Clinical study protocol

Project Name: A single-center, randomized, phase II exploratory study of adebelimab combined with carboplatin and nab-binding squamous alcohol in the treatment of resectable locally advanced oral squamous cell carcinoma

Sponsor: Sun Yat-sen Memorial Hospital, Sun Yat-sen University

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Plan signing confirmation:

Statement of Compliance

In compliance with the provisions of the Good Practice for Drug Clinical Trials and the Administrative Measures for Conducting Investigator-initiated Clinical Research in Medical and Health Institutions (Trial) and the Declaration of Helsinki, participants must be trained to carry out the study after obtaining written approval from the ethics committee and the written informed consent of the subjects.

1. Summary of the plan

Neoadjuvant immunochemotherapy can effectively improve the postoperative pathological complete response rate, improve patient survival, and reduce the risk of recurrence in oral squamous cell carcinoma (OSCC). Programmed death ligand-1 (PD-L1) plays a role in inhibiting the cancer-immune cycle by binding to negative regulators of T cell activation such as PD-1 and B7.1, and has achieved good efficacy in lung cancer, liver cancer and other cancers. Previous studies have shown that three cycles of PD-L1 inhibitor combined with chemotherapy have satisfactory efficacy and safety in locally advanced oral squamous cell carcinoma. However, in the course of three cycles of medication, due to the accumulation of drug toxic effects, the patient's tolerance to adverse reactions decreases, which increases the risk of serious adverse events and increases the psychological pressure of the patient. On this basis, this study aims to explore the efficacy of two cycles of adebelimab (PD-L1 inhibitor) combined with chemotherapy in locally advanced oral squamous cell carcinoma, and explore whether it can shorten the treatment time while achieving the equivalent of three cycles of efficacy and reducing the risk of serious adverse eventsTo further verify the efficacy and safety of PD-L1 inhibitors combined with chemotherapy in the treatment of locally advanced oral squamous cell carcinoma. In this study, the postoperative pathological complete response (PCR) rate was used as the primary outcome indicator, and the tumor objective response (ORR) rate, major pathological response (MPR) rate, 2-year disease-free survival (EFS) rate, and 2-year and 5-year overall survival (OS) rates were used as secondary outcome measures to evaluate the efficacy and long-term survival impact.

2. Introduction

2.1 Research theoretical basis/background

According to the latest data from the International Agency for Research on Cancer, the global incidence of head and neck cancer in 2022 ranks among the top ten new cancer incidences in the world [1]. Among them, the treatment guidelines for locally advanced head and neck squamous cell carcinoma (HNSCC) are risk-adapted adjuvant

radiotherapy with or without platinum-based chemotherapy, or definitive concurrent chemoradiotherapy after surgical resection. However, despite aggressive combination therapy, patients with locally advanced HNSCC remain at high risk of recurrence, distant metastasis, and death [2,3]. With the proposal of the treatment concept of preoperative induction chemotherapy, clinical studies have shown that patients who achieve tumor remission after preoperative induction chemotherapy have a higher survival rate and lower risk of distant metastasis, but the complete response rate of tumor pathology after surgery is low, and the effect has not been satisfactory [4].

Tumor immunotherapy provides the possibility to solve the above dilemma. At present, immune checkpoint inhibitors (ICIs) are widely used in oral squamous cell carcinoma (OSCC). A clinical study (KEYNOTE-048) showed that pembrolizumab (PD-1) combined with chemotherapy significantly improved the survival of patients with recurrent or metastatic oral squamous cell carcinoma [5], and has now become the first-line treatment option according to NCCN guidelines. Meanwhile, in a retrospective study by Li et al. [6], neoadjuvant chemoimmunotherapy (NACL) showed safe and encouraging efficacy in patients with locally advanced resectable OSCC. Among the 104 patients who received NACI, the pathological complete response (PCR) rate was 47.1%, the major pathological response (MPR) rate was 65.4%, and the expected 3-year disease-free survival (DFS) rate and overall survival (Overall survival, OS) rates of 89.0% and 91.3%, suggesting that NACI can effectively improve the postoperative pathological remission rate and improve the prognosis of patients.

Programmed death ligand-1 (PD-L1) plays a role in inhibiting the cancer-immune cycle by binding to negative regulators of T cell activation, such as PD-1 and B7.1 [7]. In a meta-analysis [8], the overall average incidence of grade 3 or higher adverse events was higher with PD-1 inhibitors than with PD-L1 inhibitors (OR, 1.58; 95% CI, 1.00-2.54), which may be due to the fact that PD-L1 inhibitors bind PD-L1 on the surface of tumor cells and antigen-presenting cells, but retain the normal function of PD-L2, thereby reducing the risk of potential autoimmune reactions and adverse events [9,10]. Therefore, PD-L1 inhibitors may have more therapeutic potential than PD-1 inhibitors.

