EFFECT-neo: A Prospective, Open-label, Multicenter Phase III Study to Evaluate Efficacy and Safety of Pembrolizumab Combined With Standard Chemotherapy vs. Standard Chemotherapy Given Prior to Surgery for stage IIIA- IVB Locally Advanced Head and Neck Squamous Cell Carcinoma

Version： TRH-202301V1.0

Date： 2023/03/15

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1、Background

Head and neck squamous cell carcinoma (HNSCC) refers to a series of tumors in the head and neck region, including the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, thyroid and salivary glands. Malignant tumors of the head and neck account for about 19.9% to 30.2% of all tumors in the body, and the incidence rate ranks sixth among all malignant tumors. More than 90% of the pathological types are squamous cell carcinomas [1-2]. The treatment of squamous cell carcinoma of the head and neck is mainly based on surgery. Early cases can be cured by simple surgical resection or radiotherapy, and advanced cases can be cured by surgery combined with radiotherapy or chemotherapy, which can achieve better curative effect. However, most patients with head and neck tumors are already in locally advanced (stage III-IVB) or advanced stage when they see a doctor, and may have lost the opportunity for surgery, so they can only choose comprehensive treatment based on radiotherapy and chemotherapy.

Neoadjuvant chemotherapy, also known as induction chemotherapy, refers to chemotherapy used before surgery or radiotherapy. It has good patient compliance, can reduce tumor burden, improve the rate of organ function preservation in surgical patients, eliminate potential metastatic lesions, and reduce distant metastasis. risks and other advantages [3]. Clinical research on induction chemotherapy began in the mid-1970s, and the most commonly used induction chemotherapy regimen was PF regimen (cisplatin (cisplatin, P)

+ 5-fluorouracil (5-fluorouracil, 5-FU). Along with paclitaxel (docetaxel, T), and is also exploring whether paclitaxel can be added to the induction chemotherapy regimen. For resectable HNSCC, the European GORTEC study showed that the addition of paclitaxel (T) on the basis of the PF regimen can improve the efficacy of induction chemotherapy, and its pCR rate The rate reached 13.4%, and the ORR was as high as 80%. A number of Phase II and Phase III clinical studies concluded that induction chemotherapy can reduce the rate of distant metastasis[4-6].

PD-L1 is a key negative regulator of autoreactive T cells, and plays a role in maintaining peripheral immune tolerance and suppressing autoimmunity in multiple ways, promoting T cell exhaustion and dysfunction, and tumor cells evading immune surveillance. PD-1/PD-L1 monoclonal antibody restores the function of tumor-specific T cells by blocking the combination of PD-1 and PD-L1, and achieves the effect of enhancing anti-tumor immunity. It has been used to treat a variety of tumors. Pembrolizumab is a fully humanized IgG4-kappa anti-PD-1 monoclonal antibody. The FDA approved pembrolizumab in 2016 for the treatment of platinum-resistant recurrent or metastatic head and neck squamous cell carcinoma. Currently, pembrolizumab combined with chemotherapy can be used as the first-line treatment for recurrent/metastatic head and neck squamous cell carcinoma. At the same time, pembrolizumab can also be used as a second-line treatment for recurrent/metastatic head and neck squamous cell carcinoma that is resistant to beneficiation.

The efficacy of PD-1 monoclonal antibody as a neoadjuvant therapy in head and neck squamous cell carcinoma is not yet clear, but in view of the good effect of immunotherapy in head and neck squamous cell carcinoma, induction therapy with PD-1 monoclonal antibody is considered to have a good clinical effect Application prospects [7]. At present, relevant clinical trials are underway, such as a phase III clinical trial KEYNOTE-689 (NCT03765918) for cancers of the oral cavity, oropharynx, hypopharynx, and larynx, using pembrolizumab as neoadjuvant therapy, compared with traditional surgery combined with adjuvant therapy program, and the results of the study are yet to be published. The 2020 ASCO meeting reported the study of neoadjuvant therapy nivolumab combined with carboplatin and paclitaxel for resectable locally advanced head and neck cancer. The surgery rate was 100%, CT showed no tumor progression, and the margin negative rate was 100%. , The pathological complete response rate (pCR) was 42%. Grade 3 toxicity occurred in 37% of patients, and grade 3-4 neutropenia occurred in 4 patients. It suggested that the neoadjuvant therapy of nivolumab combined with carboplatin and paclitaxel was well tolerated and the efficacy was satisfactory[7].

In summary, we speculate that, compared with the traditional induction chemotherapy regimen, the induction chemotherapy regimen of pembrolizumab combined with chemotherapy may be safer and more effective, and easier for clinical application. At present, there are no research

reports on the induction chemotherapy of pembrolizumab combined with cisplatin and nab-paclitaxel for patients with locally advanced operable head and neck squamous cell carcinoma. We intend to conduct a randomized controlled study on the efficacy and safety of pembrolizumab combined with chemotherapy as neoadjuvant therapy in Chinese patients with operable head and neck squamous cell carcinoma, and provide a basis for the neoadjuvant therapy of pembrolizumab combined with chemotherapy.

Keyword : Head and Neck Squamous Cell Carcinoma， immunotherapy， chemotherapy

Reference

[1]. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2018, 68(6):394-424.

[2]. Argiris A, Harrington K, Tahara M, et al. Evidence-Based Treatment Options in Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck. 2017;7:72

[3]. Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation[J]. J Natl Cancer Inst, 2009, 101(7): 498-506. DOI: 10.1093/jnci/djp007

[4]. Paccagnella A, Ghi MG, Loreggian L, et al. Concomitant

chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: a phase II randomized study[J]. Ann Oncol, 2010, 21(7): 1515-1522. DOI: 10.1093/ annonc/mdp573.

[5]. Licitra L, Vermorken JB. Is there still a role for neoadjuvant chemotherapy in head and neck cancer[J]? Ann Oncol, 2004, 15(1): 7-11.

[6]. Hitt R, Grau JJ, López-Pousa A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer[J]. Ann Oncol, 2014, 25(1): 216-225. DOI: 10.1093/annonc/mdt461.

[7]. Borch TH, Donia M, Andersen MH, et al. Reorienting the immune system in the treatment of cancer by using anti-PD-1 and anti-PD-L1 antibodies[J]. Drug Discov Today, 2015, 20(9):1127-1134.

2、Research purpose and research content

(1) Purpose

A randomized controlled study was conducted to investigate the efficacy and safety of adjuvant pembrolizumab combined with standard chemotherapy in Chinese patients with operable head and neck squamous cell carcinoma.

