Neoadjuvant Chemotherapy Combined with Anti-PD-1 Antibody for the Treatment of Resectable Locally Advanced Head and Neck Squamous Cell Carcinoma

Version: September 1, 2020 (V 2.0)

Principal Investigators: Prof. Kunyu Yang & Prof. Xiaomeng Zhang

Study Sites: Cancer center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology; Departmentof Otorhinolaryngology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

Disclosure Statement

This study was conducted by Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

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Protocol Summary

Topic	Neoadjuvant Chemotherapy Combined with Anti-PD-1 Antibody for the Treatment of Resectable Locally Advanced Head and Neck Squamous Cell Carcinoma (HNSCC)
Version	V2.0
Study Sites	Cancer center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology Departmentof Otorhinolaryngology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology
Principal Investigators	Prof. Kunyu Yang & Prof. Xiaomeng Zhang
Study type	Phase 2 clinical trial
Subject	Operable locally advanced squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx
Purpose	To observe and evaluate safety and efficacy of neoadjuvant chemotherapy combined with anti-PD-1 antibody in the treatment of locally advanced HNSCC
Number of Patients Planned to be Enrolled	30
Inclusion and Exclusion Criteria	Inclusion Criteria: 1. Aged between 18 and 70 years; Histologically diagnosed with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx, and resectable tumor evaluated by a head and neck surgeon prior to enrollment; 2. Locally advanced patients are defined as follows according to the 8th edition of the American Joint Committee on Cancer [AJCC] Guidelines: —Non-oropharyngeal HNSCC cancer and HPV-negative oropharyngeal cancer, stage III, IVA and IVB； —HPV-positive oropharyngeal cancer, stage II and III; HPV status for oropharyngeal cancer will be determined by p16 immunohistochemistry. 3. No prior anti-cancer therapy for HNSCC;

4. At least one evaluable target lesion according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1;

5. Eastern Cooperative Oncology Group (ECOG) performance status 0-1;

6. Normal major organ function in accordance with the following criteria:

(1) Blood routine examination (no blood transfusion within 14 days):

a. Hemoglobin (Hb) ≥90 g/L;

b. Absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L;

c. Platelet (PLT) $\geq 80\times10^9$/L;

(2) Blood biochemistry:

a. Bilirubin (BIL) <1.25× the upper limit of normal (ULN);

b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.5×ULN; for patients with liver metastasis, ALT and AST <5×ULN;

c. Serum creatinine (Cr) ≤ULN and endogenous creatinine clearance >50 mL/min (Cockcroft-Gaut formula);

7. Written informed consent before enrollment;

8. Patients who can adhere to study protocol, as judged by the investigator;

9. Negative pregnancy test result for fertile female patients;

10. Male patients and fertile female patients must agree to use two kinds of contraceptive measures (including at least one highly effective measure) during the whole study period.

Infertile female patients are those meeting at least one of the following criteria:

-Documented hysterectomy and/or bilateral oophorectomy;

-Medical confirmed ovarian function decline;

-Postmenopausal status, defined as cessation of menstruation for at least 12 consecutive months without pathological or physiological reasons, with serum follicle-stimulating hormone level in accordance with post-menopausal status.

11. Patients who are willing and able to adhere to follow-up, treatment plan, laboratory test and other study procedures.

Exclusion Criteria:

1. Prior immunotherapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA-4 antibody, or any other antibodies or drug that specifically targeted T cell co-stimulation or immune checkpoint pathways;

2. Major surgery within 4 weeks before enrollment;

3. Allergry to anti-PD-1 antibody or its excipients;

4. Any active autoimmune disease or history of autoimmune disease, such as interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, myocarditis, nephritis, hyperthyroidism, hypothyroidism (patients can be enrolled after effective hormone replacement therapy) and so on. Patients with vitiligo, or those with asthma that had been completely relieved in childhood without intervention after adulthood or only require medical intervention with bronchodilators, can be enrolled;

5. Other malignant tumors, except for those who had been cured with tumor-free survival more than 5 years, such as skin basal cell carcinoma, cervical carcinoma in situ, and papillary thyroid carcinoma;

6. Uncontrollable cardiac symptom or disease, such as (1) grade II or higher heart failure according to New York Heart Association (NYHA) cardiac function classification (2) unstable angina pectoris (3) myocardial infarction within one year (4) clinically significant supraventricular or ventricular arrhythmia requiring clinical intervention;

7. Patients who need systemic therapy with corticosteroids (>10 mg/day prednisone) or other immunosuppressive agents within 14 days before taking the study drugs, are allowed to inhale or locally use steroid and adrenal hormone (>10 mg/day prednisone) as replacement therapy;

8. Active infection requiring treatment;

9. Congenital or acquired immune deficiency (such as HIV infection), active hepatitis B (HBV-DNA $\geq 10^4$ copies/mL or 2000 IU/mL) or C (positive hepatitis C antibody, with HCV-RNA higher than the lower limit of detection range).