Currently, PD-L1 inhibitors are mostly used in lung cancer, liver cancer, and triple-negative breast cancer [11-13]. Adebrelimab, a human-derived monoclonal antibody against PD-L1, significantly improved median overall survival in the adebrelimab arm in a phase 3 clinical trial in combination with chemotherapy for small cell lung cancer [14] (median 15.3 months [95% CI; 13.2-17.5]）。 However, there is a lack of research on its application in oral squamous cell carcinoma, and the existing phase I clinical studies have confirmed its therapeutic safety and tumor activity [15]. In addition, previous studies have shown that in 28 patients with locally advanced oral squamous cell carcinoma who received three cycles of PD-L1 inhibitor (adebelimab) combined with chemotherapy, the tumor objective response (ORR) rate was 60.7% (95% CI, 40.58%-78.50%) and the complete pathologic response (PCR) rate was 35.7% (95% CI, 18.64%-55.93%)), showing satisfactory efficacy, confirming that the PD-L1 inhibitor (adebelimab) can effectively increase the PCR rate. However, in the course of three cycles of medication, due to the accumulation of drug toxic effects, the patient's tolerance to adverse reactions decreases, which increases the risk of serious adverse events and increases the psychological pressure of the patient. On this basis, this study aims to explore the efficacy of two cycles of adebelimab (PD-L1 inhibitor) combined with chemotherapy in locally advanced oral squamous cell carcinoma, explore whether it can shorten the treatment time while achieving the same efficacy as three cycles, reduce the risk of serious adverse events, and further verify the efficacy and safety of PD-L1 inhibitor combined with chemotherapy in the treatment of locally advanced oral squamous cell carcinoma.

2.2 Risk/benefit assessment

2.2.1 Known potential risks

The potential risks of this study mainly include adverse reactions after the use of PD-L1 inhibitors, the superprogress of tumor treatment caused by the study protocol itself, and the risk of sudden accidents in the study.

2.2.2 Known potential benefits

The potential benefits of the subjects in this study are: the treatment effect of the study

regimen has enabled the subjects to achieve complete or partial remission of the tumor; Subjects who accept the research program can receive a certain drug donation policy and obtain certain financial assistance; Subjects entering this clinical study can get more attention from the investigator and deal with changes in their condition in a timely manner, which is conducive to the treatment of the subject's disease.

2.2.3 Evaluation of potential risks and benefits

The main study drugs in this study are adebelimab combined with carboplatin and nab-binding shirtol. Among them, carboplatin and nab-binding shirt alcohol are the first-line recommendations for the systemic treatment of head and neck cancer in the NCCN guidelines, and the adverse reactions and safety have also been proven by many studies. As a PD-L1 inhibitor, adebelimab has been confirmed in existing clinical studies to have a certain immune response effect on advanced tumors of the head and neck. At the same time, adebelimab has been studied in a large-sample phase III clinical study in small cell lung cancer in China, and its safety has been verified, and it was approved for marketing by the National Medical Products Administration on March 3, 2023. Therefore, the clinical study protocol has a low risk of tumor progression and serious adverse events in the treatment of head and neck squamous cell carcinoma, and the subjects have certain economic benefits under the drug donation policy of the pharmaceutical company. At the same time, in future studies, researchers will pay more attention to the subject's general condition and tumor treatment, and the subjects will also gain certain clinical benefits in the study.

3. Purpose and endpoint of the study

3.1 Purpose

3.1.1 Main purpose

The main objective of this study is to explore the efficacy of adebelimab combined with chemotherapy in patients with locally advanced resectable oral squamous cell carcinoma.

3.1.2 Secondary Objectives

The secondary objective of this study is to explore the prognostic impact of adebelimab combined with chemotherapy on patients with locally advanced resectable oral squamous cell carcinoma with different drug cycles.

3.1.3 Exploratory purpose

The exploratory objective of this study is to explore the effectiveness of adebelimab combined with chemotherapy in the treatment of locally advanced resectable oral squamous cell carcinoma with different drug cycles. To explore the correlation between biomarkers and the efficacy of combination regimens.

3.2. Research indicators

3.2.1 Main indicators and definitions

Postoperative pathological complete response (PCR) rate: No residual tumor cells in the pathological sections of surgically resected primary lesions and lymph node specimens. The main judgment method is that the postoperative specimen is sent to the pathology department for fixation, sectioning, and observation. Two pathologists will read the radiograph to determine whether the tumor remains or not, and if there is a disagreement between the two, it will be discussed and decided by a third senior pathologist.

3.2.2 Secondary indicators and definitions

Major pathological response (MPR) rate: Proportion of patients with ≤ 10% of viable tumor cells in the primary lesion specimen.

Tumor objective response (ORR) rate: The proportion of patients assessed by RECIST 1.1 criteria as complete response (CR) and partial response (PR) after immunochemotherapy.

2-year disease-free survival (EFS) rate: the proportion of patients who do not experience relapse or disease progression within 2 years after completion of all treatments.

Overall survival (OS) at 2 and 5 years: Proportion of patients who survived at 2 and 5 years after completion of all treatments.

