

c. Normal saline 50 ml + central nervous antiemetics (5-HT₃ receptor antagonists, such as ondansetron 8 mg or granisetron 3 mg or tropisetron 5 mg) iv gtt (1-2 times a day or according to the severity of nausea and vomiting);

d. Ringer's solution 500 ml + vitamin C 2 g + vitamin B6 200 mg iv gtt;

e. Other auxiliary drugs such as heparin.

Day 4-6:

a. Normal saline 50 ml + central nervous antiemetics iv gtt;

b. Ringer's solution 500 ml + vitamin C 2 g + vitamin B6 200 mg iv gtt;

c. Other auxiliary drugs such as heparin.

Days 7-21: Rest (the patient needs to return to the hospital for the second camrelizumab injection on day 15).

Day 22-26: Repeat the content of Days 1-6 and perform a second course of TPF chemotherapy.

Day 27-42: Rest (return to the hospital on day 29 for the 3rd camrelizumab injection)

7.1.3 Surgery stage

Preoperative examination, 1-3 days prior to surgery.

1. Clinical examination and taking pictures to record the lesions;

2. Take enhanced CT/MRI records of head and neck region to record the tumor status, and take emission computed tomography to exclude distant metastasis;

3. 10 ml of blood and saliva collection;

Surgery day

1. Take pictures to record the operation method and the number of separated lymph nodes.

2. Collect tumor specimen and store it as described above.

7.1.4 Adjuvant therapy stage, 30 days (+/-10 days) postoperation

Prior to radiotherapy

1. Clinical examination and enhanced CT/MRI examination.
2. 10 ml of blood and saliva collection.
3. Design the plan of radiotherapy according to surgical records, silver clip markers and pathology reports.
4. Concurrent chemoradiotherapy:
 - a. Subjects with the following high-risk and poor prognostic factors: positive resection margin (less than 5mm or visible tumor cells on the resection margin); extracapsular invasion of lymph nodes.
 - b. The concurrent chemoradiotherapy plan: The subject will receive CDDP 80 mg/m² administration each 3-week cycle for 2 cycles.

7.1.5 Follow-up stage

The first follow-up will start at 90 days (+/-10 days) after the end of radiotherapy with an interval of 3 months (+/-10 days) for a total of 7 follow-ups. The contents of follow-up include:

- ① Clinical examination.
- ② 10 ml of blood and saliva collection.
- ③ Head and neck enhanced CT/MRI examination, performed at the 1, 3, 5, and 7 visits.
- ④ Assessment, management and record of the irAEs, and analyze the correlation between the irAEs and the study drug. Once identified as irAE, it should be submitted to National Medical Products Administration in time.

It is worth noting that if the patient cannot be followed up on schedule, the patient should return to hospital within two months, and the follow-up will continue as scheduled. If the patient cannot be followed up for three consecutive times, it should be considered as drop-out, and the reason for drop-out should be recorded. Though the data of drop-out patient cannot be used for the analysis of laboratory indicators for dynamic monitoring of the patient's condition, it can still be used to evaluate the safety and effectiveness of neoadjuvant immunotherapy.

7.2 Specimen processing schedule

7.2.1 Screening stage

①Collect the biopsy specimen and divide it into two pieces, one piece will be frozen with RNAlater nucleic acid preservation solution in liquid nitrogen, and the other one will be used for frozen biopsy and then taken out to be re-fixed with formalin and embed in paraffin;

②Collect 10 ml blood (EDTA anticoagulation vacuum tube) and 10 ml saliva from the subject before eating in the morning. Whole blood will be collected and processed per manufacturer's instructions of PMBC. Aliquot the upper plasma into 500 μ L/tube and store it at -80 °C for later analysis; aliquot the middle PBMC into 500 μ L/tube and freeze it in liquid nitrogen for subsequent study. Saliva will be collected and centrifugated at 2,600 g, for 15 min, the supernatant will be centrifugated at 2,600 g for 15 min. Aliquot the supernatant into 500 μ L/tube and store it in -80 °C nitrogen for subsequent study.

7.2.2 Surgery stage

On the first day after admission, collect the patient's blood and saliva, the method is described as 7.2.1;

On the surgery day, collect about $1 \times 1 \times 1$ cm³ of the most representative tumor and divide it into 3 pieces. One piece is prepared for single cell suspension following the, then frozen in a liquid nitrogen tank, and one piece is fixed with formalin, embedded in paraffin, add a piece of RNAlater nucleic acid preservation solution and freeze it in a liquid nitrogen tank.

7.2.3 Adjuvant chemoradiotherapy stage

On the first day after admission, collect the patient's blood and saliva, the method is described as 7.2.1.

7.2.4 Follow-up stage

After adjuvant radiotherapy, patients will have regular follow-up visits every 3 months for a total of 7 visits for two years. Blood and saliva will be collected every time, the method is described as above as 7.2.1, but fasting collection is not required.

8. Study drug

8.1 Drug description

Camrelizumab will be ordered from Hengrui Pharmaceutical Co., Ltd. Each bottle of 200mg can only be used once. The drug label is shown in Table 1.

Table 1				
Product description	Specifications	Size	Appearance	Storage
Lyophilized powder of camrelizumab	200 mg	20mL injection bottle	Transparent glass bottle, white powder	2-8 °C, keep away from light and freezing

8.2 Pharmacokinetics of camrelizumab

A phase I study evaluated the pharmacokinetics of camrelizumab in 49 patients with advanced solid tumors in China at different doses (1 mg/kg, 3 mg/kg, 10 mg/kg and 200 mg/time). The study showed that the in vivo exposure (C_{max}) of camrelizumab increased with the increase of dosage in the range of 1-10 mg/kg after a single administration. After multiple administration (once every 2 weeks), the average steady-state accumulation ratio calculated according to C_{max} on the 15th day of the fourth cycle is between 1.11-1.35.