(2) Research content

The trial is a prospective, randomized, multicenter study aimed at evaluating

the effectiveness and safety of pembrolizumab combined with standard chemotherapy versus standard chemotherapy in the neoadjuvant treatment of resectable locally advanced head and neck squamous cell carcinoma. The study consisted of 3 phases: screening period, treatment period and follow-up period. After all patients signed the informed consent form, they entered a screening period of up to 28 days, during which the subjects will complete the screening assessment according to the visit plan.

For patients who meet the inclusion criteria, 1:1 randomization, pembrolizumab 200mg d1 + chemotherapy (see 3.1 for detailed chemotherapy regimen) 2 cycles (experimental group), 2 cycles of chemotherapy (control group), and then stratified according to the patient's condition . If the imaging evaluation after neoadjuvant treatment is CR, adjuvant radiotherapy (60-66Gy) will be given; if the imaging evaluation is PR or SD, surgery (within 2 weeks) will be performed, followed by standard treatment. If the imaging evaluation is PD, the patients will be removed from the group and given standard treatment. The enrolled patients must closely monitor the adverse reactions of chemotherapy, and record the time, grading, treatment measures, outcome, etc. All patients were reviewed every 3 months for 1 year; after 1 year, they were reviewed every 6 months for 3 years; recurrence and survival data were recorded.

(3) Study Outcome Measures

Primary Outcome Measure:

1. Pathological complete response rate (pCR) of pembrolizumab combined with standard chemotherapy neoadjuvant therapy in patients with locally advanced head and neck squamous cell carcinoma

   pCR was defined as the absence of residual invasive squamous cell carcinoma within the primary tumor specimen on resection/needle biopsy [Time Frame: 12 week]

2. Pathological complete response rate (pCR) of standard chemotherapy neoadjuvant chemotherapy in patients with locally advanced head and neck squamous cell carcinoma

Secondary Outcome Measures:

1. The objective response rate (ORR) of neoadjuvant therapy with pembrolizumab combined with standard chemotherapy
   ORR was defined as the percentage of participants in the analysis population who have a Complete Response (CR: disappearance of all target lesions) or a Partial Response (PR: ⩾30% decrease in the sum of diameters of target lesions) per RECIST 1.1 [Time Frame: 12 week]
2. The objective response rate (ORR) of neoadjuvant chemotherapy with standard chemotherapy
3. The 1-year and 2-year event-free survival rates (1y-EFS, 2y-EFS) after pembrolizumab combined with standard chemotherapy neoadjuvant

therapy

EFS is defined as the time from randomization to any event, including disease progression, discontinuation of treatment for any reason, or death [Time Frame: 2 year]

4. The 1-year and 2-year event-free survival rate (1y-EFS, 2y-EFS) after neoadjuvant chemotherapy with standard chemotherapy
5. The functional preservation rate of pembrolizumab combined with standard chemotherapy

   Functional preservation is defined as preserving and repairing the anatomical structure of the larynx, and reconstructing the breathing and pronunciation functions of the larynx, or protecting the appearance of the tongue and physiological functions such as speech, chewing and swallowing [Time Frame: 3 year]
6. The functional preservation rate of standard chemotherapy
7. The 2-year overall survival rate (2y-OS) after Neoadjuvant pembrolizumab combined with standard chemotherapy

   OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up [Time Frame: 2 year]
8. The 2-year overall survival rate (2y-OS) after Neoadjuvant Therapy with standard chemotherapy

9. Pathological complete response rate (pCR) of pembrolizumab combined with standard chemotherapy as neoadjuvant therapy in patients of locally advanced head and neck squamous cell carcinoma with CPS (combined positive score) $\geqslant 1$
10. Pathological complete response rate (pCR) of pembrolizumab combined with standard chemotherapy as neoadjuvant therapy in patients of locally advanced head and neck squamous cell carcinoma with CPS (combined positive score) < 1
11. The 2-year event-free survival rates (2y-EFS) after pembrolizumab combined with standard chemotherapy neoadjuvant therapy with CPS (combined positive score) $\geqslant 1$
12. The 2-year event-free survival rates (2y-EFS) after pembrolizumab combined with standard chemotherapy neoadjuvant therapy with CPS (combined positive score) < 1
13. The 2-year overall survival rate (2y-OS) after Neoadjuvant pembrolizumab combined with standard chemotherapy with CPS(combined positive score) $\geqslant 1$
14. The 2-year overall survival rate (2y-OS) after Neoadjuvant pembrolizumab combined with standard chemotherapy with CPS(combined positive score) < 1
15. Incidence of Treatment-Emergent Adverse Events (TRAEs) of pembrolizumab combined with standard chemotherapy in neoadjuvant

therapy

TRAEs include 5 levels, base on Common Terminology Criteria for Adverse Events (CTCAE) is widely accepted as the standard classification and severity grading scale for adverse events in cancer therapy, clinical trials and other oncology settings.[Time Frame: 3 year]

16. Incidence of Treatment-Emergent Adverse Events (TRAEs) of neoadjuvant chemotherapy with standard chemotherapy
17. The quality of life of pembrolizumab combined with standard chemotherapy neoadjuvant therapy measured by KPS scores

    A standard way of measuring the ability of cancer patients to perform ordinary tasks. The KPS scores range from 0 to 100. A higher score means the patient is better able to carry out daily activities [Time Frame: 3 year]
18. The quality of life of standard chemotherapy neoadjuvant therapy measured by KPS scores

3、Study design

(1) Overall Study Design

- A prospective, unblinded randomized, multicenter phase III study;
- Patients who met the inclusion criteria were randomized in a 1:1 ratio and given 2 cycles of pembrolizumab 200 mg d1 + chemotherapy (see the table below for detailed chemotherapy regimens) (experimental group)

and 2 cycles of chemotherapy (control group), and were divided according to the patient's condition. layer. If the imaging evaluation is CR after neoadjuvant treatment, radiotherapy (60-70Gy) ± chemotherapy (investigator's choice) will be given as adjuvant treatment; if the imaging evaluation is PR or SD, surgery (within 2 weeks) will be performed, and then standard treatment will be given. treat.

- If the imaging evaluation is PD, standard treatment will be given.
- Enrolled patients must closely monitor the adverse reactions of chemotherapy and record the time, grade, treatment measures, outcomes, etc. All patients were reviewed every 3 months for 1 year; after 1 year, they were reviewed every 6 months for 3 years; patient recurrence and survival data were recorded.

