Reducing Excision Margins After Neoadjuvant Chemoimmunotherapy for HPV Negative Resectable Locally Advanced HNSCC（REMATCH）

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1. Study purpose / endpoint

- purpose of research

  To observe and evaluate the safety and efficacy of neoadjuvant chemotherapy combined with anti-PD-1 antibody for negative HPV therapy and for surgical reduction after operable locally advanced head and neck squamous cell carcinoma.

- Primary study endpoint

  (1) D FS (disease-free survival) rate of tumors at 2 years

  (2) Organ retention rate.

- Secondary study endpoints

  (1) ORR, pCR rate, 2y-OS;

  (2) Quality of life: EORTC-QLQ-H & N35, EORTC-QLQ-C30 quality of life scale

  (3) Safety assessment: treatment-related toxicity, using the CTCAE 4.0 standard.

2. research design

2.1 system design

This study is a prospective, single-arm, multicenter exploratory study designed to evaluate the safety and efficacy of reduced surgical coverage following neoadjuvant chemotherapy combined with anti-PD-1 antibody against HPV-negative surgically locally advanced head and neck SCC.

2.2 sample capacity

With the single group target value method, the expected 2-year DFS of this trial is 80.0%, the target value is 60%, take a=0.025 (unilateral), power=0.80, and the statistical sample size is 45 cases.Considering factors such as shedding, increasing the

number of enrolled cases by 20%, and 54 patients enrolled in this trial were proposed.When the lower limit of 95%CI of DFS in this trial is greater than 60% of the target value, "neoadjuvant chemotherapy + immunity + reduced range surgery" can be considered effective for head and neck squamous cell carcinoma and meet the requirements.

3. study population

3.1 DC

HPV negative operable locally advanced head and neck squamous cell carcinoma (oral, oropharyngeal, hypoopharyngeal, or laryngeal squamous cell carcinoma).

3.2 Selection criteria

Patients must meet all of the following conditions to be enrolled in this study:

1. Age 18-70 years, no gender;

2. Histological diagnosis of oral cavity, oropharyngeal, hypoopharyngeal or laryngeal squamous cell carcinoma; surgical resection after preoperative evaluation;

3. Evaluation criteria for negative H P V: negative P16 immunohistochemistry, that is, the negative result of p16 is less than 70%, if there is any doubt, the negative HPV FISH test shall prevail;

Local advanced, as defined by the American Joint Committee on Cancer [AJCC] Guide 8, as follows:

- -HPV-negative disease, stage III, IVa, and IVb; she has received no previous specialist oncology treatment for head and neck squamous cell carcinoma;

4. With at least one evaluable target lesion according to the RECIST version 1.1 criteria;

5.ECOG physical status is 0-1 points;

6. Main organs have normal function, that is, they meet the following standards:

(1) Routine blood examination standards shall meet: (no blood transfusion within 14 days)

a．Hb≥90g/L:

b．ANC≥1.5x10^9/L;

c．PLT≥80x10^9／L；

(2) The biochemical inspection shall meet the following standards

A. B I L <1.25 times the upper normal value (ULN);

b.ALT and AST<2.5xULN; in case of liver metastases, ALT and AST <5x ULN:

c. Serum Cr ULN, endophytic creatinine clearance of> 50ml / min (Cockcroft-Gaut formula);

7. Sign a written informed consent prior to any trial-related activities;

8. The investigator judged able to comply with the study protocol;

9. Pregnancy test (for fertile female patients) was negative at screening;

1. Fertility male patients and women at risk of fertility and pregnancy must agree to the use of two contraceptive methods (at least one is considered highly effective contraception) throughout the study period.

Unfertile women (i. e. meeting at least one of the following criteria):

-A hysterectomy and / or bilateral oophorectomy with documented records;

- -The medically confirmed decline of ovarian function;

-Postmenopausal status is defined as at least 12 consecutive months in the absence of other pathologic or physiological reasons, and the status confirmed by serum follicle-stimulating hormone (FSH) level is consistent with the postmenopausal status.