8.3 Safety summary and side effects of camrelizumab

The comprehensive treatment measures of potential camrelizumab related toxic and side effects are recorded in detail in the annex and the researcher's manual. Combined with previous clinical trials, more than 10% of the side effects were mainly reactive capillary hemangioma (79.3%), anemia, fever, fatigue, hypothyroidism, proteinuria and cough; 1% - 10% of side effects include anemia, hyponatremia, lung infection, elevated aspartate aminotransferase level, elevated glutamyltransferase level, elevated blood bilirubin level, elevated bilirubin level, abnormal liver function, decreased neutrophil count, decreased leukocyte count, thrombocytopenia, decreased lymphocyte count, hypokalemia, increased alanine aminotransferase level, pneumonia, increased blood alkaline phosphatase level and increased lipase level.

8.4 Disposal and distribution of camrelizumab

Camrelizumab is managed by a specially assigned person set up by the main investigator of the clinical trial and stored in a separate refrigerator for the clinical trial. The drug administrator shall ensure that the drug is stored in a suitable environment (temperature, light, humidity). If there is any doubt about the quality and appearance of the drug, the supply company should be contacted directly. The bottles of camrelizumab should be stored in a refrigerator at 2-8 °C away from light and avoid freezing. If it is stored in a glass cabinet refrigerator, it should be stored in the packing box. It is recommended to wear work clothes and gloves when transporting or preparing drugs.

When distributing drugs, the drug receiving form shall be signed by two persons in duplicate. The clinical research unit and the application department shall supervise the supply, use and storage of drugs and the treatment process of remaining drugs.

8.5 Injection method of camrelizumab

The patients in the test group will be injected with camrelizumab once on day 1, day 15 and day 29, with 200 mg each time. Dilute the drug into 100 ml glucose or sodium chloride injection. Infusion should be completed within 30-60 minutes.

Camrelizumab does not contain preservatives, so aseptic operation is needed. Each bottle of camrelizumab for injection should be re dissolved with 5 ml of sterile water for injection. Avoid directly spraying the water droplets on the surface of the powder, and slowly add it along the bottle wall, slowly swirl it to dissolve, and put it to the foam to dissipate, and do not shake violently. The solution shall be colorless or yellowish liquid. If visible particles are observed, stop the injection and replace the drug. Transfer 5 ml of the solution to the infusion bag containing 100 ml of glucose injection (5%) or sodium chloride injection (0.9%), and conduct intravenous infusion through a sterile, pyrogen free and low protein binding 0.2 μ M filter.

Camrelizumab should be dissolved and diluted immediately after removal from the refrigerator. Store the diluted solution at room temperature for no more than 6 hours

(including infusion time): store it under refrigeration (2-8 °C) for no more than 24 hours. If the diluted solution is stored under refrigeration, it should be restored to room temperature before use. Note that this drug should not be administered simultaneously with other drugs.

8.6 Destruction of research drugs

The investigator shall ensure that the drug is destroyed and archived in accordance with relevant regulations, guidelines, systems and procedures.

9. Safety evaluation

9.1 Safety summary

This study will use the description and grading scale of adverse event reports in the revised National Cancer Institute Common Terminology Standard for adverse events (CTCAE) version 5.0. Information on all adverse events, whether voluntarily provided by the subject, found through the inquiry of the investigator, or detected through physical examination, laboratory test or other means,

will be collected, recorded and tracked.

All adverse events experienced by subjects will be collected from the first medication, throughout the whole study process, and at least 90 days after the last treatment. Subjects who still have toxic and side effects after discontinuing the study drug should be further evaluated and followed up until the toxic and side effects disappear or are determined to be irreversible. Any preoperative and postoperative adverse events should be carefully recorded.

9.2 Adverse event

9.2.1 Definition of adverse events

Adverse event refers to any new unpleasant medical event or deterioration of previous symptoms during the use of the drug by the patient or subject, and the drug does not necessarily have a causal relationship with the treatment. Therefore, adverse events can be any adverse and unexpected manifestations (including abnormal laboratory results), symptoms or diseases temporarily related to the study drug.

Adverse events can be reported or described in the process of open inquiry, examination or evaluation at the same time. To prevent reporting bias, subjects should not ask about the specific circumstances of one or more adverse events. The medical condition / disease occurring before the start of the study treatment is considered an adverse event only when the condition worsens after the start of the study treatment (any step in the treatment procedure). Although it happened before treatment, the adverse events after signing the informed consent should also be recorded. Abnormal laboratory results or adverse events caused by them constitute adverse events only when they cause clinical symptoms or need treatment.

9.2.2 Serious adverse events (SAE)

① Serious adverse events refer to the following adverse clinical consequences:

- a) Death (excluding death caused by tumor recurrence or metastasis);
- b) Life-threatening (it means that the subject is in danger of life, not that it will be life-threatening if it worsens further);
- c) Need to be hospitalized or extended;
- d) Cause persistent or significant disability or dysfunction;
- e) Important clinical events (Although it will not immediately endanger life, cause death or

cause hospitalization, according to reasonable clinical diagnosis, the event will endanger the subject's life or require intervention, otherwise the consequences listed above will occur. These events include, but are not limited to, intensive treatment for allergic bronchospasm in the emergency or at home, vasospasm or convulsion without hospitalization. Potential drug-induced liver injury is also listed as a serious medical event)

② The following hospitalizations are not serious adverse events:

- a) Not more than 24 hours in emergency or other medical departments, except for "important medical events" or life-threatening events;
- b) Scheduled surgery before signing informed consent;
- c) Treatment or surgery according to the trial process;
- d) Routine medical examination (such as routine colonoscopy);
- e) Admission treatment planned before enrollment, but its purpose is not to treat diseases;
- f) The subjects were hospitalized due to the impact of their personal living environment (inability to housing, lack of economic capacity, etc.).