The chemotherapy regimen is as follows:

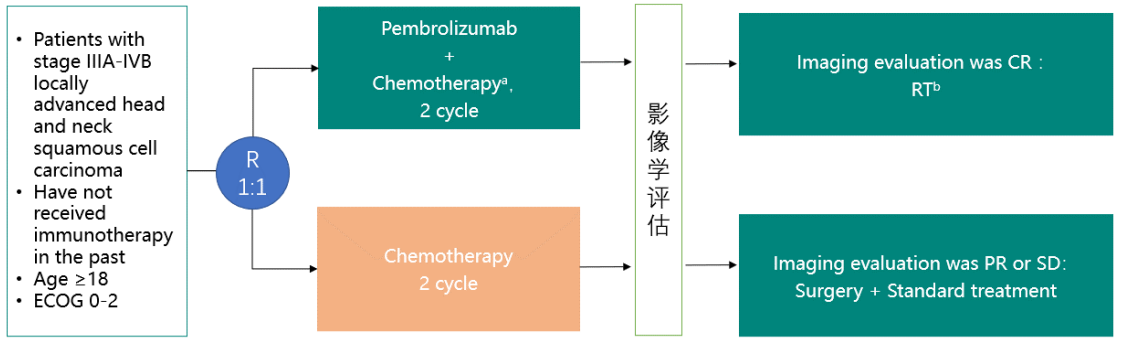
Drug	Dose/Potency	Administration route	Dosing interval
Pembrolizumab	200mg	IV	Day 1 of each 3-week cycle
Cisplatin	75mg/m^2	IV	Day 1 of each 3-week cycle
Carboplatin	AUC 2	IV	Day 1-3 of each 3-week cycle
nab-Paclitaxel	260mg/m^2	IV	Day 1 of each 3-week cycle
Docetaxel	75mg/m^2	IV	Day 1 of each 3-week cycle

Fluorouracil	750mg/m^2	IV	Day 1-5 of each 3-week cycle
Nedaplatin	80-100mg/m^2	IV	Day 2-4 of each 3-week cycle
Liposomal paclitaxel	135-175mg/m^2	IV	Day 1 of each 3-week cycle

(2) Study duration

Based on the calculation that all 10 centers enroll 7-8 patients per month, 272 patients are planned to enroll, and the enrollment time will take about 4 years. The adverse reactions of chemotherapy must be closely monitored, and the time, grading, treatment measures, and outcome should be recorded. and so on.

(3) Study flow chart



N=272

Note: If the imaging evaluation is PD, the group will be removed from the group and given standard treatment.

Primary endpoint: pCR

Secondary endpoints: 1y/2y-EFS c, functional preservation rate, 2y-OS, safety, etc.

a. Chemotherapy drugs include: cisplatin, carboplatin, nedaplatin, paclitaxel liposome, albumin-paclitaxel, docetaxel, and fluorouracil; the experimental group recommends TP, and the control group recommends TPF.
b. Pathological biopsy of the primary tumor location must be taken before radiotherapy.
c. EFS refers to the time from randomization to the occurrence of any event, including disease progression, discontinuation of treatment for any reason, or death.

(4) Study object

1. Inclusion criteria

The following conditions must be met at the same time:

1) Patients with stage IIIA-IVB head and neck squamous cell carcinoma

confirmed by histology and/or cytology;

2) Have not received immunotherapy in the past;
3) The researchers believe that he can safely receive pembrolizumab combined with chemotherapy or neoadjuvant chemotherapy;
4) Age ⩾18 years;
5) ECOG 0-2;
6) Measurable disease as defined by RECIST v1.1;
7) Organs function normally;
8) Female and male participants of reproductive potential must agree to use appropriate contraception throughout the study period and for 180 days after the last study treatment;
9) Male participants must not donate sperm throughout the study and for 180 days after the last study treatment.

2.Exclusion Criteria:

1) Presence of distant metastasis;
2) Female subjects with a positive urine pregnancy test within 72 hours before the start of the study or within 24 hours after starting radiation therapy (with or without cisplatin);
3) received a live vaccine within 30 days before enrollment;

4) Diagnosed with immunodeficiency or receiving systemic steroid treatment or any other form of immunosuppressive treatment within 7 days before enrollment;
5) Have imaging detectable (even if asymptomatic and/or previously treated) central nervous system metastases and/or cancerous meningitis;
6) Have undergone surgery before commencing the study or have failed to recover adequately from toxicity or complications resulting from the intervention;
7) Previous allogeneic tissue/solid organ transplant;
8) Severe hypersensitivity reaction (≥Grade 3) to pembrolizumab or any of its excipients, radiotherapy, platinum, paclitaxel, 5-FU or their analogs;
9) Have an active autoimmune disease requiring systemic therapy in the past 2 years;
10) History of (non-infectious) pneumonia requiring steroid treatment;
11) Have a history of human immunodeficiency virus (HIV) infection;
12) Have a history of hepatitis B or be positive for hepatitis B virus (defined as a positive reaction to hepatitis B surface antigen [HBsAg]) or active hepatitis C (defined as detection of hepatitis C virus [HCV] ribonucleic acid).

13) Have any medical history, treatment, or laboratory abnormalities that could confound the study results, interfere with participant participation throughout the study, or be detrimental to the best interests of the participant (e.g., Hashimoto's thyroiditis, etc.);

14) Have a known history of mental illness or substance abuse disorder

3. Exit criteria

Subject withdrawal refers to the interruption of a clinical trial by a subject for any reason. Subjects must withdraw from this trial for the following reasons:

1) Discussed by MDT before operation, the imaging assessment was progressive disease (PD)
2) Serious noncompliance with the requirements of this trial
3) Clinical signs or laboratory test results suggestive of pregnancy
4) Taking illegal drugs, or using other substances that the researchers believe are likely to cause toxicity or otherwise affect the research results
5) Diseases or conditions that occurred during the trial, which, in the judgment of the investigator, significantly affected the evaluation of clinical status and study endpoints
6) another cancer
7) Subject lost to follow-up

8) Those who interrupted taking the study drug for more than 28 days

9) Subject died

10) In all cases, the reason for withdrawal must be documented on the case report form and in the subject's medical record.

11) The subject himself or his legal representative requests to withdraw

12) In the opinion of the investigator, continued participation in the trial would be detrimental to the subject's health

13) Subjects were blinded for any reason

14) Specific requirements for trial sponsors

The studies did not accept healthy volunteers and did not involve vulnerable groups.

(5) Definitions of Treatment/Intervention Groups and Controls

Experimental Arm：Pembrolizumab+ standard chemotherapy

Active Comparator Arm：Standard chemotherapy

(6) Randomization, allocation concealment, and blinding

1. Methods for generating random sequence assignments

Simple random method

2. Method of random assignment

Take random number table and random remainder grouping.