10. With anti-cancer therapy at other oncology departments;

11. With live vaccine within 4 weeks before receiving the study treatment;

12. History of psychotropic drug abuse, or alcohol or drug abuse;

13. Pregnant or lactating women;

14. Other factors that may lead to midway withdrawal, such as other severe diseases (including mental disorders) requiring combination therapy, severe abnormalities of laboratory test values, family or social factors, and those may affect patient safety or data collection, as judged by the investigator;

15. Patients with T4b oral, laryngeal or hypopharyngeal carcinoma, or P16 oropharyngeal carcinoma, or unresectable tumor as deemed by the surgeon;

16. Active tuberculosis;

17. Severe infection within 4 weeks before receiving the study treatment

	(including but not limited to hospitalization due to infection, bacteremia or complications of severe pneumonia); 18. Prior systemic immunity stimulation drugs (including but not limited to interferon or interleukin-2) within 4 weeks before receiving the study treatment, or still within five drug half-lives (whichever was longer).
Treatment Regimen	Neoadjuvant immunotherapy: After enrollment, patients will be administered camrelizumab 200 mg once every three weeks for three times in total before surgery (days 1, 22 and 43, respectively). Camrelizumab will be given by intravenous infusion for 30 min (no less than 20 min and no more than 60 min). Neoadjuvant chemotherapy: After enrollment, patients will be administered chemotherapy (docetaxel combined with cisplatin [DP] or albumin-bound paclitaxel combined with cisplatin [AP]) for three 21-day cycles before surgery. Surgery: Surgery will be performed at one to four weeks after the completion of 9-week neoadjuvant therapy. Adjuvant radiotherapy: Adjuvant radiotherapy will be given at 4 weeks after surgery. Radiotherapy alone or concurrent chemoradiotherapy will be performed based on the postoperative pathological results. Irradiation dose: DT50Gy/25F radiotherapy alone at low-risk areas; 60Gy/30F for patients with positive margin; and 66-70Gy/33-35F on sites without residual tumor. Cisplatin combined with concurrent radiotherapy will be given to patients with positive margin or extracapsular invasion of lymph nodes.
Endpoints	Primary endpoints: Pathological complete response (pCR) rate, and treatment-related adverse events (TRAEs) in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Secondary endpoints: Major pathological response (MPR) rate, objective response rate (ORR), 2-year disease-free survival (DFS) rate, 2- and 5-year overall survival (OS) rates
Safety	Vital signs and laboratory indicators will be evaluated to determine adverse events (AEs) and serious AEs (SAEs).

Duration of Study	The enrollment is expected to last for 24 months. Each patient will be followed until death or withdrawal from the study, or until the last patient has been followed for 24 months. Date of the first enrolled patient / start of the study: July 1, 2019 Date of the last enrolled patient: May 18, 2021 Date of the last patient to be withdrew / end of the study: May 18, 2023 (24 months after the last patient is enrolled) Planned date to lock database: May 18, 2023
Data Statistics	Case report form: Case report form (CRF) will be used to record data in this study. All data on each patient will be recorded in a timely and truthful manner. As original data, CRF cannot be modified. Corrections should be made after signing the name and date by the investigator. CRF is in duplicate, and kept by the statistician and investigator after the end of the study, respectively. Establishment of database: After receiving the CRF, data manager will check the data and feedback the possible problems to the investigator. The investigator should verify the data and reply to the data manager as soon as possible. And then, data manager will establish a database and complete the data entry. After checking without mistakes, the database will be locked by the principal investigators, data manager and statistician. To ensure data security, unauthorized personnals cannot get access or change data. All data must have backups. Any data change must be done after getting written consent from all the principal investigators, statistician and data manager. Analysis method: Descriptive analysis will be adopted to describe endpoints.

List of Abbreviations

The abbreviations and special terms used in this protocol are listed below.

Abbreviation	Full Name
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Albumin-bound paclitaxel combined with cisplatin
APM	Antigen processing machinery
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BIL	Bilirubin
BUN	Blood urea nitrogen
CI	Confidence interval
CPS	Combined positive score
Cr	Creatinine
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTL	Cytotoxic T lymphocyte
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Full Name
ESMO	European Society for Medical Oncology
Hb	Hemoglobin
HLA	Human leukocyte antigen
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
MHC	Main histocompatibility complex
MPR	Major pathological response
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
pCR	Pathological complete response
PD-L1	Programmed cell death-ligand 1
PD-L2	Programmed cell death-ligand 2
PD-1	Programmed cell death-1
PFS	Progression-free survival
PLT	Platelet
PR	Partial response
RCCEP	Reactive cutaneous capillary endothelial proliferation

Abbreviation	Full Name
RECIST	Response Evaluation Criteria In Solid Tumors
TGF	Transforming growth factor
TPF	Docetaxel, cisplatin and 5-fluorouracil
TPS	Tumor proportion score
TRAE	Treatment-related adverse event
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor

1. Background

1.1 Epidemiology of Head and Neck Squamous Cell Carcinoma (HNSCC)

The head and neck cancer is a group of malignant tumors that occur in the upper respiratory tract and upper gastrointestinal tract (including oral cavity, oropharynx, hypopharynx, and larynx). Head and neck cancer is the sixth most common malignant cancer and the eighth most common cause of cancer death worldwide [1]. HNSCC is the most common pathological type, and 60%-70% of patients with HNSCC had locally advanced disease without distant metastasis at diagnosis. Currently, most hospitals adopted the comprehensive therapy by surgery combined with radiotherapy, chemotherapy and targeted therapy for the treatment of HNSCC [2]. However, the efficacy is not ideal with 2-year progression-free survival (PFS) rate less than 40% and 5-year overall survival (OS) rate about 20%-30% [3]. Local-regional recurrence is the main failure pattern after the comprehensive therapy for locally advanced HNSCC. The median survival of recurrent or metastatic HNSCC is only about 10 months after current standard treatment regimen [4]. Moreover, for patients with newly diagnosed locally advanced HNSCC, radical surgery with a wide range causes severe dysfunctions such as dysphonia, dysphagia, dyspnea, as well as physical defects and social difficulties, which seriously affects the quality of life of patients. Therefore, exploring more effective treatment regimens for locally advanced HNSCC has become a particularly urgent issue.