3.2.3 Security indicators

The above safety indicators are based on the test results before the enrollment of the subjects, and the blood draw results of each cycle of treatment shall prevail, and will be interpreted by the investigator's team.

4. Study population

4.1 Selection criteria

(1) Aged between 18 and 75 years;

(2) Patients with stage III-IVB tumors with non-oropharyngeal cancer who have pathologically confirmed head and neck squamous cell carcinoma (oral cavity, including buccal, tongue, gingival, floor of mouth, palate, and maxillary sinuses) according to the 8th edition guidelines of the American Joint Committee on Cancer (AJCC);

(3) Evaluating resectable tumors by head and neck surgeons before enrollment to rule out clinical evidence of distant metastasis;

(4) At least one measurable tumor lesion according to RECIST 1.1, the efficacy evaluation criteria for solid tumors;

(5) The performance status of the Eastern Cooperative Oncology Group (ECOG) was 0-1;

(6) Blood routine: white blood cell count (WBC) ≥3.0×109/L; Absolute neutrophil count (ANC) ≥ 1.5×109/L; Platelets (PLT) ≥ 100×109/L; Hemoglobin level (HGB) ≥ 9.0 g/dL (no corresponding supportive care such as transfusion and leukocyte increase within 7 days);

(7) Liver function: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 times the upper limit of reference value (ULN) in patients without liver metastasis; albumin (ALB) ≥ 30 g/L;

(8) Renal function: serum creatinine ≤1.5 times ULN or creatinine clearance (CrCl) ≥ 50mL/min (using Cocroft/Galt formula); Urine protein (UPRO) < (++), or 24-hour urine protein < 1.0 g;

(9) HPV status of oropharyngeal cancer was determined using p16 IHC. If > 70% of

tumor cells exhibit strong diffuse nuclei and cytoplasmic staining, the sample is considered p16 positive;

(10) Have not participated in other clinical trial projects within the past 30 days;

(11) Patients who voluntarily participate in this project and sign the informed consent form.

4.2 Exclusion Criteria

(1) The patient has abnormal blood indicators and abnormal liver and kidney function, and cannot tolerate the course of this clinical study after multidisciplinary consultation and evaluation;

(2) The patient has previously suffered from tumors in other parts of the country, or has undergone anti-tumor treatment such as surgery, chemotherapy, and radiotherapy in the past;

(3) Unable to complete the entire clinical research process due to personal, social and economic reasons;

(4) Previous serious systemic diseases that cannot be cured or controlled by drugs.

4.3 Lifestyle considerations

If the subject needs to use drugs, treatments or surgeries unrelated to this study in the clinical study, the investigator needs to evaluate whether the reason for the need for the drug, treatment and surgical treatment is the adverse events caused by the study, such as accidents or other reasons that cause the subject to need additional treatment modalities, then consider whether the treatment has an impact on the course of the study, If the impact is too great, it is recommended that the subject receive conventional treatment after withdrawal and the subject data be sealed.

4.4 Screening failed

Screening failure refers to the situation where the subjects do not meet the inclusion criteria or fall under the exclusion criteria after multidisciplinary evaluation after enrollment and recruitment. This study will inform the subjects who failed the screening based on the results of multidisciplinary consultation and give the best treatment recommendations at present.

4.5 Recruitment and Retention Strategies

The main offline location is the Department of Oral and Maxillofacial Surgery of Sun Yat-sen Memorial Hospital, including but not limited to posters, leaflets, seminars, etc. to attract more subjects, and each interested patient will register on-site, leave contact information and continue to carry out one-on-one explanation of the plan. If the subject is financially difficult, the investigator team will assist the subject in applying for a public welfare fund to reduce the financial burden of the subject.

5. Research design

5.1 General design

This study aims to explore the efficacy of PD-L1 inhibitors combined with carboplatin and nab-binding shirt alcohol in different cycles of treatment in resectable locally advanced oral squamous cell carcinoma, and to compare the differences between short-course therapy (two cycles) and long-course therapy (three cycles). This study is a single-center, randomized phase II exploratory study. Block randomization was used to generate random sequences through a central random system. The specific operation is to allocate the subjects who meet the inclusion criteria to the short-course treatment group or the long-course treatment group in a ratio of 1:1, and the randomization form is generated by an independent statistician by a third-party randomizer independent of the research team through the Interactive Web Response System (IWRS), and the subjects who meet the randomization criteria are randomized through the randomization system, and the subjects are given a unique randomization number, which is recorded in the case report form (CRF). The block length is dynamic block size to ensure that the researcher cannot predict the grouping outcome. At the same time, this study uses blinded endpoint evaluation, and during the evaluation of outcome indicators (such as imaging results, pathological results, etc.), the evaluators (such as radiologists, pathologists) do not know the grouping of the subjects. During the study, patients should be followed up regularly, and the tumor regression rate, tumor residual rate and psychological changes of patients in the short-course group and the long-course

group should be comparatively analyzed and recorded, so as to provide preliminary research data for subsequent neoadjuvant therapy studies with different drug cycles.