3. Blinding and unblinding

The trial was an open-label, non-blinded study.

(7) Study program

1. Study treatment/Intervention Period

The experimental group received pembrolizumab 200 mg d1 + chemotherapy regimen, q21d*2 cycles (experimental group), and the control group received chemotherapy regimen, q21d*2 cycles (control group), and were later stratified according to the patient's condition. If the imaging evaluation is CR after neoadjuvant treatment, radiotherapy (60-70Gy) ± chemotherapy (investigator's choice) will be given as adjuvant treatment; if the imaging evaluation is PR or SD, surgery (within 2 weeks) will be performed, and then standard treatment will be given. treat. If progressive disease (PD) occurs, treatment is carried out according to routine diagnosis and treatment.

1.1 Evaluation stage

Treatment cycle: A treatment cycle (course of treatment) refers to every 3 weeks from the start of the first study drug application.

1.2 Screening stage

Before taking study drug, the following information should be collected during the screening phase:

1) An informed consent form must be signed before starting any trial-related procedures; recruitment into this trial means signing an informed consent form.
2) Use RECIST and iRECIST standards for tumor radioactivity assessment.

3) All suspicious lesions require imaging scanning. If bone metastases are suspected, a bone scan should be performed.
4) Conduct a complete physical examination on the subject and collect relevant medical history. Note: Relevant symptoms and signs that have existed before recruitment (signing of informed consent) and have not progressed at the time of signing of informed consent should be recorded on the medical history page.
5) Symptoms and signs that existed before recruitment (signing the informed consent form) and were progressing when signing the informed consent form, as well as symptoms and signs that appeared or worsened after recruitment (even before starting to take the study drug), According to NCI-CTCAE version 5.0 guidelines, adverse events should be recorded on the adverse events page.
6) 12-lead electrocardiogram (ECG).
7) Vital signs: After the subject rested for 5 minutes, measure and record his blood pressure (mmHg), heart rate (beats/min), respiratory rate (beats/min) and body temperature (°C).
8) Virus testing: anti-HIV, syphilis antibodies, anti-HCV, five hepatitis B tests, and HBV-DNA.
9) Laboratory tests: Routine blood tests, blood biochemistry, routine urine tests, thyroid function, cortisol, pancreatic amylase and lipase tests are required, and other tests such as lymphocyte

subpopulation, CPS test and oropharyngeal cancer p16 test (non-must).

10) Demographic information: age, gender, weight, height, race.
11) Concomitant combined medications and treatments.

1.3 Observation period

During treatment, a blood routine (required), urine routine, stool routine + occult blood, liver and kidney function and electrolytes, thyroid function, and pancreatic function tests (if necessary, the researcher can add the above based on the actual situation of the subject) examine). AEs were observed and recorded at any time during the research process. An electrocardiogram is performed once every cycle. If symptoms such as precordial pain and palpitations occur, the myocardial enzyme spectrum should be detected immediately, the electrocardiogram should be checked at any time, and cardiac color ultrasound should be performed; vital signs, PS score, physical examination, and fasting should be performed once every cycle. Blood glucose monitoring and comprehensive coagulation examination. Note: After 2 cycles of neoadjuvant therapy, imaging evaluation is required.

1.4 Follow-up period

Eligible patients will undergo an imaging evaluation after completion of radiotherapy (including receiving CCRT or postoperative RT). Imaging evaluations will be performed every 3 months within the next 1 year

(brain MRI or brain CT and bone scan examinations will be determined by the researcher whether and when the patient needs them); after 1 year, reexamination will be performed every 6 months for 3 years. . If the subject received any subsequent anti-cancer treatment after completion of treatment, treatment details (at least for the first treatment) will be collected. Post-trial follow-up will end at the time of the final overall survival (OS) analysis. If a subject discontinues medication due to an adverse event or abnormal clinical laboratory test values, the subject should be followed up until the adverse event resolves, the subject's condition becomes stable, or 30 days (whichever occurs first).

2. Supply of Investigational Drug/Treatment/Intervention

Cisplatin, carboplatin, nedaplatin, liposome paclitaxel, albumin-paclitaxel, docetaxel, fluorouracil and other drugs are provided by this research center, and patients routinely pay for treatment. Pembrolizumab is purchased at the patient's own expense during the entire treatment process. The policy of charitable drug donation is: purchase 2 cycles and add 2 cycles, and purchase 2 more cycles and then donate the drug to 15 cycles.

3. Chemotherapy dose adjustment

Pretreatment before chemotherapy:

Adequate hydration therapy must be performed prior to cisplatin administration. Standard chemotherapy can only be given after the infusion of pembrolizumab injection is completed.

Dose adjustment

For the dose adjustment of cisplatin, carboplatin, nedaplatin, paclitaxel liposome, nab-paclitaxel, fluorouracil and docetaxel in the regimen, please refer to the approved product instructions. During the study, if the researcher judges that the toxicity of chemotherapy drugs is intolerable (such as grade 4 hematological toxicity, ≥ grade 3 febrile neutropenia and ≥ grade 3 non-hematological toxicity (except nausea and vomiting) etc.), the dose of chemotherapy drugs can be adjusted upon the judgment of the researcher. In principle, 2 dose adjustments are allowed, and it is recommended that the first dose adjustment be 75% of the original dose, and the second adjustment be 50% of the original dose

Treatment adjustments for pembrolizumab-related immune-related AEs

Dosing suspension or discontinuation may be required based on individual patient safety and tolerability. Dosage increases or decreases are not recommended.

Table 1 Treatment Modifications for irAEs Associated with Pembrolizumab

Adverse Reaction	Severity[a]	Dosage Modification
IMMUNE-MEDIATED ADVERSE REACTIONS		
Pneumonitis	Grade 2	Withhold[b]
Pneumonitis	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[b]
Colitis	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver[c]	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold[b]
Hepatitis with no tumor involvement of the liver[c]	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[d]	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold[b]
Hepatitis with tumor involvement of the liver[d]	ALT or AST increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with renal dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[b]
Nephritis with renal dysfunction	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative dermatologic conditions	Suspected SJS, TEN, or DRESS	Withhold[b]
Exfoliative dermatologic conditions	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue

Neurological toxicities	Grade 2	Withhold[b]
Neurological toxicities	Grade 3 or 4	Permanently discontinue
Hematologic toxicity in patients with cHL or PMBCL	Grade 4	Withhold until resolution to Grade 0 or 1
OTHER ADVERSE REACTIONS		
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
Infusion-related reactions	Grade 3 or 4	Permanently discontinue

Other allowed pembrolizumab dose interruptions

Treatment with pembrolizumab may be discontinued for conditions other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study treatment. Unless otherwise discussed with the investigator, subjects should resume study treatment within 3 weeks of planned discontinuation. The reason for the discontinuation should be documented in the subject's study record.