9.2.3 Unexpected adverse events

Any adverse events not covered in the informed consent form are unexpected adverse events.

9.2.4 Expected adverse events

The adverse events involved in the investigator's manual and informed consent documents are considered as expected adverse events.

9.3 Sorting and reporting of serious adverse events

After the subject signs the informed consent to participate in the clinical trial study, whether it is related to the study drug or not, all serious adverse events should be sorted and collected, including those that may be related to the treatment procedure.

Within 24 hours after the occurrence of serious adverse events, the researcher shall report to the ethics committee, the provincial drug administration, Safety Supervision Department and Registration Department of the State Drug Administration and the local health administrative department in time. All reports shall have written materials for inspection and verification, and shall be archived as test data.

9.4 Non-serious adverse events

Non-serious adverse events refer to the types of adverse events that do not belong to serious adverse events.

All non-serious adverse events should be recorded during treatment and at least 90 days after the last injection treatment. Non-serious adverse events should be tracked to whether they are resolved and whether the symptoms persist or turn into serious adverse events. Non-serious adverse events leading to the interruption or withdrawal of study drugs or adverse events at the end of treatment also need to be followed up as appropriate. All non-serious adverse events need to be carefully recorded in the paper or electronic medical record system.

9.5 Abnormal laboratory test results

For adverse events and laboratory abnormalities found during the study, the case report form should be improved. Serious adverse event case report (paper or electronic) shall be reported as appropriate.

- a) Laboratory test results of any serious or serious adverse events;
- b) Any abnormal index of laboratory results requiring drug withdrawal;
- c) Any abnormal index of laboratory results requiring special treatment;

Researchers should try to use clinical terms rather than laboratory terms, such as anemia and low hemoglobin.

9.6 Gestation

If the subject finds pregnancy after the start of the study, including within six half-lives after drug injection, the subject will permanently stop the clinical trial. Unless pregnancy is contraindicated, the subject must undergo the prescribed study suspension and follow-up procedures. If necessary, other appropriate pregnancy follow-up procedures should be considered. The researcher should report to the ethics committee of School and Hospital of Stomatology Wuhan University and Hubei Food and Drug Administration within 24 hours.

Follow up information on the pregnancy process, including perinatal and neonatal outcomes, must be reported on the pregnancy monitoring form. Any pregnancy that occurred in a female partner of a male subject should also be reported to the investigator. The information about this pregnancy should be reported to the ethics committee of School and Hospital of Stomatology Wuhan University.

9.7 Overuse

Overuse refers to conscious or unconscious overuse. All overuse should be reported as serious adverse events.

9.8 Other safety precautions

The deterioration found in the mid-term or final physical examination, ECG, X-ray examination and other potential risk assessment (whether it belongs to the examination in the test process or not) shall be recorded as non-serious or serious adverse events and reported as appropriate.

10. Effectiveness evaluation

The objective remission rate (imaging and pathological remission rate), recurrence rate, progression free survival rate, one-year survival rate and overall survival rate were evaluated.

In this clinical trial, all subjects underwent imaging examination at baseline, before operation and every two months after operation, and all subjects underwent pathological biopsy and surgical pathological biopsy. The clinical tumor imaging evaluation was carried out through the solid tumor efficacy evaluation standard version 1.1 (see the research manual), and the pathological grading was carried out by hematoxylin eosin staining of pathological sections.

All patients' imaging examinations (enhanced CT or MRI) were confirmed by independent imaging experts in a blind manner. All subjects with curative effect evaluation of CR, PR, SD and PD shall be reviewed by the person in charge first, and the imaging data of all curative effect evaluation (image film or image examination CD) shall be retained, and finally evaluated and confirmed by independent imaging experts. Similarly, the pathological examination of all patients is confirmed by independent pathologists in a blind manner. For the subjects evaluated as pathological complete remission (pCR), pathological partial remission (pPR) and non-pathological remission (Non-resp), the person in charge shall review and retain all evaluated pathological data (microscope photos or pathological sections). Finally, they should be evaluated and confirmed by independent pathological experts. The exploratory research on the tissue, blood and saliva samples will be carried out by the laboratory personnel in a blind state, and the blindness will be uncovered after the experimental data are obtained.

11.Exploratory study

11.1 Tissue and body fluid analysis

Tumor cells, infiltrating lymphocytes, and other cells in the tumor microenvironment (such as tumor-associated fibroblasts, lymphatic endothelial cells, vascular endothelial cells, and vascular endothelial cells) and their surface molecular changes were compared before and after treatment using immunohistochemistry, flow cytometry, and other methods.

Tumor samples were sequenced for DNA or RNA before and after therapy to assess tumor mutational burden (TMB), microsatellite instability (MSI), and mismatch repair (MMR).

Flow cytometry, ELISA, Western blotting, and other techniques were used to assess extracellular vesicles (EVs), lymphocytes, and the molecules they contain in blood and saliva, as well as to dynamically monitor the changes at various treatment phases.

11.2 Screening of immune response markers for anti-PD-1 therapy

The researchers looked at the associations between the patients' baseline markers, especially the PD-L1 composite positive score (PD-L1 CPS), MSI, MMR, and EVs subgroup molecules, and the efficacy of neoadjuvant treatment.

The changes of each indicator before and after treatment were studied, as well as the relationship between them and the efficacy of neoadjuvant therapy and the patients' prognosis.

Screen the indicators with clear clinical significance and possible biomarkers from the above data, and evaluate their sensitivity and specificity as tumor diagnostic markers or treatment effectiveness markers, as well as their practicality as biomarkers for predicting immunotherapy efficacy.

11.3 Indicators to be detected

This study's preliminary design includes the detection of tumor cells, immune cells, monocytes, extracellular vesicles, and their subgroups.