5.2 Research and design process

5.2.1 Study the specific implementation process

This study starts with the recruitment of subjects, undergoes pathological biopsy to confirm the diagnosis, and is enrolled after initial screening according to the inclusion and exclusion criteria, and after signing the informed consent formThis study employs block randomization to generate random sequences through a central random system. The specific operation is to allocate the subjects who meet the inclusion criteria to the short-course treatment group or the long-course treatment group in a 1:1 ratio, and the randomization form is generated by an independent statistician and a third-party randomizer independent of the research team through the interactive web response system (IWRS), and the subjects who meet the randomization criteria are randomized through the randomization system, and the subjects are given a unique randomization number, which is recorded in the case report form (CRF). The block length is dynamic block size to ensure that the researcher cannot predict the grouping outcome. At the same time, this study uses blinded endpoint evaluation, and during the evaluation of outcome indicators (such as imaging results, pathological results, etc.), the evaluators (such as radiologists, pathologists) do not know the grouping of the subjects.

Short-course group (two cycles): Albumin-bound paclitaxel 260 mg/m2, carboplatin AUC=5, and adebelimab 1200 mg intravenously on the first day of each three-week course of treatment every three weeks. A total of two cycles were performed, and surgery was performed 21 days after the end of the second cycle, and radiotherapy and chemotherapy were performed according to the pathological stage after surgery. Patients who did not require radiotherapy were maintained with a PD-L1 inhibitor (adebelimab) as a single agent, and patients who required chemoradiotherapy were maintained as a single agent at the same time, and the duration of medication for all patients was one year (from the time of the first dose at the initial diagnosis to the time of the last dose after surgery).

Long-course group (3 cycles): Intravenous albumin-bound paclitaxel 260 mg/m2, carboplatin AUC=5, and adebelimab 1200 mg on the first day of each 3-week course every three weeks. A total of three cycles were performed, and surgery was performed 21 days after the end of the third cycle, and radiotherapy and chemotherapy were performed according to the pathological stage after surgery. Patients who did not require radiotherapy were maintained with a PD-L1 inhibitor (adebelimab) as a single agent, and patients who required chemoradiotherapy were maintained as a single agent at the same time, and the duration of medication for all patients was one year (from the time of the first dose at the initial diagnosis to the time of the last dose after surgery).

All enrolled patients were given conventional medication to prevent vomiting in each cycle, while dexamethasone was given intravenous injection before each dose for allergy prevention.

5.2 Research schedule

project	sift	Medication			surgery	Follow				
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Follow-up time	Before enrollment 1 day	After enrollment 1 day	After V2 3 weeks	After V3 3 weeks	3 weeks after V4 or 3 weeks after V3	Postoperatively 1 month	Postoperatively 3 months	Postoperatively 6 months	Postoperatively 1 year	Postoperatively 2 years
sign Informed consent	√									
Enter the queue screening	√									
population Statistical data	√									
medical history	√		√	√	√	√	√	√	√	√
ECOG score	√	√	√	√	√	√	√	√	√	√
physical	√	√	√	√	√	√	√	√	√	√

examination										
Vital signs	√	√	√	√	√	√	√	√	√	√
electrocardiogram	√		√	√	√					
Blood routine	√		√	√	√	√	√			
Blood biochemistry	√		√	√	√	√	√			
Liver function	√		√	√	√	√	√			
Coagulation function	√		√	√	√	√	√			
Pathological examination PD-L1 assay	√				√					
HPV test	√									
Echocardiography	√									
Infectious disease examination Hepatitis B, hepatitis C, HIV, syphilis	√									
Imaging tests	√				√			√	√	√
complication and adverse event assessment		√	√	√	√	√	√	√	√	√

5.3 Ways to reduce bias

Block randomization was used to generate random sequences through a central random system. The specific operation is to allocate the subjects who meet the inclusion criteria to the short-course treatment group or the long-course treatment group in a 1:1 ratio, and the randomization form is generated by an independent statistician and a third-party randomizer independent of the research team through the interactive web response system (IWRS), and the subjects who meet the randomization criteria are randomized

through the randomization system, and the subjects are given a unique randomization number, which is recorded in the case report form (CRF). The block length is dynamic block size to ensure that the researcher cannot predict the grouping outcome. At the same time, this study uses blinded endpoint evaluation, and during the evaluation of outcome indicators (such as imaging results, pathological results, etc.), the evaluators (such as radiologists, pathologists) do not know the grouping of the subjects. Standardized operations to ensure that researchers perform the study according to unified standards, and that the treatment and medication processes of all patients are consistent. Ensure sufficient sample size to reduce random error. Regularly review data collection and processing processes to ensure study integrity and subject safety, ensuring data accuracy. Blinded endpoint assessment, during the evaluation of outcome indicators (such as imaging results, pathological results, etc.), the evaluator (such as radiologists, pathologists) is unaware of the grouping of subjects.