1.2 EXTREME Regimen is the Standard Treatment for Recurrent or Metastatic HNSCC

About two-thirds of patients with newly-diagnosed HNSCC had stage III-IV disease. For these patients, multidisciplinary comprehensive treatment is required due to wide range of tumor invasion or cervical lymph node metastases. About 20%-40% of patients can be cured after reasonable surgery, radiotherapy and chemotherapy [5, 6], but most of the patients have to experience repeated surgery, radiotherapy and chemotherapy due to recurrence or metastasis, which severely decreases the quality of life. For patients with recurrent or metastatic HNSCC, EXTREME regimen (cetuximab plus platium and fluorouracil) is recommended based on National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines. It improves the median survival by about 2 months compared with platium plus fluorouracil, but the efficacy remains unsatisfactory [7].

1.3 Immunotherapy is Effective for Recurrent or Metastatic HNSCC

With remarkable efficacy, cancer immunotherapy has been widely used in clinical practice in recent years. For example, the role of immunotherapy for metastatic melanoma is irreplaceable [8]. A series of studies on advanced non-small cell lung cancer (NSCLC) indicated that the efficacy of immunotherapy was significantly better than that of conventional chemotherapy for patients with tumor proportion score (TPS) ≥50% [9]. For patients with locally advanced NSCLC, if immunotherapy matainance was used after standard concurrent chemoradiotherapy, the PFS was three times longer than that of control group [10].

HNSCC is a tumor with a high degree of immunodeficiency [11]. In an ideal state, the immune system performs an active killing effect by identifying tumor-associated antigens or specific antigens. Therefore, the tumor cells with low immunogenicity may escape immune surveillance and immune clearance. In HNSCC, inhibiting expression of anti-tumor antigens is the main mechanism of immune escape. Human leukocyte antigen (HLA) is the human body's main histocompatibility complex (MHC), which delivers signals between tumor antigen peptides and cytotoxic T lymphocytes (CTLs). In addition, the expression of anti-tumor antigens depends on antigen processing machinery (APM). Studies have shown that

HNSCC cells reduce the anti-tumor immunity of T cells by down-regulating the expression of HLA class I antigens, increasing the expression of programmed cell death-ligand 1 (PD-L1) and over-expressing transforming growth factor (TGF)-beta and vascular endothelial growth factor (VEGF) [12]. The above immune deficiency is common in HNSCC tumor microenvironment.

HNSCC has a relatively high mutation burden and immunotherapy has achieved good results in treating HNSCC. The European Society for Medical Oncology (ESMO) presented KEYNOTE-048 study on advanced HNSCC in 2018 [13]. The study compared the efficacy between anti-programmed cell death-1 (PD-1) antibody pembrolizumab and standard EXTREME regimen for patients with recurrent or metastatic HNSCC. The results showed that pembrolizumab was as effective as EXTREME regimen for the overall patients. For patients whose tumor expressed PD-L1 with combined positive score (CPS) ≥20 and ≥1, pembrolizumab was more effective than EXTREME regimen (N=255; median: 14.9 vs 10.7 months; hazard ratio [HR]: 0.61 [95% CI 0.45-0.83]; P=0.0007; and N=512; median: 12.3 vs 10.3 months; HR: 0.78 [95% CI 0.64-0.96]; P=0.0086), with lower toxicity. The results provided high-level evidence for pembrolizumab as first-line treatment for recurrent or metastatic HNSCC.

Although the immunotherapy had better efficacy than conventional chemotherapy in the treatment of recurrent or metastatic HNSCC, the results remains unsatisfactory. In KEYNOTE-048 study, patients with CPS ≥20 only accounted for 44% of all patients; the overall effective rate was only 23.3% and the median PFS was 3.4 months; the median OS was only increased by 4.2 months.

Cancer immunotherapy before surgery may be more effective than adjuvant therapy after surgery and treatment for advanced disease. According to a clinical study on operable NSCLC [14], the overall response rate of immunotherapy was no higher than 20% in advanced disease, but reached 45% in the neoadjuvant setting, and the patients benefited from the therapy, regardless of PD-L1 expression. Another study has also shown that [15] neoadjuvant immunotherapy was effective for recurrent glioma which was once considered insensitive to immunotherapy. Some investigators discovered that for recurrent glioblastoma, if patient received pembrolizumab before the second surgery, the efficacy was better than that if he or she received pembrolizumab after surgery, with median survival of 412 days and 228 days, respectively. CheckMate 358 was a phase 1/2 clinical study of neoadjuvant immunotherapy for HNSCC[16]. Patients received surgery after nivolumab treatment for twice, and the results have shown that nearly half of HNSCC patients had tumor shrinkage (11/23) with response rate of 50% (5/10) in patients with HPV-positive disease and 46.3% (6/13) in those with HPV-negative disease. Time for surgery was not postponed as well.