Tissue biopsies and surgically resected specimens, as well as drainage fluids, blood, and saliva from patients with oral squamous cell carcinoma, will be analyzed for immune response markers. All samples were analyzed using multicolor flow cytometry, immunohistochemistry and in situ hybridization techniques to look for candidate immune response markers related to anti-PD-1 therapy, including expression in peripheral blood lymphocytes, tumor-infiltrating lymphocytes, lymph nodes, and tumor cells.

Table 2 Protein molecular detection	
Molecular	Molecular function
CD4, CD8	Involved in the interaction of T cell receptors with antigen presenting cells
CD25	IL-2 receptor, involved in suppressing antitumor immunity
HLA-DR	Expression of immune recognition antigens
CD45RO	Enhance anti-tumor immunity
FoxP3	It plays an important role in the formation of regulatory T cells and participates in the inhibition of anti-tumor immunity
LAP	Potential markers of activated regulatory T cells
PD-1/PD-L1	Inhibition of anti-tumor immunity, PD-1 is the therapeutic target of camrelizumab
LAG-3	Collaborate PD-1 suppresses anti-tumor immunity
ICOS	Stimulates T cells to act on tumor cells
CTLA-4	Immune checkpoint molecules that suppress antitumor responses

12. Management of adverse events

12.1 Infusion reaction

There have been reports of camrelizumab infusion reaction during injection, and clinical symptoms and signs should be closely monitored following treatment. Fever, chills, stiffness, headache, rash, pruritus, Alsace illness, hypotension, hypertension, bronchospasm, or other allergic-like events might happen as a result of infusion reactions. For patients with Grade 1 infusion reactions, therapy can be continued under close monitoring; If an infusion reaction of grade 2 occurs, the infusion rate can be slowed or the infusion can be stopped. Antipyretic and analgesic anti-inflammatory drugs, and also antihistamines, may be recommended. When the symptoms have subsided, the medicine can be restarted but must be closely monitored. Grade 3 or higher infusion responses must be stopped instantly and reported as serious adverse events (SAEs). Infusion reactions were graded according to the NCI CTCAE (version 5.0) guidelines. Recommendations for the treatment of infusion reactions are as follows:

Grade 1 infusion reaction: A mild reaction that does not need stopping the infusion. Keep an eye on things until the symptoms disappear. In the future, 30 minutes before re-dosing, take 50 mg diphenhydramine and (or) paracetamol/acetaminophen 325-1000 mg orally.

Grade 2 infusion reaction: A moderate reaction that necessitates treatment or suspension of infusion, and requires symptomatic medication, such as antihistamines, nonsteroidal anti-

inflammatory drugs, anesthetics, corticosteroids, intravenous infusion, and so on; preventive medication can be given up to 24 hours in advance. Stop the camrelizumab injection and replace it with intravenous saline, intravenous diphenhydramine 50 mg, or paracetamol/acetaminophen 325-1000 mg; monitor the patient attentively until the symptoms disappear. Corticosteroid treatment can also be applied in the proper situations. If the symptoms disappear, the injection can be resumed at half the initial rate of infusion. If no symptoms appear 30 minutes after the re-injection, the injection can be continued at the original infusion rate, although close monitoring is still necessary. If the infusion reaction occurs again, no further infusion treatments will be administered. In the future, 30 minutes before re-dosing, take 50 mg diphenhydramine and/or paracetamol/acetaminophen 325-1000 mg orally. Corticosteroid treatment can also be utilized as necessary.

Grade 3 or 4 Infusion reactions: Serious infusion reactions, Grade 3 reactions: symptoms that do not improve after long-term symptomatic treatment or infusion suspension; initial infusion reactions that reappear with the second infusion; other severe symptoms that require hospitalization [such as kidney damage, pulmonary infiltration].

12.2 Immune-related adverse events

Immune-related adverse events can occur during and after immunotherapy is ended, and then they can affect any tissue or organ and, in severe cases, result in the patient's death. Suspected immune-related adverse events should be fully examined to rule out other possible causes. The majority of immune-related adverse events were reversible and may be handled with drug discontinuation, corticosteroid injections, or supportive care. Most grade 2 and some specific grade 3 or 4 immune-related adverse events need drug discontinuation during therapy, and some grade 3 and 4 immune-related adverse events require permanent stop. Furthermore, if any recurring grade 3 immune-related adverse events after therapy, grade 2 or 3 immune-related adverse events that did not improve to grade 0-1 within 12 weeks from the last dose, the corticosteroid cannot be reduced to a 10 mg/day equivalent dose of prednisone within 12 weeks of the last dose, the drug should be stopped permanently. The descriptions here are based on the first version of the NCCN Guidelines for the Management of Immunotherapy-Related Toxicity, published in 2019. (Refer to the Research Manual for details).

12.2.1 Immune-Related Skin Adverse Events

Immune-related cutaneous adverse events occurred in 2.8% of camrelizumab patients, with 1.3 % having grade 1, 0.8% having grade 2, and 0.7% having grade 3. For grade 1 or 2 rash, symptomatic therapy or topical corticosteroids can be given. Camrelizumab treatment should be stopped, and symptomatic treatment or topical corticosteroids should be offered in the case of a grade 3 rash. If a grade 4 rash, Scottish-Johnson syndrome, or toxic epidermal necrolysis occurs, camrelizumab treatment should be discontinued completely.

12.2.2 Immune-related gastrointestinal adverse events

In previous treatment, the incidence of immune-related gastrointestinal adverse events was 0.9%, of which 0.7% had immune-related diarrhea, all grade 3, 0.1% had grade 3 colitis, and 0.1% had grade 5 colitis. Patients should be followed for signs and symptoms associated with immune-related gastrointestinal adverse events, such as stomach ache, diarrhea, mucus or bloody stools, and infection and disease-related causes should be eliminated in the case of immune-related gastrointestinal adverse events. Camrelizumab therapy should be deferred for grade 2 or 3 immune-related diarrhea or colitis, and should be completely discontinued for grade 4 or recurring grade 3 immune-related gastrointestinal adverse events. At the same time, the potential risk of intestinal perforation should be considered and confirmed by imaging and/or endoscopy if necessary.