5.4 Definition of end of study

End of this study is defined as the last subject to complete the last follow-up or lost to follow-up or die.

5.5 Statistical analysis

5.5.1 Sample size and calculation basis

The primary endpoint of this study is the pathological complete response rate of the short-course group and the long-course group, and the signed informed subjects are randomly arranged to enter the short-course group or the long-course group. This study is defined as a pre-experimental study, considering the disgrouping rate of about 15%, a total of 70 people are planned to be included in the short-course group (two cycles) and the long-course group (three cycles), and the randomization is 1:1, that is, 35 people will be included in the short-course group and the long-course group.

5.5.2 Data analysis set

Statistical analysis will be calculated using SAS statistical software (V.9.4, SAS Institute) statistical analysis software, and the main indicators will be two-sided test, and the control type 1 error α is 0.05. If confidence intervals need to be calculated, if

otherwise specified, calculate 95% confidence intervals on both sides.

(1) Full analysis set (FAS): composed of all subjects who received at least one drug/treatment and received efficacy evaluation. This dataset was derived from all subjects after minimal and reasonable method of rejecting subjects.

(2) safety analysis set (SS): a group of people who have used at least one drug/received one treatment and have at least one safety evaluation data. In the safety analysis, all patients will be analyzed by the actual drug group received.

(3) Per-protocal set (PPS): All subjects who met the trial protocol and did not use concomitant drugs that affected the efficacy evaluation, had good medication compliance (between 80% and 120%), excluded major protocol violations, and were judged to have a significant impact on the results. All protocol deviations from the trial protocol that result in the exclusion of subjects from the conforming protocol set will be described in detail in the Statistical Analysis Plan (SAP) and completed prior to data lock-in.

5.5.3 Statistical analysis plan

Demographic and other baseline characteristics: Based on the FAS set, the demographic data, medical history, vital signs, and other baseline data are statistically described, in which the mean, standard deviation, minimum, maximum, and median are given for the measurement data (age, BMI, weight, blood pressure, etc.); Aggregate data (gender, tobacco and alcohol history, etc.) give the frequency and corresponding percentages.

Efficacy index analysis: The main index was a two-sided test, and the control α of error was 0.05. The primary endpoint (PCR rate) was estimated at points, and the Clopper-Pearson exact probability method was used to estimate the two-sided 95% confidence interval. The secondary efficacy indicators were analyzed using FAS and PPS analysis sets. For survival measures, median survival time and its two-sided 95% confidence intervals were calculated. For the rates of each indicator, point estimation was performed and Clopper-Pearson exact probability method was used to estimate the two-sided 95% confidence interval. For the continuity index, if it meets the normal distribution, its mean and two-sided 95% confidence interval are calculated based on

the normal distribution method, otherwise the median and two-sided 95% confidence interval are calculated based on the percentile method.

Safety index analysis: The SS set was used to statistically describe the safety indicators such as the incidence of adverse events/serious adverse events and the incidence of adverse reactions, and the details of each adverse event for each subject were described in a list, including the type and severity of adverse events. Compare and evaluate the changes before and after treatment of laboratory indicators, vital signs, electrocardiogram and other safety-related indicators, and give a statistical description of the clinical evaluation (normal, abnormal no clinical significance, abnormal clinically significant, unchecked) before and after treatment.

Principles for the processing of missing/deleted/lost data are filled in by LOCF (last observation carried forward) for the analysis of the main indicators, that is, the data of the main indicators that cannot be observed are filled with the last observation data; Secondary and security metrics are not filled.

6. Research intervention

6.1 Study intervention content

This study starts with the recruitment of subjects, undergoes pathological biopsy to confirm the diagnosis, and is enrolled after initial screening according to the inclusion and exclusion criteria, and after signing the informed consent form。 In this study, block randomization was adopted, and subjects who met the inclusion criteria were assigned to the short-course treatment group or the long-course treatment group in a 1:1 ratio by computer-generated random sequences, and the random sequences were generated by independent statisticians using statistical software (such as SAS or R), and the block length was set to dynamic blocks to ensure balance between groups. Random sequence concealment is sealed and opaque envelopes to ensure that researchers cannot predict the grouping results. After the subjects sign the informed consent form and complete the screening assessments, the randomization envelope will be opened by the study center personnel. Automatically assign subjects to the short-course or long-course

treatment group based on the results in the envelope, and the assignment results cannot be changed. The randomization number is tied to the subject's unique ID and recorded in the case report form (CRF). At the same time, this study uses blinded endpoint evaluation, and during the evaluation of outcome indicators (such as imaging results, pathological results, etc.), the evaluators (such as radiologists, pathologists) do not know the grouping of the subjects. The following are specific intervention methods:

Short-course group (two cycles): Albumin-bound paclitaxel 260 mg/m2, carboplatin AUC=5, and adebelimab 1200 mg intravenously on the first day of each three-week course of treatment every three weeks. A total of two cycles were performed, and surgery was performed 21 days after the end of the second cycle, and radiotherapy and chemotherapy were performed according to the pathological stage after surgery. Patients who did not require radiotherapy were maintained with a PD-L1 inhibitor (adebelimab) as a single agent, and patients who required chemoradiotherapy were maintained as a single agent at the same time, and the duration of medication for all patients was one year (from the time of the first dose at the initial diagnosis to the time of the last dose after surgery).