The above studies on three tumors indicated that immunotherapy may have different efficacy in different stages during tumor development. Compared with the immunotherapy for patients with recurrent or metastatic advanced tumors, the neoadjuvant immunotherapy is more effective. Neoadjuvant immunotherapy has two advantages. First, compared with adjuvant therapy, neoadjuvant immunotherapy is easier to induce immunity system to produce anti-tumor immunity as the primary tumor provides the immune system with abundant tumor-associated antigens and tumor-specific antigens. Second, compared with salvage therapy or palliative therapy, it is easier to activate the anti-tumor immune response at early stage as the patients have better nutritional status and immune function than those experienced multiple therapies in the advanced setting. For patients with response, neoadjuvant immunotherapy can reduce the size of tumor, downstage the tumor, reduce the surgical damage and increase the rate of complete resection. More importantly, neoadjuvant immunotherapy produces anti-tumor immunity (activated

killer T cells) with an abscopal effect [16] to eliminate micrometastasis. Furthermore, the effector T cells featured with immunological surveillance to further reduce the recurrence and metastasis of tumors after surgery.

According to the studies on lung cancer and HNSCC, neoadjuvant immunotherapy with a single drug showed an effective rate of 45%-50%, much higher than 20% in the second-line setting. However, it also meant that about 50% of patients were not effectively treated before surgery, which delayed the time for surgery. Therefore, it is necessary to combine with other effective treatments.

1.4 Higher Clinical and Pathological Response Rate Can be Achieved by Neoadjuvant Chemotherapy Combined with Anti-PD-1 Antibody

The NADIM study of neoadjuvant immunotherapy combined with chemotherapy for NSCLC was a single-arm, open-label, multicenter phase 2 study, involving patients with resectable IIIA-N2 NSCLC [17]. Patients received chemotherapy combined with nivolumab, and then sequential surgery and adjuvant immunotherapy for one year. The neoadjuvant therapy included three cycles of 360 mg nivolumab IV Q3W combined with 200 mg/m^2 paclitaxel and carboplatin AUC6 IV Q3W. After neoadjuvant therapy, assessment was performed according to the Response Evaluation Criteria In Solid Tumors (RECIST). Surgery was carried out on the 3rd or 4th week after three cycles of neoadjuvant therapy. Adjuvant therapy included 240 mg nivolumab IV Q2W for 4 months and 480 mg nivolumab IV Q4W for 8 months. A total of 46 patients were included in this study. The primary endpoint was 24-month PFS rate, and objective pathological response was adopted for exploratory analysis of efficacy. In this study, 20 patients underwent surgery and their tumors were resectable. According to the assessment of overall clinical response, 10% of patients achieved complete response (CR) and 60% achieved partial response (PR). According to the assessment of pathological response after surgery, 13 patients (65.0%; 95% CI 40.8-84.6%) achieved pathological CR (pCR), and three (15.0%) achieved major pathological response (MPR) that was defined as patients with <10% viable tumor cells. The results suggested that if chemotherapy was combined with immunotherapy as neoadjuvant therapy for patients with resectable locally advanced NSCLC, the anti-tumor efficacy was remarkable and the pCR rate exceeded expectations. In a clinical study (NCT02716038) of atezolizumab combined with carboplatin and paclitaxel [18], the pathological response rate after two cycles of neoadjuvant therapy was raised to 50%, of which 21.3% was pCR. The pathological response rate of these two clinical studies was significantly better than that of conventional neoadjuvant chemotherapy.

Currently, there are little clinical data on the neoadjuvant therapy of chemotherapy combined with anti-PD-1 antibody for locally advanced HNSCC. However, the KEYNOTE-048 study indicated that anti-PD-1 antibody alone as the first-line treatment for recurrent or metastatic HNSCC resulted in an effective rate of 16.9%, significantly lower than 36% with the EXTREME regimen. Chemotherapy combined with anti-PD-1 antibody was as effective as EXTREME regimen. Therefore, it is believed that neoadjuvant chemotherapy combined with immunotherapy before surgery is more effective than immunotherapy alone.

1.5 Neoadjuvant Chemotherapy Combined with Immunotherapy May be an Optimal Regimen for Locally Advanced HNSCC

A meta-analysis of MACH-NC study reported the impact of different sequential chemotherapy on the survival rate of patients with locally advanced HNSCC [19]. In this study, concurrent

chemoradiotherapy was the main regimen to improve the survival rate, but both neoadjuvant chemotherapy and adjuvant chemotherapy failed to improve the survival rate, because only two of the 31 included studies obtained survival benefit. However, these included studies were completed in early era with design limitations. Moreover, the survival benefit was observed in 15 subgroups where 5-fluorouracil combined with cisplatin was given. The recent clinical studies on stage III HNSCC, such as PARADIGM [20], DeCIDE [21], and GORTEC [22], also indicated that inductive chemotherapy failed to bring survival benefits. However, PARADIGM and DeCIDE did not complete the enrollment. Moreover, 10%, 8.8%, and 16.5% of patients in PARADIGM, DeCIDE and GORTEC studies, did not receive concurrent chemoradiotherapy after inductive chemotherapy, and the treatment-related mortality was 1.4%, 2.9%, and 6.6%, respectively. All these factors reduced the survival benefit of inductive chemotherapy. In addition, in Western countries, a large proportion of patients with HNSCC had HPV-positive oropharyngeal cancer, which was sensitive to chemoradiotherapy, with favorable prognosis after concurrent radiochemotherapy. However, patients with HPV-positive oropharyngeal cancer were uncommon in China. In the above three studies, patients received concurrent radiochemotherapy after inductive chemotherapy. However, HNSCC patients in China were more likely to select surgery. Therefore, it is still of practical importance to explore the role of neoadjuvant chemotherapy in the comprehensive treatment for locally advanced HNSCC in China.