12.2.3 Immune-related hepatic adverse events

On prior therapy, the incidence of immune-related hepatic adverse events was 9.1%, including 0.1% for grade 2, 7.0% for grade 3, 1.5% for grade 4, and 0.5% for grade 5. Changes in liver function and the related symptoms and signs of hepatitis should be followed once a month during regular treatment of patients, and infections and underlying disorders should be eliminated. If immune-related hepatic adverse events occur, liver function tests should be performed more often. Camrelizumab treatment should be discontinued for grade 2 immune-related hepatic adverse events. If there are grade 3 or 4 immune-related hepatic adverse events, camrelizumab treatment should be stopped completely.

12.2.4 Immune-related pancreatic adverse events

There were no immune-related pancreatic adverse events in prior therapy. The incidence of immune-related amylase or lipase increase was 1.3%. Lipase increase was 1.0%, with grade 3 at

0.6% and grade 4 at 0.4%. The amylase increase was 0.3%, all of which were grade 3.

12.2.5 Immune-related endocrine adverse events

①High blood sugar

On prior treatment, the incidence of elevated blood glucose was 1.5%, 0.8% for grade 1, 0.6% for grade 3, and 0.1% for grade 4. The incidence of diabetes was 0.2%, all of which were grade 3. Patients' blood glucose levels, as well as any related clinical signs and symptoms, should be closely monitored. Camrelizumab treatment should be deferred in type 1 diabetes patients with poor glycemic control, and insulin replacement therapy should be halted until symptoms disappear. Camrelizumab must be permanently stopped in patients with life-threatening grade 4 type 1 diabetes. Blood glucose levels should be evaluated in the future to ensure that insulin replacement treatment is effective.

②Thyroid changes

In previous treatment, the incidence of hypothyroidism was 20.5%, including 12.8% for grade 1 and 7.7% for grade 2; the incidence of hyperthyroidism was 6.7%, of which 5.7% for grade 1 and 1.0% for grade 2; The incidence of thyroiditis was 0.3%, with 0.2% for grade 1 and 0.1% for grade 2. Patients should be closely monitored for changes in thyroid function and corresponding clinical symptoms and signs. For symptomatic grade 2-3 hypothyroidism, camrelizumab therapy should be withheld and thyroid hormone replacement therapy initiated as needed. Camrelizumab should be discontinued in patients with symptomatic grade 2-3 hyperthyroidism, and antithyroid medications should be used as needed. Camrelizumab withholding and hormonal treatment may be explored if acute thyroid inflammation is suspected. Camrelizumab treatment can be continued if symptoms of hypothyroidism or hyperthyroidism improve and thyroid function tests return to normal. If you have life-threatening hyperthyroidism or hypothyroidism, Camrelizumab should be stopped completely. Thyroid function should be evaluated in the future to ensure that hormone replacement treatment is effective.

③Adrenal gland changes

Adrenal insufficiency occurred in 0.4% of patients with previous treatment, with grade 1 in 0.1%, grade 2 in 0.2%, and grade 3 in 0.1%. Adrenal insufficiency symptoms should be closely monitored in patients. Camrelizumab treatment should be discontinued for symptomatic grade 2

adrenal insufficiency, and physiologic corticosteroid replacement therapy should be administered as clinically necessary until symptoms disappear. Camrelizumab must be stopped completely if patients have Grade 3-4 adrenal insufficiency. Adrenal function and hormone levels should be monitored continuously to ensure proper corticosteroid replacement treatment.

④Changes in the central system

Hypophysitis occurred in 0.1% of previous treatments and was grade 1. Patients with hypophysitis should be closely monitored for signs and symptoms (including hypopituitarism and secondary adrenal insufficiency) and other etiologies should be excluded. Camrelizumab should be withheld for symptomatic grade 2-3 hypophysitis, and hormone replacement treatment should be given as clinically necessary. Corticosteroids can be administered if acute hypophysitis is suspected. For life-threatening grade 4 hypophysitis, camrelizumab must be permanently discontinued. Adrenal function and corticosteroid levels should continue to be monitored to ensure appropriate corticosteroid replacement therapy.

12.2.6 Immune-related pulmonary adverse events

On prior treatment, the incidence of immune-related pulmonary adverse events was 2.7%, including 0.1% for grade 1, 0.9% for grade 2, 1.0% for grade 3, 0.3% for grade 4, and 0.4% for grade 5. Clinical symptoms and signs should be monitored during the treatment process, and suspected immune-related pneumonia cases should be confirmed by imaging examinations, with other causes being excluded out. If grade 2 immune-related pneumonitis develops, the drug should be stopped immediately, and if grade 3 or higher or recurring grade 2 immune-related pneumonitis occurs, the drug should be stopped permanently.

12.2.7 Immune-related adverse renal events

On prior therapy, the incidence of immune-related renal adverse events was 0.4%, including 0.1% for grade 2 and 0.3% for grade 3. Changes in renal function, as well as accompanying symptoms and indicators of nephritis, should be examined on a monthly basis during therapy. If immune-related nephritis develops, renal function tests should be performed more often. The vast majority of patients with high serum creatinine are asymptomatic. Other possible causes of renal impairment should be ruled out. Camrelizumab should be stopped if serum creatinine levels increase to a level of 2 or 3. A grade 4 serum creatinine increase should permanently discontinue

camrelizumab therapy.