Long-course group (3 cycles): Intravenous albumin-bound paclitaxel 260 mg/m2, carboplatin AUC=5, and adebelimab 1200 mg on the first day of each 3-week course every three weeks. A total of three cycles were performed, and surgery was performed 21 days after the end of the third cycle, and radiotherapy and chemotherapy were performed according to the pathological stage after surgery. Patients who did not require radiotherapy were maintained with a PD-L1 inhibitor (adebelimab) as a single agent, and patients who required chemoradiotherapy were maintained as a single agent at the same time, and the duration of medication for all patients was one year (from the time of the first dose at the initial diagnosis to the time of the last dose after surgery).

All enrolled patients were given conventional medication to prevent vomiting in each cycle, while dexamethasone was given intravenous injection before each dose for allergy prevention.

6.2 Preparation/Handling/Storage/Duties

Medication use must be documented in the patient's medical record and in the appropriate location of the CRF. After enrollment and at the 1st and 2nd month follow-up, the executive nurse will receive the corresponding numbered drugs from the drug administrator, and the remaining drugs and packaging boxes will be returned to the drug administrator. If the drug is found to be damaged at the time of collection or during the preparation process, this box of drugs cannot be used, the damaged drugs will be treated as empty bottles, and other undamaged drugs will be returned to the drug administrator together with the packaging box. The research center should have a dedicated person responsible for the management of the trial drug, including receiving, distributing, counting and recycling. The investigator should ensure that the test drug is stored in a safe, independent and locked place in the study center, and the storage conditions should meet the preservation requirements of the trial drug. No one can be contacted without the consent of the investigator. Empty boxes should be stored and managed in the same way as the test drug.

6.3 Study intervention adherence

After each dose, the subject should be asked to return to the research center for review periodically, and the compliance of the study can be verified according to the subject's review situation. In the follow-up visit, the research team members must communicate with the subject by telephone and reasonably arrange the subject's follow-up visit.

6.4 Concomitant treatment

If the subject has hypertension, diabetes, coronary heart disease and other diseases that require long-term drug control, the investigator and relevant specialists should evaluate the impact of the disease and the relevant research protocol and determine the dosage and duration of adjuvant drugs.

6.4.1 Rescue

The life-threatening dangers of subjects during the implementation of the clinical research plan should be implemented in accordance with the clinical rescue plan, such as cardiopulmonary resuscitation, emergency airway management, emergency surgical treatment, relevant records during hospitalization should be recorded in the medical

record system, and the occurrence after discharge should be recorded in the adverse event record form.

7. Study intervention discontinuation/subject suspension and withdrawal

7.1 Discontinuation of study intervention

If the level 3 adverse events of CTCAE version 5.0 standard reach 30% of the number of subjects in this study, the study should be suspended, and the drug safety of the study protocol should be discussed, and the dose of the drug in the study protocol should be adjusted (the chemotherapy dose was adjusted to 50% of the recommended dose, and adebelimab was suspended), and follow-up should continue during the suspension of the study to maintain the follow-up records of the original subjects.

7.2 Subject discontinuation/withdrawal from the study

When the subject is dissatisfied with the treatment effect of the study protocol or his own finances, he or she should actively communicate with the subject, encourage the subject to actively treat and help him apply for public welfare funds to complete the treatment.

7.3 Loss to follow-up

The investigator should retain the contact information of multiple subjects and the contact information of the subject's family after the subject is enrolled, and the investigator should actively contact the subject by phone after the subject is discharged from the hospital, keep abreast of the condition and arrange the subject to be admitted to the hospital in advance for the next stage of treatment.

8. Adverse events and unexpected events

Adverse events (AEs) are untoward medical events that occur after a subject receives treatment, but are not necessarily causally related to treatment. An adverse event can be any unfavorable and unintended sign (including abnormal laboratory findings), symptoms, or disease associated with the use of treatment measures in time, regardless of whether they are related to treatment measures. This includes, but is not

limited to: (1) exacerbation of pre-existing disease prior to the use of study treatment measures; (2) Increased frequency or exacerbation of episodic events that already existed before the use of study treatment measures; (3) Abnormal changes detected or diagnosed after the use of study treatment measures, although such abnormal changes may have existed before treatment; (4) Exacerbation of disease or symptoms that already persisted before the start of the study.