According to the above clinical studies of inductive chemotherapy, patients with locally advanced HNSCC were more sensitive to chemotherapy, and neoadjuvant chemotherapy alone could achieve a response rate of about 70%. The efficacy may be better if it was combined with immunotherapy.

1.6 Clinical Study Progress on Camrelizumab

Camrelizumab (SHR-1210) developed by Jiangsu Hengrui Pharmaceutials Co., Ltd. is a humanized anti-human PD-1 monoclonal antibody. Multiple screening tests have shown that camrelizumab can bind to humanized PD-1 with high affinity and high specificity, and can effectively block PD-1 to bind to its ligand PD-L1 or PD-L2 at the protein and cell levels. Various in vitro experiments have confirmed that camrelizumab efficiently activated human immune cells. In a humanized PD-1 transgenic mouse model of tumor, camrelizumab effectively inhibited the growth of colon cancer and melanoma with a significant anti-tumor rate. The crystal structure and characterization analysis showed that the binding epitope of camrelizumab to human PD-1 was different from that of similar products, laying the foundation for its proprietary intellectual property rights.

Many clinical studies have been done on camrelizumab. The phase 2 and multicenter study of camrelizumab as the second- or latter-line treatment for Chinese patients with advanced hepatocellular carcinoma [23], led by Professor Shukui Qin and Professor Zhenggang Ren, was announced as late-breaking abstract at the ESMO Annual Meeting in October 2018. The results showed that the objective response rate (ORR) reached 13.8%, and the 6-month OS rate was 74.7%. Two phase 1 studies of camrelizumab explored the efficacy and safety of camrelizumab as the second-line treatment and camrelizumab combined with chemotherapy as the first-line treatment for patients with recurrent or metastatic nasopharyngeal carcinoma. According to the results, the ORR in the second-line treatment was 34%; but it was up to 91% in the first-line treatment and the disease control rate reached 100% [24]. In December 2014, Jiangsu Hengrui Pharmaceutials Co., Ltd. submitted a clinical trial application for camrelizumab, and was approved by China Food and Drug Administration in February 2016. In November 2016, phase 2 and 3 clinical trials were approved. In May 2019, camrelizumab was approved

by China Food and Drug Administration for sales.

Therefore, neoadjuvant chemotherapy combined with immunotherapy (camrelizumab) is used for patients with locally advanced HNSCC in this study, aiming to ensure an effective anti-tumor treatment before surgery and obtain better efficacy.

2. Study Profile

2.1 Purpose

The purpose of this study is to observe and evaluate safety and efficacy of neoadjuvant chemotherapy combined with anti-PD-1 antibody in the treatment of locally advanced HNSCC.

2.2 Primary Endpoints

The primary endpoints include pCR rate, and treatment-related adverse events (TRAEs) in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

2.3 Secondary Endpoints

The secondary endpoints include MPR rate, ORR, 2-year disease-free survivail (DFS) rate, 2-year OS rate and 5-year OS rate.

2.4 Enrolled population

Patients with operable locally advanced HNSCC (oral cavity, oropharynx, hypopharynx or larynx).

3. Subject Selection and Withdrawal

3.1 Inclusion Criteria

1. Age between 18 and 70 years;

2. Histologically diagnosed with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx, and resectable tumor evaluated by a head and neck surgeon prior to enrollment;

3. High-risk disease according to the 8th edition of American Joint Committee on Cancer (AJCC) guideline:

—Non-oropharyngeal HNSCC cancer and HPV-negative oropharyngeal cancer, stage III, IVA and IVB；

—HPV-positive oropharyngeal cancer, stage II and III;

HPV status for oropharyngeal cancer was determined by p16 immunohistochemistry.

4. No prior anti-cancer therapy for HNSCC;

5. At least one evaluable target lesion according to RECIST 1.1;

6. Eastern Cooperative Oncology Group (ECOG) performance status 0-1;

7. Normal major organ function in accordance with the following criteria:

(1) Blood routine examination: (no blood transfusion within 14 days)

a. Hemoglobin (Hb) ≥90 g/L;

b. Absolute neutrophil count (ANC) ≥1.5×10^9/L;

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(2) Blood biochemistry

a. Bilirubin (BIL) <1.25× the upper limit of normal (ULN);

b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.5×ULN; for patients with liver metastasis, ALT and AST <5×ULN;

c. Serum creatinine (Cr) ≤ULN and endogenous creatinine clearance >50 mL/min (Cockcroft-Gaut formula);

8. Written informed consent before enrollment;

9. Patients who can adhere to study protocol, as judged by the investigator;

10. Negative pregnancy test result for fertile female patients;

11. Male patients and fertile female patients must agree to use two kinds of contraceptive measures (including at least one highly effective measure) during the whole study period.