12.2.8 Immune-related hepatic adverse events

On prior therapy, the incidence of immune-related hepatic adverse events was 9.1%, including 0.1% for grade 2, 7.0% for grade 3, 1.5% for grade 4, and 0.5% for grade 5. During the treatment, the changes of liver function and the corresponding symptoms and signs of hepatitis should be monitored every month, and infection and the cause related to the underlying disease should be excluded. If immune-related hepatitis develops, liver function tests should be performed more often. Camrelizumab treatment should be avoided in patients with grade 2 immune-related hepatitis. For grade 3 or 4 immune-related hepatitis, camrelizumab treatment should be permanently discontinued.

12.2.9 Immune-related adverse cardiovascular events

Immune-related platelet count reductions occurred in 1.7% of patients with prior therapy, including 1.2% for grade 3 and 0.5% for grade 4. Patients should be closely monitored for platelet levels and signs and symptoms of bleeding tendencies, and other causes of thrombocytopenia should be ruled out. When grade 3 thrombocytopenia occurs, camrelizumab treatment should be suspended, and supportive care should be given until the patient recovers to grade 0-1. Corticosteroid therapy should be administered based on clinical assessment and whether or not camrelizumab treatment may be begun. In the event of grade 4 thrombocytopenia, the drug should be permanently discontinued and symptomatic treatment should be taken actively, and corticosteroid therapy should be given if necessary.

The incidence of immune-related myocarditis was 0.3%, with grade 1 being 0.2% and grade 5 being 0.1%. Clinical signs and symptoms of myocarditis should be followed, and if immune-related myocarditis is suspected, an appropriate examination should be performed to confirm the etiology and rule out other possibilities, as well as necessary tests such as myocardial enzymes. Camrelizumab treatment should be stopped if grade 2 myocarditis occurs, and corticosteroid therapy should be started. The safety of continuing camrelizumab treatment after myocarditis has recovered to grade 0-1 is unknown. Patients with grade 3 or 4 myocarditis should be treated with corticosteroid medication for the rest of their lives, and their myocardial enzymes and cardiac function should be closely monitored.

12.2.10 Other immune-related adverse events

In the previous treatment, immune-related myositis (0.2%) and conjunctivitis (0.3%) also occurred. For other suspected immune-related adverse reactions, adequate evaluation should be performed to confirm the etiology and exclude other etiologies. Depending on the severity of the adverse events, camrelizumab treatment should be withheld for the first occurrence of a grade 2 or 3 immune-related adverse events. Camrelizumab treatment must be permanently discontinued for any recurrent grade 3 immune-related adverse reaction (excluding endocrine disease) and any grade 4 immune-related adverse reaction. Corticosteroids should be used only when clinically needed.

13. Research Management

13.1 Amendments to the Scheme

The "Clinical Research Protocol", "Clinical Research Case Report Form" and "Investigator's Manual" are formulated by the principal investigator, and the principal investigator and all investigators discuss and formulate the clinical research plan. Any changes to the trial protocol were approved by the Institutional Review Board in the form of an amended protocol. The principal investigator will be responsible for the coordination and development of clinical trial protocol modifications.

13.2 Informed Consent

The investigator will explain to each subject the nature, purpose, procedures involved, expected duration, potential risks and benefits of the study. Each subject will be informed that participation in the study is voluntary, that personal data in the trial will be kept confidential, that he/she can withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent treatment. Informed consent will be in the form of a standard written statement and submitted to the Institutional Review Board for approval prior to use. Only after signing the informed consent form can they be enrolled in the study. According to "Good Clinical Practice for Drugs", the contents of the signed informed consent form include the consent to authorize the subject's information to the relevant research institutions, including research sponsors, research institutions, regulatory agencies or ethics committees, and the subject's information. Include all hospital admissions and medical history of the subject.

13.3 Code of Ethics and Practice for the Management of Drug Clinical Trials

Clinical trial research shall comply with the management standards for drug clinical trials, and

follow the following contents:

- a) "Good Clinical Practice for Drugs" promulgated by China Food and Drug Administration;
- b) "Management Measures for Clinical Trial Projects of Wuhan University Stomatological Hospital;
- c) The International Ethical Guidelines for Human Biomedical Research issued by the International Committee of the Organization of Medical Sciences;
- d) Declaration of Helsinki.

13.4 Regulatory authorities

This clinical trial was supervised by the Ethics Committee of Wuhan University Stomatological Hospital, the Clinical Research Center of Wuhan University Stomatological Hospital and the National Medical Products Administration (NMPA).

13.5 Principal Investigator (PI) Responsibilities

The principal investigator in charge of a clinical trial should be a clinical expert in the relevant specialty of the drug research, who must have the knowledge of the specialty and have extensive clinical experience in the specialty to deal with the medical problems that may occur in the subjects. The principal investigator is mainly responsible for the following tasks:

- a) coordination, development, submission and acquisition of treatment protocols, and approval of subsequent amendments thereto;
- b) Prepare the investigator's manual, develop standard operating procedures, and design case report forms;
- c) ensure the use of the correct version scheme;
- d) be responsible for the overall work of this research and supervise the progress of the research;
- e) review and reporting of serious adverse events;
- f) Review data of all departments, test data processing and statistics;
- g) Assist in the writing of test reports.

14. Data Management and Security Controls

This clinical trial uses an electronic data capture system (EDC) to fill in an electronic case report form (eCRF).

14.1 Data collection

Researchers can only log on to the EDC system after they have been trained. The principal investigator (PI) or data entry staff (CRC) entered the data into the EDC system according to the eCRF filling guidelines. PI or CRC are allowed to revise the data in question, but the revision date, the signature of the reviser, and necessary explanations must be recorded truthfully, but the original records cannot be covered up.

After the database is locked, the investigator will receive a CD-ROM or file copy of the subject data. The original eCRF is preserved by Wuhan University Stomatological Hospital and is not allowed to be provided in any form except for representatives authorized by the state.