2. Patients who are willing and able to follow visit arrangements, treatment plans, laboratory tests, and other research procedures.

3. Signed and dated informed consent indicating that the patient (or legal representative, if permitted by local guidelines / practice practices) has been informed of all relevant aspects of the study.

3.3 Exclusion criteria

Subjects will not be enrolled in this study if they meet any of the following conditions:

1. Previous immunotherapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-CTLA-4 antibodies (including ipilimumab) or any other antibodies or drugs specifically targeted to the T cell co-stimulation or immune checkpoint pathway.
2. Major surgery for the first 4 weeks prior to enrollment;
3. Those who have proven allergies to PD-1 antibody or its excipients;
4. Any active autoimmune disease or a history of autoimmune disease (such as interstitial pneumonia, uveitis, enteritis, hepatitis, hypopusitis, vasculitis, myocarditis, nephritis, hyperthyroidism, reduced thyroid function (hormone replacement therapy can be included): vitiligo or asthma in childhood, adults without any intervention, need bronchodilator medical intervention asthma patients can be included);
5. Other malignant tumors that have suffered previously or at the same time (except for malignant tumors that have been cured and have survived without cancer for more than 5 years, such as skin basal cell carcinoma, cervical carcinoma in situ, and papillary thyroid carcinoma, etc.);
6. Heart clinical symptoms or diseases that fail to be controlled, such as: (1) heart failure of grade NYHAII or above (2) unstable heart pattern pain (3) patients who have ever had myocardial infarction within 1 year (4) patients with clinically meaningful supraventricular or ventricular arrhythmias who require clinical intervention;
7. Subjects requiring systemic treatment with corticosteroids (> 10mg / day of prednisone efficacy dose) or other immunosuppressive agents within 14 days before administering the study drug, allowing inhaled or topical use of steroids and efficacy doses of prednisone in the absence of active autoimmune disease;
8. Active infections requiring treatment;
9. Patients with congenital or acquired immune function defects (e. g., HIV-infected persons), active hepatitis B (HBV-DNA 104 copy number / ml or 2000IU / ml), or hepatitis C (hepatitis C antibody is positive, and HCV-RNA is above the lower limit of detection of the analytical method);

10. The patient has received other oncology specialties before the visit;

11. Live vaccine was received within 4 weeks of starting study treatment;

12. Known history of psychotropic substance abuse, alcohol abuse, or drug use;

13. Pregnant or lactating women;

14. From the judgment of the investigator, the subject has other factors that may cause him to terminate the study, such as other serious diseases (including mental illness) requiring combined treatment, seriously abnormal laboratory tests, family or social factors that may affect the safety of the subject or the collection of trial data;

15. Patients that the surgeon believes cannot be radically removed;

16. Active pulmonary tuberculosis;

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

18 Received systemic immunostimulatory drugs (including but not limited to interferon or interleukin-2 [IL-2]) or remained in the half-life of five drugs (older of both).

3.4 Subjects' exit criteria

The ① developed a treatment failure as prescribed by the protocol.

The ② presents with unacceptable therapeutic toxicity.

③ with development may significantly affect clinical status assessment or diseases that require interrupted treatment.

④ patients may be withdrawn from this study at any time for any reason.

Exit procedure: Patients should be asked about the cause of their withdrawal and any adverse events that have occurred, and, if possible, they should be observed and evaluated by the investigator.Serious or unexpected adverse reactions should be followed-up.Once the patient exits or stops the trial, the investigator should try to obtain information about the patient.The researchers should do their best to complete the final evaluation and record their efforts.The results of these evaluations and observations, together with a description of the reasons for patient withdrawal, must be recorded in the original data.The main reasons for withdrawal or suspension must

be recorded in the case report form (CRF), and the relevant follow-up study steps (discharge visit) must be completed where possible.