Infertile female patients are those meeting at least one of the following criteria:

-Documented hysterectomy and/or bilateral oophorectomy;

-Medical confirmed ovarian function decline;

-Postmenopausal status, defined as cessation of menstruation for at least 12 consecutive months without pathological or physiological reasons, with serum follicle-stimulating hormone level in accordance with post-menopausal status.

12. Patients who are willing and able to adhere to follow-up, treatment plan, laboratory test and other study procedures.

3.2 Exclusion Criteria

1. Prior immunotherapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA-4 antibody, or any other antibodies or drug that specifically targeted T cell co-stimulation or immune checkpoint pathways;

2. Major surgery within 4 weeks before enrollment;

3. Allergry to anti-PD-1 antibody or its excipients;

4. Any active autoimmune disease or history of autoimmune disease, such as interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, myocarditis, nephritis, hyperthyroidism, hypothyroidism (patients can be enrolled after effective hormone replacement therapy) and so on. Patients with vitiligo, or those with asthma that had been completely relieved in childhood without intervention after adulthood or only require medical intervention with bronchodilators, can be enrolled;

5. Other malignant tumors, except for those who had been cured with tumor-free survival more than 5 years, such as skin basal cell carcinoma, cervical carcinoma in situ, and papillary thyroid carcinoma;

6. Uncontrollable cardiac symptom or disease, such as (1) grade II or higher heart failure according to New York Heart Association (NYHA) cardiac function classification (2) unstable angina pectoris (3) myocardial infarction within one year (4) clinically significant supraventricular or ventricular arrhythmia requiring clinical intervention;

7. Patients who need systemic therapy with corticosteroids (>10 mg/day prednisone) or other immunosuppressive agents within 14 days before taking the study drugs, are allowed to inhale or locally use steroid and adrenal hormone (>10 mg/day prednisone) as replacement therapy;

8. Active infection requiring treatment;

9. Congenital or acquired immune deficiency (such as HIV infection), active hepatitis B (HBV-DNA ≥104 copies/mL or 2000 IU/mL) or C (positive hepatitis C antibody, with HCV-RNA higher than the lower limit of detection range);

10. With anti-cancer therapy at other oncology departments;

11. With live vaccine within 4 weeks before receiving the study treatment;

12. History of psychotropic drug abuse, or alcohol or drug abuse;

13. Pregnant or lactating women;

14. Other factors that may lead to midway withdrawal, such as other severe diseases (including mental disorders) requiring combination therapy, severe abnormalities of laboratory test values, family or social factors, and those may affect patient safety or data collection, as judged by the investigator;

15. Patients with T4b oral, laryngeal or hypopharyngeal carcinoma, or P16 oropharyngeal carcinoma, or unresectable tumor as deemed by the surgeon;

16. Active tuberculosis;

17. Severe infection within 4 weeks before receiving the study treatment (including but not limited to hospitalization due to infection, bacteremia or complications of severe pneumonia);

18. Prior systemic immunity stimulation drugs (including but not limited to interferon or interleukin-2) within 4 weeks before receiving the study treatment, or still within five drug half-lives (whichever was longer).

3.3 Withdrawal Criteria

Patients may be withdrawn from the study due to the following reasons:

1. Withdrawal of consent and refusal of further follow-up;

2. Any clinical adverse reactions, laboratory test abnormities or concurrent diseases, not in accordance with best benefit if patients continue the study, as judged by the investigator;

3. Any other conditions judged by the investigator. For example, patients lose their ability to freely express their will due to incarceration or isolation.

4. Disease progression by imaging examinations;

The first progression by RECIST 1.1 needs to be confirmed 4-6 weeks later (except for patients with rapid progression or significantly clinical progression);

Patients with confirmed progression can continue the study treatment until second radiographic progression if the clinical symptoms are stable (a. no significantly clinical symptoms or changes in laboratory indicators; b. no deterioration in ECOG performance status; c. Non-rapid progression or progression with no involvement of vital organs/sites [such as spinal cord compression]);

5. Loss to follow-up;

6. Death;

7. Termination of the study by the sponsor.

Withdrawal procedures:

The investigators should ask about the reasons and the adverse events that occurred when the patient decided to withdraw from the study. If possible, they should observe and evaluate this patient. When the patient suffered from serious or unexpected adverse reactions, the investigator should follow up. Once the patient withdrew from the study, the investigator should try to obtain the patient's information. Moreover, the investigator should try to complete final evaluation and record their efforts. The evaluations, observations, along with patient's reasons for withdrawal from the study, must be recorded in the original data. Patient's reasons for withdrawal from the study must be recorded in the case report form (CRF) as well, and the subsequent procedures (discharge follow-up) must be completed as much as possible.

3.4 Treatment Discontinuation Criteria

Discontinuation of the study treatment doesn't mean withdrawal from the study. Patients who discontinue the study treatment must continue the follow-up as per the protocol.
Patients must discontinue the study treatment if they meet one of the following criteria:

1. Patients ask to discontinue the study treatment;
2. When imaging examinations or clinical characteristics demonstrate disease progression, patients should discontinue the study treatment unless they meet the criteria of continuing treatment after progression;
3. Pregnancy during the study period;
4. Any clinical adverse events, laboratory tests abnormities or other medical conditions, leading to no more benefits for patients;
5. Patients cannot continue the study due to the general deterioration of health status;
6. Loss to follow-ip;
7. Death;
8. Other reasons judged by the investigator;

3.5 Early Termination or Suspension of Study

The study can be early terminated or suspended for the right reason. This may be due to change in decision by ethics committee, or efficacy or safety issues of the study drugs. The personnale or organization who decide to suspend/terminate the study needs to send written notice with recorded reason

to the investigators. The investigators need to inform the ethics committee and explain the reason.