In the trial, the investigator should conduct a comprehensive analysis according to the specific circumstances of the adverse events and the subject's past history, concomitant diseases and concomitant medications, etc., to judge the relationship between adverse events and treatment measures. The relationship between adverse events and treatment measures is divided into "definitely related, likely related, possibly related, possibly irrelevant, and unrelated" :(1) unrelated: adverse events are not related to treatment measures; (2) May be irrelevant: the occurrence of adverse events is more likely to be related to other factors, such as medication or concomitant diseases, or the time of occurrence of the event indicates that it is unlikely to have a causal relationship with treatment measures; (3) May be related: The occurrence of adverse events may be caused by treatment measures. It cannot be ruled out whether it may be caused by other factors, such as medication or concomitant diseases. The occurrence of adverse events and treatment measures had a reasonable chronological sequence, and the causal relationship between events and treatment measures could not be ruled out. (4) It is likely to be related: the occurrence of adverse events may be caused by treatment measures. There is a reasonable chronological sequence of events and treatment measures; (5) Affirmation: The type of adverse event has been confirmed to be caused by treatment measures and cannot be explained by other reasons, such as medication and concomitant diseases. The timing of the event strongly suggests causation.

The criteria for determining the severity of adverse events can be based on the common adverse event evaluation criteria CTCAE version 5.0 (U.S. Department of Health and Human Services). If you are outside the above list of criteria, you can refer to the following criteria: (1) Mild: symptomatic or signful but tolerable; (2) moderate;

Discomfort is enough to interfere with normal life; (3) Severe: Unable to carry out normal activities. All information about adverse events, whether mentioned by the patient, discovered by the investigator, or discovered through physical examination, laboratory tests, etc., should be recorded in the study medical record and case report form. During the trial, the time, duration, signs and severity of adverse events, measures taken, outcomes, and relationship to treatment measures should be carefully observed and recorded, and appropriate follow-up should be performed.

Possible adverse events include: (1) Chemotherapy complications: common complications caused by albumin shirt alcohol are: neutropenia; bradycardia of the cardiovascular system; skin reactions; Complications after carboplatin treatment include: bone marrow suppression; Anaphylaxis; peripheral neurotoxicity; nausea and vomiting; Treatment: If there are adverse reactions to chemotherapy above grade 3, the chemotherapy dose will be halved in subsequent treatment; If the follow-up chemotherapy drug injection cannot be tolerated after being evaluated by the investigator, the tumor will be removed after surgical evaluation after complication treatment; (2) Tumor hyperprogression: If the subject finds tumor hyperprogression during clinical examination during the 3 courses of treatment, the imaging examination will confirm whether there is tumor hyperprogression, and the tumor will be removed after preoperative evaluation and continued treatment in the oncology department. (3) Surgical complications: anesthesia accidents occurring in the perioperative period; cardiovascular and cerebrovascular accidents; Intraoperative important neurovascular injury; The flap survived after surgery; Postoperative reoperation is possible; Treatment: Clinical treatment will be carried out according to the complications of normal surgery, and at the same time, detailed records will be recorded in the subject's medical record to evaluate whether the surgical complication is related to the preoperative clinical trial; (4) Immune complications (adebelimab): immune pneumonia; immune hepatitis; Diarrhoea; Nephritis; hypothyroidism; skin reactions; adrenalinetis; thrombocytopenia; Treatment: If there is a grade 2 adverse reaction, the administration will be suspended until it recovers to grade 0-1, and if there is a grade 3 adverse reaction, the drug will be

permanently stopped.

The investigator should use medical terms/concepts to document AEs or SAEs. Its type, degree, time of appearance, duration, treatment measures, and treatment are recorded in detail. On the basis of comprehensive consideration of comorbidities and concomitant medications, its correlation with the study treatment measures was evaluated. All AEs (including SAEs) should be documented on the CRF's adverse event table. Any patient must be evaluated for toxicity as long as treatment is administered. The occurrence of any adverse events (AEs) should be graded according to the NCI Common AE Grading Criteria (NCI-CTCAE version 5.0).

9. Data collection and management

9.1 Case Report Forms/Electronic Data Records

Before the start of the study, a Redcap electronic database or EDC database was established based on the contents of the paper case report form.

9.2 Data management

The original data should be uniformly recorded in the research medical record, and according to the content of the research medical record, the investigator himself or the designated or authorized trained personnel can complete the completion of the case report form and the data entry in the electronic database to ensure the completeness and accuracy of the information. In order to ensure the accuracy of the data, the researcher conducts self-inspection no less than twice a year, regularly assigns personnel to the sub-center for project quality control, and accepts inspections by hospital and school management departments. If it is found that the data registered in the case report form/electronic database is inconsistent with the original record (study medical record), the investigator should organize timely verification of the data, modify the errors in accordance with the requirements of GCP regulations, and explain accordingly if necessary.

10. Ethical requirements

This study complies with the Good Practice for Drug Clinical Trials and the Measures for the Administration of Investigator-initiated Clinical Research in Healthcare Institutions (Trial) and the Declaration of Helsinki. This study can only be carried out after the protocol is approved by the Ethics Committee of our hospital before the trial begins. During the research process, if the protocol must be revised, the revised protocol must be resubmitted to the ethics committee for review, and the researcher must wait until the ethics committee agrees before implementing the new plan.