14.2 Data curation

The completed medical records and related research documents will be submitted to the research center for centralized review and data collation. The time and content of data submission are as follows:

When each subject participates in clinical trial registration:

- a) Registration form
- b) Signed informed consent
- c) Eligibility Checklist
- d) Source documentation related to eligibility and randomization

Within two weeks after registration is complete:

- a) Baseline Study Case Report Form
- b) Relevant source files

Within two weeks after preoperative adjuvant chemotherapy:

- a) Study Case Report Form
- b) Relevant source files

Investigators will be monitored, audited, and inspected by clinical trial-related bodies, including ethics committees, government regulators, and university quality management teams. Researchers should ensure that they have equipment capabilities for clinical trial research (eg pharmacy, laboratory, etc.).

14.3 Discussion Meetings

The study session will officially start once a subject has been enrolled. Study team members

participating in the trial included: study coordinators, data managers, study nurses, investigators, collaborators, and statisticians.

Key topics discussed at the meeting included: relative to expected enrollment rates, subject characteristics, subject compliance, data validity and completeness, toxicities, procedures for collecting blood samples and transferring to the laboratory and further research.

14.4 Quality Control

In order to ensure the quality of clinical trials, before the start of clinical trials, the Clinical Research Center of Wuhan University Stomatological Hospital and PI jointly discuss and formulate clinical research plans. Provide protocol training to all relevant investigators participating in clinical trials.

The PI requests Hengrui Medicine to arrange a clinical monitor. Clinical supervisors must follow the Good Clinical Practice (GCP) and standard operating procedures, conduct clinical supervision of research units on a regular basis or according to the actual situation, supervise the progress and progress of clinical trials, and check and confirm the records and reports of all data , The eCRF is filled in correctly and completely to ensure that the clinical trial is carried out in accordance with the clinical trial protocol, and the investigator should actively cooperate with the clinical supervisor. The clinical monitor or data manager will challenge the data in question to the PI or CRC in the form of an electronic challenge form, and the PI or CRC must respond to the challenge and make corrections or interpretations of the data in question, if necessary Questions are issued several times until the problem data is resolved. Medical leaders and data managers regularly perform consistent comparisons of SAEs.

At the end of the trial project, data managers and medical staff will conduct final quality control of all data in the database, summarize all protocol deviations and protocol violation events during the trial, and hold a data verification meeting. After the data in the database meets the quality requirements, the database will be locked and the test will be unblinded, and the data managers will export the data for data analysis by the statistical department.

15. Statistical analysis plan

15.1 Study design

It is estimated that the pCR rate of Camrelizumab for oral squamous cell carcinoma is 20%.

The pCR rate is expected to be 70% in the Camrelizumab plus TPF induction chemotherapy group.

Based on no statistical hypothesis and accuracy controlling, the sample size is described as follows.

The study is an exploratory research with two parallel groups with 1:1 randomization and no formal statistical assumptions.

The pCR rate of the Camrelizumab group is expected to be 20%. In order to ensure that the lower limit of the 90% confidence interval for the observed pCR is not less than 10%, at least 27 subjects need to be enrolled. Considering 20% dropout, the required sample size is 34 cases. It is estimated that the pCR rate of the Camrelizumab combined with TPF induction chemotherapy group is 70%. The lower limit of the 90% confidence interval of the observed pCR can be guaranteed not to be lower than 50% if 27 subjects enrolled in the group. Considering 20% dropout, the required sample size is 34 cases. In summary, the required total sample size is 68 cases.

15.2 Data Analysis Plan

15.2.1 Analysis of the basic characteristics of patients with locally advanced oral squamous cell carcinoma

The main statistics were the mean, standard deviation, median, maximum value, minimum value, gender, smoking, drinking, betel nut chewing and other data of the subjects' age, height, weight and other data, and the confidence interval.

15.2.2 Biosafety analysis of camrelizumab for preoperative treatment of advanced oral squamous cell carcinoma

Biosafety mainly analyzes the following indicators:

- Drug-related adverse events occurring within 90 days or 30 days (or longer) after the last dose of camrelizumab;
- Drug-related serious adverse events that occurred within 90 days or 30 days (or longer) after the last dose of camrelizumab;
- The most serious side effects in the laboratory results.

15.2.3 The efficacy of camrelizumab for preoperative treatment of advanced oral squamous cell carcinoma:

Pearson correlation coefficient was used to analyze the objective response rate (imaging, pathological response rate), recurrence rate, etc. and 95% confidence interval; progression-free survival rate, one-year survival rate, overall survival rate, median survival time and its 96% Confidence intervals were analyzed by Kaplan-Meier. Survival data were analyzed using Kaplan-Meier survival curves, Log-rank test and Cox proportional hazards model. Results of Cox proportional hazards model were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Descriptive analysis was used for other secondary indicators.

15.2.4 Exploratory Immune-Efficacy Correlation Analysis

For normally distributed data, Student's t-test and paired t-test were used for unpaired and paired data analysis, respectively. For normally distributed data, unpaired and paired analyses were performed using the nonparametric Mann-Whitney or Wilcoxon signed rank test. The correlation between continuous variables was analyzed by the Pearson correlation coefficient. Fisher's exact test was used to test the correlation between two categorical variables.

16. Prospective research plan

March 2021 to October 2022

Complete subject recruitment, formulate and complete all treatment plans, record subject information, adverse events, collect patient tissue, blood, and saliva samples, and follow up during the same period.

October 2022 to June 2023

Complete the follow-up of all subjects, record adverse events, disease outcomes, etc., collect blood and saliva samples from patients during the follow-up period, and complete laboratory research.

June 2023 to October 2023

Complete data sorting and analysis, and complete thesis writing and submission.