The study may be early terminated or suspended due to the following reasons:

1. Confirmed unexpected, significant, or unacceptable risk;
2. Current efficacy results supporting early termination;
3. Confirmed ineffective study drugs;
4. Major mistake found during the study period;
5. Difficulty in completing the study and low compliance to the study protocol due to slow enrollment, protocol deviations or other reasons;
6. Incomplete or unavailable data;
7. Study results with no values.

4. Treatment Regimen

4.1 Neoadjuvant Immunotherapy

After enrollment, patients will be administered camrelizumab 200 mg once every three weeks for three times in total before surgery (days 1, 22 and 43, respectively). Camrelizumab will be given by intravenous infusion for 30 min (no less than 20 min and no more than 60 min).

4.2 Neoadjuvant Chemotherapy

After enrollment, patients will be administered chemotherapy (docetaxel combined with cisplatin [DP] or albumin-bound paclitaxel combined with cisplatin [AP]) for three 21-day cycles before surgery.

4.3 Surgery

Surgery will be performed at one to four weeks after the completion of 9-week neoadjuvant therapy. Surgical delay was defined as the delay in the planned surgery of no more than 49 days after the first day of the third treatment cycle.

4.4 Adjuvant Radiotherapy

Adjuvant radiotherapy will be given at 4 weeks after surgery. Radiotherapy alone or concurrent chemoradiotherapy will be performed based on the postoperative pathological results. Irradiation dose: DT50Gy/25F radiotherapy alone at low-risk areas; 60Gy/30F for patients with positive margin; and 66-70Gy/33-35F on sites without residual tumor. Cisplatin combined with concurrent radiotherapy will be given to patients with positive margin or extracapsular invasion of lymph nodes.

4.5 Follow-up

Regular follow-up was performed after patients completed the treatment.

Study Flowchart

Stage	**Screening**	**Neoadjuvant therapy**	**Surgery**	**Adjuvant therapy**			**Follow-up**		**Study completion or early termination**
		PD-1 + Chemotherapy for 3 cycles (days 1, 22, and 43)	**Day 64-91**	**Margin-negative: radiotherapy alone**		**Margin-positive: concurrent chemoradiotherapy + PD-1**	**Safety follow-up**	**Survival follow-up (every 90 days for the first two years, and every 180 days for the next three years)**	
				Radiotherapy (4 weeks after surgery)	**After radiotherapy**	**PD-1 for 6 cycles**			
Time window		**Q3W (±3 days)**		**±7 days**	**±3 days**	**Q3W (±3 days)**	**±7 days**	**±15 days**	
Collection of medical history									
Determination of inclusion / exclusion criteria	√								
Written informed	√								

consent									
Baseline questionnaire (smoking history, etc.)	√								
Past medical history and treatment history	√								
Concomitant drugs and accompanying diseases	√	√	√	√	√	√	√	√	√
Diagnosis and efficacy indicators	√								
Tumor tissue specimen	√								
Physical examination	√	√	√	√	√	√	√	√	√

Locally enhanced MRI	√	Q6W	Before surgery	√	√	Q6W		√	√
Liver ultrasound								√	√
Chest enhanced CT or PET-CT	√						√	√	√
KPS GPA score	√	√	√	√	√	√	√	√	√
Quality of Life Scale	√	√	√	√	√	√	√	√	√
Hematuria routine; liver and kidney function	√	√	√	√	√	√	√	√	√
Lymphocyte subpopulation	√	Q6W		√	√		√		
Six tests for cytokines	√	Q6W		√	√		√		
Electrocardiogram	√	√	√	√	√	√	√	√	√

5. Sample Size

This study used a single-arm design. NCSS PASS 15 (LLC. Kaysville, Utah, USA, ncss.com/software/pass) was used for sample size calculation. According to previous reports, the pCR rate with docetaxel, cisplatin and 5-fluorouracil (TPF) for resectable locally advanced HNSCC was 13.4%. Based on the early data of the study treatment, the estimated pCR rate with camrelizumab plus inductive chemotherapy for resectable locally advanced HNSCC was 34%. Assuming an one-sided α of 0.025 and power of 80%, 27 patients were needed in this study. Considering a dropout rate of 10%, the calculation yielded 30 patients.

6. Grading and Treatment of Toxicity

6.1 Definition of Clinically Significant Toxicity

1. Grade 4 hematological toxicity, grade ≥3 thrombocytopenia accompanied with bleeding, or grade ≥3 neutropenia accompanied with fever and infection;

2. Grade 3 or above non-hematological toxicity (except for abnormal laboratory test indicators), hypertension, rash, diarrhea, nausea and vomiting that cannot be controlled after symptomatic treatment;

3. Grade 3 or above abnormal laboratory test indicators that require medical intervention, lead to hospitalization, or last 7 days or more;

4. Discontinuation of camrelizumab for more than 14 days due to related toxicity (during the first cycle or dose delay at the second cycle);

Definition of patients who do not complete tolerability evaluation: during the tolerability observation period, the dosage of camrelizumab was less than 90% of prescribed dose due to non-clinically significant toxicity (such as injection reaction, etc.).