4. Research intervention

4.1 Study intervention description

The study protocol intervention is: the second cycle of chemotherapy, a week after the third cycle of chemotherapy imaging and endoscopic tumor evaluation, according to the RECIST1.1 standard, tumor withdrawal more than 50% of patients, lymph node type positive lymph node area selective regional lymph node dissection, primary area according to the original imaging scope and endoscopic scope, combined with intraoperative pathological quick examination, narrow the surgical scope under the premise of R0.

5. stages of research

- Screening period

  The screening period begins with the signing of the informed consent form to enrollment or screening failure.Subjects must sign the informed consent form before performing the screening procedure specified in this study.For the presigned laboratory tests and imaging assessments done prior to routine clinical care, the relevant data can be used during the prescribed window period.

  Informed consent was signed 28 days before treatment, collected baseline questionnaire, demographic data, previous disease history and treatment history, combined medication and concomitant diseases, physical examination, imaging examination of tumor lesions (CT, E US or MRI), KPSGPA score, quality of life scale, hematuria routine liver and renal function test, electrocardiogram, adverse events and combined medication, and check the entry criteria; and collected tumor tissue specimens.

- stage of therapy

  Combined medication and concomitant diseases, physical examination, KPS score, quality of life scale, hematuria and routine urinary liver and renal function

tests, electrocardiogram, and adverse events were recorded during the neoadjuvant therapy and during each preoperative cycle;

Combined medication and concomitant diseases, physical examination, KPSGPA score, quality of life scale, hematuria routine liver and kidney function testing, electrocardiogram, and adverse events before postoperative adjuvant therapy;

- Safety follow-up period

During the neoadjuvant treatment period and in each preoperative cycle, the patients recorded the combined medication and concomitant diseases, physical examination, KPS, GPA score, quality of life scale, routine liver and renal function testing of hematuria, electrocardiogram, and adverse events;

Combined medication and concomitant diseases, physical examination, KPS, GPA score, quality of life scale, hematuria routine liver and kidney function testing, electrocardiogram, and adverse events before postoperative adjuvant therapy;

6. appraise

6.1 Primary and secondary endpoints / outcome evaluation

- Main evaluation indicators

(1) Tumor D FS (disease-free survival) rate at 2 years

(2) Organ retention rate

- Secondary study evaluation indicators

(1) ORR, pCR rate, 2y-OS;

(2) Quality of life: EORTC-QLQ-H & N35, EORTC-QLQ-C30 quality of life scale

6.2 safety evaluation

- Safety assessment: Treatment-related toxicities, using the CTCAE4.0 criteria

7. Adverse events and serious adverse events

7.1 Follow-up of the AE / SAE

All AE / SAE should be reported regardless (from ICF signing until 4 weeks after the last study drug administration).Four weeks after the last medication, only

considering the SAE associated with the study drug was reported.All should be followed up to disappearance, remission to baseline level or level 1, reached a stable state, or reasonably explained (e. g. loss to follow-up, death), and timely and accurately recorded in the CRF table.

7.2 Adverse events were reported

Collection of adverse event information should be started from the subject signing the informed consent until the first visit after the last medication (within 4 weeks).For each visit, the investigator should inquire about the adverse events occurring after the last visit.The investigator shall follow up until the end of the adverse events, have a stable status, make remission to the baseline level or level 1, receive reasonable explanation, be lost to follow-up, and die; and timely and accurately record them in the CRF table.

7.3 Reporting of serious adverse events

The collection period for serious adverse events (SAE) shall start since the subject signed the informed consent form until 4 weeks after the last use of the study drug (including the last day of 4 weeks).In case of SAE, the investigator must immediately fill in the Serious Adverse Event Report Form, within 24 hours of notification, sign and date, and immediately submit it to the ethics committee office and the project leader of Zhengda Tianqing Pharmaceutical Group Co., Ltd.