Pembrolizumab AE management

Immune-Related Pneumonia:

Among patients receiving pembrolizumab, a total of 278 (4.4%) patients developed pneumonia, 122 (1.9%), 70 (1.1%), and 15 grade 2, 3, 4, and 5 cases, respectively. (0.2%) and 12 cases (0.2%), the median time to the onset of pneumonia was 3.2 months (range 2 days to 26.8 months), and the median duration was 2.0 months (range 1 day to 25.34 months) . Patients with a history of previous chest radiation had a higher incidence of pneumonia (8.1%) than those without prior chest radiation (3.3%).

Pneumonia led to discontinuation of pembrolizumab in 105 (1.7%) patients. 151 patients recovered from pneumonia, and 2 patients recovered with sequelae. Among patients with non-small cell lung cancer, a total of 160 patients (5.7%) developed pneumonia, 62 cases (2.2%), 47 cases (1.7%), and 14 cases (0.5%) of grade 2, 3, 4, and 5 pneumonia respectively and 10 cases (0.4%) in NSCLC patients with previous thoracic radiotherapy, the incidence of pneumonia was 8.9%.

Immune-related colitis:

Among patients receiving pembrolizumab, colitis occurred in 115 patients (1.8%), with 33 (0.5%), 66 (1.0%), and 4 (1.0%) grade 2, 3, and 4 cases, respectively. 0.1%), the median time to onset of colitis was 4.3 months (range 7 days to 24.3 months), the median duration was 0.9 months (range 1 day to 10.5+ months), and colitis resulted in 31 cases (0.5%) patients discontinued pembrolizumab treatment. Eighty-nine patients recovered from colitis, and 2 patients had sequelae after recovery.

Immune-Related Hepatitis:

Hepatitis occurred in 57 (0.9%) patients receiving pembrolizumab, with 9 (0.1%), 36 (0.6%), and 9 (0.1%) grade 2, 3, and 4 cases, respectively. %), the median time to hepatitis onset was 2.8 months (range 8 days to 21.4 months), the median duration was 1.1 months (range 1 day to 20.9+ months), and hepatitis resulted in 24 cases (0.4%) patients discontinued pembrolizumab treatment. 39 cases of hepatitis were cured.

Immune-related nephritis:

Among patients receiving pembrolizumab monotherapy, a total of 25 patients (0.3%) developed nephritis, 8 patients (0.1%), 14 patients (0.2%) and 1 patient (<0.1%). The median time to onset of nephritis was 3.5 months (range 12 days to 21.4 months). Median duration was 1.9 months (range 6 days to >12 months). Nephritis led to discontinuation of pembrolizumab in 10 (0.2%) patients. 15 patients recovered from nephritis, and 3 patients recovered with sequelae. In patients with non-squamous NSCLC treated with pembrolizumab plus pemetrexed lead chemotherapy (Cn=488), the incidence of nephritis (all grades) was 1.4%, and the incidence of grade 3 nephritis was 0.8%, The incidence of grade 4 nephritis was 0.4%.

Immune-Related Endocrine Diseases:

A total of 47 (0.7%) patients receiving pembrolizumab developed adrenal insufficiency, including 20 (0.3%), 20 (0.3%), and 3 patients with grade 2, 3, or 4 (<0.1%). The median time to onset of adrenal insufficiency was 5.4 months (1 day to 17.7 months). Median duration was not reached (3 days to over 26.2 months). Four patients (0.1%) discontinued the drug due to adrenal insufficiency. Sixteen patients with adrenal insufficiency were cured, and 4 patients were cured with sequelae.

Among the patients treated with pembrolizumab, a total of 39 patients (0.6%) developed hypophysis , with 14 (0.2%), 21 (0.3%), and 1 (0.3%)

grade 2, 3, and 4 cases (<0.1%). The median time to onset of hypophysis was 5.6 months (range 1 day to 17.7 months). Median duration was 3.3 months (range 3 days to 20+ months). Hypophysis led to discontinuation of pembrolizumab in 8 (0.1%) patients. Eighteen patients recovered from hypophysis, and 9 patients recovered with sequelae.

Hyperthyroidism occurred in a total of 263 (4.1%) patients receiving pembrolizumab, with 68 (1.1%) and 7 (0.1%) grade 2 or 3 cases, respectively. The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 23.2 months). Median duration was 1.9 months (range 4 days to 29.2+ months). Hyperthyroidism led to discontinuation of pembrolizumab in 3 (<0.1%) patients. 207 patients (78.7%) were cured of hyperthyroidism, and 5 patients were cured with sequelae.

Hypothyroidism occurred in a total of 696 (11.0%) patients receiving pembrolizumab, with 513 (8.1%) and 8 (0.1%) grade 2 or 3 cases, respectively. The median time to onset of hypothyroidism was 3.4 months (range 1 day to 20.5 months). Median duration was not reached (range 2 days to 32.6+ months). Two patients (<0.1%) discontinued pembrolizumab due to hypothyroidism. Hypothyroidism was cured in 159 patients (22.8%), and 10 patients were cured with sequelae. Among 909 HNSCC patients treated with pembrolizumab monotherapy, hypothyroidism occurred in 16.1% (all grades) and grade 3 in 0.3%. Among 276 HNSCC patients treated with pembrolizumab combined with platinum and 5-FU

chemotherapy, the incidence of hypothyroidism was 15.2%, all grade 1 or 2.

Immune-Related and Skin Adverse Reactions:

Among patients receiving pembrolizumab, a total of 93 (1.5%) patients experienced immune-related severe skin reactions, with 12 (0.2%) and 67 (1.1%) grade 2, 3, or 5 cases, respectively. %) and 1 case (<0.1%). The median time to onset of severe skin reactions was 3.2 months (range 3 days to 19.4 months). Median duration was 1.8 months (range 1 day to 27.3+ months). Severe skin reactions led to discontinuation of pembrolizumab in 9 (0.1%) patients. 67 cases of severe skin reactions were cured.

4. Concomitant treatment and follow-up

If a certain drug treatment is considered necessary for the subject's health and is not expected to interfere with the evaluation of pembrolizumab or interact with it, it can continue to be used during the study.