Treatment for adverse events (AEs)

1. Reactive cutaneous capillary endothelial proliferation (RCCEP) - grading and treatment recommendations

Based on clinical observations and expert opinions, together with skin-related adverse reactions caused by immunotherapy as specified in ESMO guidelines, the grading and treatment recommendations for RCCEP are listed as follows:

RCCEP	Manifestation	Treatment recommendations
Grade 1	Multiple or single nodule(s) with a maximum diameter of ≤10 mm, with or without	Study treatment can be continued. For patients with ulceration and bleeding, local treatment is strengthened

	ulceration and bleeding	to prevent infection.
Grade 2	Multiple or single nodule(s) with a maximum diameter of ≥10 mm, with or without ulceration and bleeding	Study treatment can be continued. Observation or local treatment, such as laser or surgical resection, can be taken if necessary. For patients with ulceration and bleeding, local treatment is strengthened to prevent infection.
Grade 3	Generalized nodules throughout the body, complicated with skin infection	Study treatment needs to be interrupted and resumed only after the RCCEP recover to grade 1 or lower. Observation or local treatment, such as laser or surgical resection, can be taken if necessary. For patients with concurrent infection, anti-infective treatment is given.

Note:

1. No grading is specified for grade 4 life-threatening RCCEP and grade 5 death because they did not occur in the study.

2. RCCEP is a unique adverse reaction caused by immunotherapy. Extending the treatment interval may reduce the severity and occurrence range. Now, there remains no effective preventive measures. Therefore, it is necessary to closely observe the growth and surface changes of the nodules. When it is ulcerated, Yunnan white powder is given, and if necessary, antibiotic ointment is given to prevent infection.

6.2 Treatment for Other Immune-related AEs

Immune-related AEs	**Treatment recommendations**
Grade 1	Immunotherapy can be continued.
Grade 2	Immunotherapy needs to be interrupted and resumed only after immune-related AEs recover to grade 1 or lower. If the symptoms last for more than one week, corticosteroids (0.5-1 mg/kg/day of prednisone or equivalent) should be given.
Grade 3/4	High-dose corticosteroids (1-2 mg/kg/day of prednisone or equivalent) should be given, and dose can be reduced after immune-related AEs recover to grade 1 or lower. Appropriate drug prevention from pneumocystis carinii pneumonia should be given for patients who have been treated with prednisone 20 mg or equivalent dose for at least 4 weeks.
Symptoms still	Immunosuppressant replacement therapy should be used, such as infliximab 5

exist after at least 3 days of intravenous corticosteroids	mg/kg or mycophenolate mofetil (for hepatitis). If the symptons last 2 weeks or more, infliximab 5 mg/kg should be given again.
Grade 4 toxicity	Immunotherapy needs to be terminated immediately (unless for endocrinopathy which can be controlled by hormone replacement therapy). Part of patients with grade 3 immune-related AEs can resume the immunotherapy.

Immunotherapy also needs to be terminated when the following situations occur:

1. Grade 2 immune-related AEs last 6 weeks or more. However, if endocrinopathy of patients treated with PD-1/PD-L1 inhibitors can be controlled by hormone replacement therapy, the immunotherapy can be continued;
2. Patients treated with CTLA-4 inhibitor cannot reduce the dose of corticosteroids to 7.5 mg or less (prednisone); or patients treated with PD-1/PD-L1 inhibitor cannot reduce the dose of corticosteroids to 10 mg/day or less within 12 weeks;
3. Grade 2-4 ocular toxicities which cannot be improved to grade 1 or lower after 2 weeks of systemic therapy or local immunosuppressant treatment.

7. Data Management

7.1 Case Report Form

CRF will be used to record data in this study. All data on each patient will be recorded in a timely and truthful manner. As original data, CRF cannot be modified. Corrections should be made after signing the name and date by the investigator. CRF is in duplicate, and kept by the statistician and investigator after the end of the study, respectively.

7.2 Establishment of Database

After receiving the CRF, data manager will check the data and feedback the possible problems to the investigator. The investigator should verify the data and reply to the data manager as soon as possible. And then, data manager will establish a database and complete the data entry. After checking without mistakes, the database will be locked by the principal investigators, data manager and statistician. To ensure data security, unauthorized personnals cannot get access or change data. All data must have backups. Any data change must be done after getting written consent from all the principal investigators, statistician and data manager.

7.3 Analysis Method

Descriptive analysis will be adopted to describe endpoints.

8. Ethic Regulations and Informed Consent

8.1 Ethic Regulations

This clinical study should be strictly conducted in accordance with Declaration of Helsinki and Good

Clinical Practice by the State Food and Drug Administration. Before the start of the study, it must be approved by the ethics committee. During the study, any modifications should be approved by the ethics committee.

8.2 Informed Consent

All patients must sign a written informed consent form before enrollment to protect the legal rights and interests. The investigators have the responsibility to fully and comprehensively introduce the purpose of the study, drug actions, the possible side effects and risks to the patients or their legal representatives, so that they know their rights, risks and benefits. Conversation is a very important informed consent process. If the patient and his or her legal representative have no reading ability, a witness shall participate in the informed consent process. After verbal agreement, the patient and his or her legal representative shall sign the informed consent form. The copy of the informed consent form and the contact information of the investigators and the ethics committee must be provided to the patients if required.

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