SAE occurring 90 days after the last use of the study drug is generally not reported unless suspected as related to the study drug.The SAE should document in detail the symptoms, severity, correlation with the test drug, time of the drug, occurrence, treatment, measures taken, time and manner of follow-up, and outcome.If the investigator considers that a C. SAE is not related to the test drug and potentially related to the study condition (e. g., termination of original therapy, or comorbidities in the course of the trial), this relationship should be detailed in the narrative section of the SAE report form.If the intensity of an occurring SAE or its relationship with the subject drug changes, a follow-up report should be submitted immediately.If the investigator considers that the previously reported SAE information is misreported, it can make the correct, cancel or downgrade

instructions in the follow-up report and report them according to the SAE reporting procedure.

7.4 Adverse event reporting of special concern

If it is also a serious adverse event, please fill in the CFDA Serious Adverse Event Report Form simultaneously, and report it to the relevant units according to the SAE procedure.

7.5 Pregnancy report

If a female subject is pregnant during the clinical trial, the subject will immediately terminate the study medication and fill in the Pregnancy Report / Follow-up Form within 24 hours of the investigator's knowledge of the pregnancy.

If the male subject's partner is pregnant during the clinical trial, the subject will continue the clinical trial and complete the Pregnancy Report / Follow-up Form within 24 hours after the investigator learns that the subject's partner is pregnant.

The investigators will follow up the pregnancy results until 1 month after the mother delivers them.

If the pregnancy result is stillbirth, spontaneous abortion, and fetal malformation, it is considered as SAE, and it needs to be reported according to the time limit requirements of SAE.

8. Statistical analysis and statistical methods

After receiving the CRF, the data administrator will check the data and feedback the possible questions to the researcher, who should verify and reply as soon as possible.The data administrator establishes the database in time and enters the data twice.After the database is reviewed, the main researchers, data administrators and statisticians will lock the data.In order to ensure data security, irrelevant personnel can not approach and modify the data, and the data must be backed up.Any data change must be signed by a consent form from the principal investigator, the statistician and the data administrator.

8.1 Selection of the data for the statistical analysis

- Full Analysis set (Full Analysis Set): Efficacy of all cases on medication

and taken at least once according to the Intituality analysis (ITT) principle.For case data that failed to observe the full course of treatment, the last observation data was carried forward to the study final result (LOCF).

- Compliance protocol set (Per-protocol Set): all cases that met the study protocol, had good compliance, took no medication ban during the study period, and completed the contents specified in the case report form.No fill-in was made for the missing data.Statistical analysis of drug efficacy was performed for both FAS and PPS.

- Safety Analysis Set (Safety Analysis Set): All patients with all enrolled cases, who have used the study medication at least once, and who have had post-medication safety records, belong to the safety analysis set.This dataset was used for the security analysis.

8.2 Statistical analysis plan

All statistical analyses will be computed using the SPSS 26.0 statistical analysis software programming.All statistical tests were two-sided, and a P-value less than or equal to 0.05 would be considered the difference tested as statistically significant, with credible intervals using 95% confidence.

Baseline data were analyzed by the full analysis set, and all efficacy indicators were analyzed by the full analysis set and compliance protocol set; the safety analysis used the safety analysis set.All data will be calculated according to the data type: mean, standard deviation, median, minimum and maximum values for continuous variables, and frequency and percentage for categorical data; Kaplan-Meier method will be used, and survival curve drawn if necessary; the above analysis will provide corresponding 95% credible interval if necessary.

Baseline is generally defined as the last observation before the first administration (including the day).

- efficacy analysis: D FS (disease-free survival) rate, organ retention rate, ORR, pCR rate, 2y-OS, and quality of life scale assessment at 2 years
- safety analysis:

1) Describe the drug exposure volume;

2) The incidence of adverse events, serious adverse events, the severity, and the causal relationship with the study drug were counted.
3) Vital signs, laboratory examination values, ECG, and changes relative to the baseline levels of the subjects at each follow-up point will be given descriptive statistics.Data that deviate from the reference value range will also be counted.

Combined medication and concomitant therapy will be categorized statistics.