All concomitant medications must be reported on a Case Report Form (CRF). In addition, any diagnoses, treatments, or procedures performed during the trial should be documented, including dates, indications, interventions, and a description of any clinical findings.

Patients were not allowed to receive any other anti-cancer treatment during the trial.

Any other medications necessary for the patient may be used at the

investigator's discretion. Prophylactic use of drugs for the treatment of nausea, vomiting, antiallergic, acute cholinergic reactions, and diarrhea is permitted. Including a small amount of oral steroids for a short period of time to resist vomiting and stimulate appetite.

All subjects should spare loperamide (imodium); hematopoietic growth factors (such as G-CSF or GM-CSF) should be used in the treatment of febrile neutropenia and Level 3 and above have decreased white blood cells and neutrophils, but they cannot be used as preventive drugs. Growth factors should be discontinued at least 48 hours before the start of the next cycle of chemotherapy. Palliative surgery was allowed during treatment. Palliative radiotherapy is permitted for non-target lesions during treatment, but should be carefully evaluated for disease progression. Whether study treatment should be interrupted during radiotherapy may be at the discretion of the investigator or delayed until the patient recovers from acute reversible adverse reactions.

The following concomitant treatments are permitted:

In accordance with the guidelines of the American Society of Clinical Oncology (ASCO) and relevant domestic clinical guidelines, the use of recombinant human granulocyte colony-stimulating factor, erythropoietin, interleukin 11, and recombinant human thrombopoietin is allowed.

Supportive treatment: including antiemetic, antidiarrheal, acid

suppression, antipyretic, antiallergic, diabetes treatment, hypertension treatment, use of antihypertensive drugs, use of analgesics, use of antibiotics and others (including but not limited to blood products usage of).

Each subject will have a treatment visit and a safety assessment visit every 3 weeks (± 3 days) during postoperative treatment, and the planned follow-up time is 3 years; tumor imaging will be performed every 12 weeks after surgery or starting concurrent chemoradiotherapy Medical examination and efficacy evaluation. If the subject has terminated the study treatment and his imaging evaluation did not reach PD, tumor imaging examination and efficacy evaluation should still be performed every 6 weeks (±7 days) until the disease progresses and new anti-tumor treatment is started , died or lost to follow-up. After the subject terminates the study treatment, a safety follow-up should be conducted 30 days (±7 days) after the last dose, and AEs related to the study drug should be collected within 90 days after the last dose (or before starting new anti-tumor treatment) with all SAE. All subjects who have received pembrolizumab injection at least once will be followed up every 3 months (±14 days) after the end of treatment until the end of the study, death or loss of follow-up.

(8) Evaluation

During the observation period of treatment, a blood routine (mandatory),

urine routine, stool routine + occult blood, liver and kidney function and electrolytes, thyroid function, and pancreatic function tests (if necessary, the researcher can test the subject based on the actual situation) In addition to the above inspection). AEs were observed and recorded at any time during the research process. An electrocardiogram is performed every cycle. If symptoms such as precordial pain and palpitations occur, the myocardial enzyme spectrum should be detected immediately, the electrocardiogram should be checked at any time, and a cardiac color ultrasound should be performed; vital signs, PS score, physical examination, and fasting should be performed once every cycle. Blood glucose monitoring and comprehensive coagulation examination. During the follow-up period, an imaging evaluation will be performed after the completion of radiotherapy (including CCRT or postoperative RT). Imaging evaluations will be performed every 3 months within the next 1 year (brain MRI or brain CT and bone scan examinations will be determined by the researcher whether and when the patient needs them); after 1 year, reexamination will be performed every 6 months for 3 years. . If the subject received any subsequent anti-cancer treatment after completion of treatment, treatment details (at least for the first treatment) will be collected. Post-trial follow-up will end at the time of the final overall survival (OS) analysis. If a subject discontinues medication due to an adverse event or abnormal clinical laboratory test values, the subject should be followed

up until the adverse event resolves, the subject's condition becomes stable, or 30 days (whichever occurs first). After subjects terminate study treatment, safety follow-up should be conducted 30 days (±7 days) after the last dose, and AEs related to the study drug should be collected within 90 days after the last dose (or before starting new anti-tumor treatment) With all SAE. All subjects who have received at least one pembrolizumab injection treatment will undergo survival follow-up every 3 months (±14 days) after the end of treatment until the end of the study, subject death or loss to follow-up.

1. Imaging Evaluation

Evaluate the curative effect according to the standard of RECIST version 1.1.

According to RECIST version 1.1, if there is more than one measurable lesion at baseline assessment, all lesions should be recorded and measured, and the total number of lesions should not exceed 5 (not more than 2 per organ), e.g., only one or two cumulative For patients with organs, a maximum of 2 or 4 target lesions were selected as the baseline measurement lesions.

Measurable lymph nodes must meet the following criteria: short axis $\geq$ 15 mm measured by CT. The baseline only needs to detect the short diameter, and usually the short diameter of the nodule is used to judge whether the nodule has metastasized. Choose a plane from sagittal plane or coronal

plane), take the minimum value as the short diameter.

The calculated sum of the diameters of all target lesions (including the longest diameter of non-nodular lesions and the shortest diameter of nodular lesions) will be reported as the sum of baseline diameters. If lymph node diameters are included, only the short diameter is counted as mentioned above. The sum of the baseline diameters will serve as a reference value for the baseline level of disease.

All other lesions, including pathological lymph nodes, can be considered as non-target lesions and do not need to be measured, but should be recorded at baseline assessment, such as "present", "absent" or "clear progress" in rare cases. Extensive target lesions can be documented with target organs (eg, extensive liver metastases). The best type of CT scan is a diagnostic-quality helical or multislice CT with oral and intravenous contrast enhancement. If there is a contraindication to intravenous contrast enhancement, conventional CT should be used for evaluation of thoracic tumors. Abdominal and pelvic scans should be performed with MRI with intravenous contrast or CT with oral contrast. Brain scans should be performed with MRI or CT with intravenous contrast, if necessary. For suspicious new lesions, imaging examinations can be performed in combination with clinical indications. Patients who achieved a CR or PR were confirmed at a time point of $\geq$ 4 weeks.