17. Informed consent

Clinical trial name: Neoadjuvant PD-1 Blockade, Camrelizumab, in Resectable Oral Squamous Cell Carcinoma

Research Institutions: Department of Oral and Maxillofacial Surgery, School and Hospital of Stomatology, Wuhan University

Dear patients:

We invite you to participate in a clinical trial here. This informed consent form provides you with information to help you decide whether to participate in this clinical trial. Please read the following carefully for a while. If there are any questions or terms that are unclear, you can discuss it with your doctor. This study has been reviewed by the Ethics Committee of School and Hospital of Stomatology, Wuhan University.

Background

Oral squamous cell carcinoma is the most common tumor in the world. After surgery combined with radiotherapy and chemotherapy, patients with local advanced oral squamous cell carcinoma (OSCC) still have high recurrence and metastasis rates. At present, neoadjuvant immunotherapy researchs have achieved good results in other cancers, and the experimental studies of PD-1 mAb have also shown that it can significantly improve the survival rate of patients with advanced inoperable OSCC. Camrelizumab is a PD-1 inhibitor approved in China and has achieved good results in classic Hodgkin's lymphoma, esophageal cancer, hepatocellular carcinoma, non-small cell lung cancer, nasopharyngeal carcinoma and other diseases. As a new adjuvant, Camrelizumab is worthy of our in-depth study and evaluation of its role in resectable OSCC.

Objects

To clarify the safety and efficacy of camrelizumab combined with TPF chemotherapy as a neoadjuvant therapy for patients with local advanced OSCC, and to study the key molecular events and regulatory mechanisms in which patients can benefit from the above neoadjuvant therapy. To screen the liquid biopsy markers that can be used to accurately predict treatment effectiveness.

Research process

A total of 68 subjects will be enrolled in this trial were divided into two groups by randomization. One group received “camrelizumab + TPF chemotherapy, surgical resection and radiotherapy” sequence treatment; one group received “TPF chemotherapy, surgical resection and radiotherapy” sequence treatment. Follow-up will be performed every three months. If you have other special circumstances, you can return to the doctor at any time.

Relevant examinations involved during the entire treatment period include: blood, saliva and tissue biopsy samples, imaging studies during treatment; blood and saliva collection every three months and semi-annual imaging studies during follow-up

Risks and adverse reactions

Adverse reactions caused by camrelizumab: Common adverse reactions include reactive capillary hemangioma, anemia, fever, fatigue, hypothyroidism, proteinuria and cough. There may be some risks and adverse reactions that are currently unpredictable.

Adverse reactions caused by TPF chemotherapy: TPF chemotherapy may have myelosuppression, gastrointestinal reactions, liver and kidney dysfunction, cardiotoxicity, pulmonary fibrosis, and life-threatening if severe organ failure.

Adverse reactions caused by surgery: Due to the patient's condition (critical, complicated, poor

systemic conditions), individual differences, sudden complications may occur during and after surgery, and multiple organ failure (such as heart failure, respiratory failure, liver failure, renal failure, DIC Etc.) or unpredictable changes in the condition can be life-threatening.

Adverse reactions caused by radiotherapy: There will be loss of appetite, fatigue, local edema, dry mouth, odorlessness, restricted mouth or neck, radiation or skin or mucous membrane reaction, skin pigmentation. Due to the difference in tumor sensitivity to radiation, there may be exist insensitive for radiotherapy, tumor residual, and tumor recurrence.

Benefits of participating

If you agree to participate in this study, you will likely receive direct medical benefits, but may not benefit. We hope that the information from this study will be instructive in the future for patients with the same condition.

In this study, you will receive a drug subsidy of up to 8,000 yuan and a transportation subsidy of 1,500 yuan. During this clinical study, if you are physically impaired or have a serious adverse event, you can get free treatment or get compensation according to the law.

You may choose not to participate in this study, or have the right to withdraw at any stage of the trial without any reason, and your medical treatment and benefits will not be affected as a result. In addition to participating in this study, you have the following options: Surgical treatment, radiation (chemotherapy) treatment sequence therapy.

Informed consent signature

If you fully understand the content of this clinical trial and agree to participate in the study, you will sign this informed consent, in duplicate, by the investigator and the patient or the client.

1. I confirm that I have read and understood the informed consent form of this study. The problems that may arise and the relative solutions have been explained to me, and I have the opportunity to ask my own questions. I have explicitly participated in the study as a voluntary act, and refusing to participate in the study will not harm any benefit I deserve.

2. I have learned and agreed that the person in charge of this work at the School and Hospital of Stomatology, Wuhan University and the Medical Ethics Committee of the Wuhan University Stomatological Hospital have the right to review the research records and case data. I agree to provide the samples needed for clinical research for clinical trial studies. I agree that the above-mentioned personnel can directly obtain my research records.

Full name of patient

Date

Full name of legal representative

Date

Full name of researcher

Date

References

1. Uppaluri R, Zolkind P, Lin T, Nussenbaum B, Jackson RS, *et al.* Neoadjuvant pembrolizumab in surgically resectable, locally advanced HPV negative head and neck squamous cell carcinoma (HNSCC). ***Journal of Clinical Oncology***. 2017; 35(15_suppl):6012-6012.
2. Wise-Draper TM, Old MO, Worden FP, O'Brien PE, Cohen EEW, *et al.* Phase II multi-site investigation of neoadjuvant pembrolizumab and adjuvant concurrent radiation and pembrolizumab with or without cisplatin in resected head and neck squamous cell carcinoma. ***Journal of Clinical Oncology***. 2018; 36(15_suppl):6017-6017.
3. Zhong LP, Zhang CP, Ren GX, Guo W, William WN, Jr., *et al.* Randomized phase III trial of induction chemotherapy with docetaxel, cisplatin, and fluorouracil followed by surgery versus up-front surgery in locally advanced resectable oral squamous cell carcinoma. ***J Clin Oncol***. 2013; 31(6):744-751.