Neoadjuvant treatment specimen selection method:

Imaging was PR or SD	Gross specimen preparation is consistent with the initial resection specimen
	Regardless of the size of the tumor, at least 1-5 representative regional tissues should be sent for examination
	Diagnosis of Pathological complete response requires careful sampling as with initial resection specimens
	The percentage of residual tumor should be reported (in 10% increments) based on evaluation of multiple specimen sections.
Imaging was CR	Select at least 2 points for pathology

2. Safety assessment

The trial will conduct a safety analysis of all subjects who received at least one dose of study drug. The physical examination, vital sign data (heart rate, blood pressure, respiration rate, and temperature), body weight, incidence of adverse events, and abnormal laboratory values will be summarized. In addition to this, a summary of the reasons for discontinuation of medication or dose change etc. will be made. The trial will use NCI-CTCAE version 5.0 to assess toxicity and reported serious adverse events.

Biomarkers refer to indicators that can be used to objectively mark and

evaluate the normal physiological process, pathological process and pharmacological response to treatment of the human body. Using an exploratory approach in this trial, the trial sponsor hopes to use tissue and plasma protein biomarkers to help better understand the impact of immunotherapy as first-line treatment of HNSCC on its prognosis. Assess PD-L1 expression in tumor tissue at baseline, etc. These tests are of experimental nature, and need to obtain the approval of the ethics committee and the informed consent signed by the subjects to voluntarily participate in the additional gene pharmacology test of this study.

(9) Adverse Event Report

1. Adverse event

Serious adverse events resulting from protocol-mandated interventions were reported only after informed consent was obtained but before study drug treatment was initiated. All adverse events will be reported after initiation of study drug treatment and up to 28 days after the last study drug dose. Any serious adverse events thought to be related to previous study drug treatment after 28 days after the last dose of study drug were also reported. All adverse events need to be recorded in the AE section of the CRF.

2. Definition of Adverse Events

An adverse event is any unfavorable medical condition that occurs in a

subject or in a clinical trial subject taking a pharmaceutical product. Adverse events do not necessarily have a causal relationship with treatment. Thus, an adverse event may be any unfavorable and unexpected sign (including abnormal laboratory results), symptom, or disease temporally associated with the investigational product or device, whether or not considered to be related to the medicinal product or device. Whether considered to be related to the drug itself, adverse events related to the use of drugs in humans include the following:

(1) Adverse events that occur during normal clinical use of the drug

(2) Adverse events caused by accidental or intentional overdose

(3) Adverse events caused by drug abuse

(4) Adverse events caused by drug withdrawal

Even if it is not related to the research product itself, if there are good reasons to believe that the adverse event is only caused by the subject's participation in this trial (such as adverse events or serious adverse events caused by interruption of antihypertensive drugs during the washout period), must be reported as an adverse event.

Any clinical manifestation that did not achieve the expected efficacy, even if it had been recorded as a data point in the case report form (CRF), was not recorded as an adverse event. However, if the criteria for a "serious" adverse event are met, it must be faithfully recorded and reported.

Within the extended scope of the above definition, the events that

occurred before signing the informed consent and starting to take the study drugs will also be considered as adverse events, so their relevant data will be collected.

3. Check result is abnormal

The investigator is responsible for assessing the causal relationship between all adverse events and the study drug. The principal investigator can entrust a clinician related to this trial to be responsible for this work, but the responsibility is still borne by the principal investigator. Investigators must maintain a list of relevant qualified persons whom they have commissioned for this work

4. Serious Adverse Event

A serious adverse event is any adverse medical condition occurring at any dose if it:

(1) cause death

(2) life-threatening

(3) Hospitalization or prolonged hospitalization is required

(4) Causes persistent or permanent disability or incapacity

(5) Causes congenital deformities or birth defects

(6) Other important medical events (including abnormal laboratory test results and others that need to be discussed with the investigator or relevant personnel of the sponsor). The event may not be immediately life-threatening, result in death or hospitalization, but, based on

appropriate medical judgment, may endanger the subject, or require intervention to prevent any of the consequences listed in the above definition to avoid the above-mentioned occurrence of any event.

Life-threatening: "Life-threatening" in the definition of "serious adverse event" means that the subject has a risk of death when the adverse event occurs. However, it does not refer to adverse events that may cause death if they are more serious.

Hospitalization: Any event resulting in hospitalization or prolonged hospitalization was considered a serious adverse event.

However, it should be noted that invasive treatments during hospitalization may meet the criteria of 'medically significant' and thus may be reported as serious adverse events based on clinical judgment. In addition, local regulations take precedence if local health authorities have more strictly defined requirements.

A disability is a severe impairment of a person's ability to perform daily living.

Medically important event: Any adverse reaction is considered serious because it has the potential to harm the subject and may require invasive treatment to prevent other serious conditions from occurring. For the determination of medically important events, see the "WHO Adverse Event Terms - List of critical terms. These terms refer to or may describe a serious disease state.

Because it may be associated with a serious disease state, events reported in this way ensure adequate attention and may trigger more decisive action than reporting under other terms.

5. Severity Evaluation

The following criteria shall be used for grading:

The intensity or severity of adverse events should be documented using the National Cancer Institute-Common Toxicity Criteria Version 5.0 (NCI-CTCAE v.5.0).

6. Relevance judgment

The evaluation of the relationship between adverse events and study drug treatment is the clinical judgment made by the investigator based on all available data when completing the case report form.

A rating of "not relevant" should include:

There is a clear alternative explanation, such as bleeding at the surgical site or irrationality, e.g., subject was involved in a car accident, but there is no indication that the drug caused disorientation in the subject that contributed to the accident; found several days after the first dose cancer.

A rating of "Related" means that it is reasonable to suspect that the adverse event is related to treatment with the investigational drug.

Factors considered in assessing adverse event and study drug relationship are:

(1) Chronological sequence: Adverse events should occur after medication. The length of time between dosing and event should be assessed in the clinical record of adverse events.

(2) Recovery after drug withdrawal, drug relapse: When considering the common clinical course of adverse events, the reaction of the subject after drug withdrawal or after drug re-administration should be considered at the same time.

(3) Basic diseases, concomitant diseases, and concurrent diseases: Each report should evaluate the natural history and course of the disease being treated, as well as any other diseases that the subject may have.

(4) Concomitant medication or treatment: Other drugs or treatments that the subject is receiving should also be considered together to determine whether there is any suspected possibility of causing adverse events.

(5) Pharmacology and pharmacokinetics of the test drug: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study drug and the pharmacodynamics of individual subjects should be considered。

(10) Data management and statistical analysis

1. Quality management: the principle of double entry of data, quality control in the process of multi-center research data collection, data cleaning and verification

To comply with GCP guidelines, monitoring and review procedures defined/agreed by the trial sponsor will be followed. Each test center will be inspected regularly by an inspector to ensure that the test is carried out in accordance with the requirements of the test protocol, GCP and legal affairs. The monitoring content includes going to the test center to check the completeness and clarity of the case report form (CRF) on the spot, checking the original records of the inspection, and clarifying management matters

2. Statistical Analysis

2.1 Sample size determination

α=0.05; β=0.8; combined with the previous control group in the oral cancer phase III clinical study, the TPF pCR rate was 13.4%. Assuming that the experimental group is better than the control group (2 times superior effect, that is, the pCR reaches 26.8%), set pCR Reaching 30% is the superiority test. Calculate the sample size of the experimental group and the control group as 136 people, as follows:

$$N1=\{z1-\alpha/2*\sqrt{\bar{p}*\bar{q}*(1+1/k)}+z1-\beta*p1*q1+\sqrt{(p2*q2/k)}\}2/\Delta2$$

$$q1=1-p1$$

$$q2=1-p2$$

$$\bar{p}=(p1+kp2)/\ (1+K)$$

$$\bar{q}=1-\bar{p}$$

$$N1=\{1.96*\sqrt{0.202*0.798*(1+1/1)}+0.84*\sqrt{0.27*0.73}+((0.134*$$

0.866)/1)}2/0.1362

N1=136

N2=K*N1=136

2.2 Analysis population

The main population of effectiveness analysis:

i. Intention-to-treat (ITT) population, defined as all subjects participating in the study.

ii. People in different CPS states.

iii. The population for safety analysis consists of all subjects who have received at least one dose of study drug

2.3 Efficacy Analysis and Statistical Methods

Short-term efficacy indicators:

pCR determines the pCR ratio through time-to-time results. If you want to perform stratified analysis on CPS $\geq$ 1 and CPS < 1, you can apply Miettinen method to carry out weighted analysis under 95% two-sided confidence interval.

Long-term efficacy indicators:

The 2y-OS and 1y/2yEFS rates will be analyzed using the Kaplan-Meier method, plotted from the beginning of the pembrolizumab combined with chemotherapy group to the data censored (including distant metastasis, local treatment failure, Death) time Kaplan-Meier graph, while calculating mEFS, mOS difference (95% two-sided confidence

interval).

2.4 Safety Analysis and Statistical Methods

All safety parameters will be summarized by treatment group in a descriptive summary table. NCI-CTCAE version 5.0 will be used to monitor the adverse reactions of the subjects. Treatment-induced adverse events, drug-related adverse reactions, trial procedure-related adverse reactions, and safety experimental parameters will be summarized by treatment group and CTC class.

2.5 Interim analysis

The trial plans to conduct an interim efficacy analysis when enrollment reaches 70% (i.e. after enrollment of 190 patients)

(11) Data Collection and Management

1. Case Report Forms/Electronic Data Records

Entries in the case report form (CRF) must be verifiable from the source file or entered directly into the CRF. In the latter case, what is recorded in the CRF will be considered the original source. Identification of verified source data parameters and source documents must be documented. Trial documents and all original data should be retained until notified by the trial sponsor for destruction.

2. Data management

Describe the scheme for entry, coding, confidentiality and storage,

including any relevant measures to improve data quality (such as double entry, data range checking, etc.)

To comply with GCP guidelines, monitoring and review procedures defined/agreed by the trial sponsor will be followed. Each test center will be inspected regularly by an inspector to ensure that the test is carried out in accordance with the requirements of the test protocol, GCP and legal affairs. The monitoring content includes going to the test center to check the completeness and clarity of the case report form (CRF) on the spot, checking the original records of the inspection, and clarifying management matters.

3. Subject rights protection and informed consent

Subjects will be given a core information and informed consent form.

Before starting this trial, the investigator must have obtained the written permission/consent of the ethics committee/institutional review board for the written informed consent and any written information provided to the subjects. Written approval from the ethics committee/institutional review board and approved subject information/informed consent must be documented in the trial file.

Written informed consent must be obtained from the subject before any trial-related procedure begins. The date that the subject participated in this trial and signed the informed consent form should be accurately recorded in the subject file.

In accordance with relevant laws and/or regulations, all subjects participating in this trial will be able to enjoy the insurance provided by the trial sponsor.

All records that personally identify subjects will be kept confidential and will not be made public to the extent permitted by relevant laws and/or regulations. The names of the subjects will also not be submitted to the trial sponsor. On the case report form, only the subject number is recorded. If the subject's name or initials appear in any other documentation (such as a pathology report), the subject's name or initials must be removed before a copy of the document is submitted to the trial sponsor. Research results stored on computers will be kept in accordance with local data protection laws. Subjects will be informed in writing that representatives of the trial sponsor, the ethics committee/institutional review board, or health authorities may inspect their medical records for verification of the information collected; all personal information for inspection will be kept under the strictest Confidentiality and compliance with local data protection laws. If the trial results are made public, the identities of the participants will remain confidential. The Investigator will maintain a list so that the subject's records can be identified.

4. Use and publication of data

All materials and test results of this trial, as well as all intellectual property rights thereof, belong to the sponsor of this trial. Trial sponsors

may use the data for a variety of purposes, such as submitting it to government authorities or disclosing it to other investigators. The trial sponsor confirms that the investigator can disclose the trial results when the trial is completed. Manuscripts or abstracts submitted by researchers will be reviewed promptly and will not be rejected without reason. If there is a disagreement between the parties, the content to be published should be discussed in order to find a mutually satisfactory solution.

Reference:

[1]. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2018, 68(6):394-424.

[2]. Argiris A, Harrington K, Tahara M, et al. Evidence-Based Treatment Options in Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck. 2017;7:72

[3]. Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation[J]. J Natl Cancer Inst, 2009, 101(7): 498-506. DOI: 10.1093/jnci/djp007

[4]. Paccagnella A, Ghi MG, Loreggian L, et al. Concomitant

chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: a phase II randomized study[J]. Ann Oncol, 2010, 21(7): 1515-1522. DOI: 10.1093/annonc/mdp573.

[5]. Licitra L, Vermorken JB. Is there still a role for neoadjuvant chemotherapy in head and neck cancer[J]? Ann Oncol, 2004, 15(1): 7-11.

[6]. Hitt R, Grau JJ, López-Pousa A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer[J]. Ann Oncol, 2014, 25(1): 216-225. DOI: 10.1093/annonc/mdt461.

[7]. Borch TH, Donia M, Andersen MH, et al. Reorienting the immune system in the treatment of cancer by using anti-PD-1 and anti-PD-L1 antibodies[J]. Drug Discov Today, 2015, 20(9):1127-1134.