Each enrolled patient must sign an informed consent form. A copy of the informed consent form and contact information of the investigator and ethics committee must be provided to the subject. This study will collect clinical data and personal information of research subjects for scientific research, which will involve the privacy rights of patients. The participants and data analysts of this study have signed confidentiality agreements and will not disclose patients' personal information and disease-related information to any individuals and institutions unrelated to this study. The collected patient data is managed in a unified manner to prevent personal privacy leakage.

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Informed consent

Project Name: A single-center, randomized, phase II exploratory study of adebelimab combined with carboplatin and nab-binding squamous alcohol in the treatment of resectable locally advanced oral squamous cell carcinoma

Research unit: Sun Yat-sen Memorial Hospital, Sun Yat-sen University

Version number: V3.0

Version date: 2025-07-21

Dear Study Participants,

We invite you to participate in a study titled "A Single-center, Randomized, Phase II Exploratory Study of Adebelimab in Combination With Carboplatin, Nab-Binding Purple Platinol in the Treatment of Resectable Locally Advanced Oral Squamous Cell Carcinoma".

This informed consent form will detail the relevant information, purpose, research process, any potential benefits and risks, and your rights before you make a decision to participate in this study, please read the following information carefully, and if you have any questions, please ask the study doctor or researcher if you have any questions. You can discuss it with your family as well as friends and have plenty of time to think about it. If you are enrolled in another study, let your study doctor or researcher know.

If you have learned more about this study and decide to participate, you will need to sign this informed consent form and we will provide you with a copy of the signed informed consent form.

1、Background

According to the latest data from the International Agency for Research on Cancer, the global incidence of head and neck cancer in 2022 ranks among the top ten new cancer incidences in the world. Among them, the treatment guidelines for locally advanced head and neck squamous cell carcinoma (HNSCC) are risk-adapted adjuvant radiotherapy with or without platinum-based chemotherapy, or definitive concurrent chemoradiotherapy after surgical resection. However, despite aggressive combination therapy, patients with locally advanced HNSCC remain at high risk of recurrence, distant metastasis, and death. With the proposal of the treatment concept of preoperative induction

chemotherapy, clinical studies have shown that patients who achieve tumor remission after preoperative induction chemotherapy have a higher survival rate and lower risk of distant metastasis, but the complete response rate of tumor pathology after surgery is low, and satisfactory results have not been achieved.

Tumor immunotherapy provides the possibility to solve the above dilemma. At present, immune checkpoint inhibitors (ICIs) are widely used in oral squamous cell carcinoma (OSCC). A clinical study (KEYNOTE-048) showed that pembrolizumab (PD-1) combined with chemotherapy significantly improved the survival of patients with recurrent or metastatic oral squamous cell carcinoma, and has now become the first-line treatment option according to NCCN guidelines. Meanwhile, in a retrospective study, Neoadjuvant chemoimmunotherapy (NACL) showed safe and encouraging efficacy in patients with locally advanced resectable OSCC. Among the 104 patients who received NACI, the pathological complete response (PCR) rate was 47.1%, the major pathological response (MPR) rate was 65.4%, and the expected 3-year disease-free survival (DFS) rate and overall survival (Overall survival, OS) rates of 89.0% and 91.3%, suggesting that NACI can effectively improve the postoperative pathological remission rate and improve the prognosis of patients.

PD-L1 and PD-L2 are two ligands of PD-1. PD-L1 can be expressed by both tumor and immune cells, and PD-L1 is a useful biomarker for predicting the response to PD-1/PD-L1 antibodies in patients with different types of cancer. PD-L1 plays a role in inhibiting the cancer-immune cycle by binding to negative regulators such as PD-1 and B7.1 activated by T cells. PD-L1 inhibitors are currently less used in tumor treatment in clinical practice, mainly in small cell lung cancer. In terms of head and neck squamous cell carcinoma, there are also phase I clinical studies that have confirmed the therapeutic safety and tumor activity of PD-L1 inhibitors. In one meta-analysis, PD-1 inhibitors had a higher overall average incidence of grade 3 or higher adverse events than PD-L1 inhibitors (OR, 1.58; 95% CI, 1.00-2.54), possibly because PD-L1 inhibitors bind PD-L1 on the surface of tumor cells and antigen-presenting cells, but retain the normal function of PD-L2, thereby reducing the risk of potential autoimmune reactions and adverse events. Therefore, PD-L1 inhibitors may have more therapeutic potential than PD-1 inhibitors.

Previous studies have shown that PD-L1 inhibitor (adebelimab) combined with chemotherapy has shown satisfactory efficacy, confirming that PD-L1 inhibitor (adebelimab) can effectively increase the

PCR rate. However, due to the accumulation of toxic effects of drugs, patients' tolerance to adverse reactions decreases, increasing the risk of serious adverse events and increasing the psychological stress of patients. On this basis, this study aims to explore the efficacy of adebelimab (PD-L1 inhibitor) combined with chemotherapy in locally advanced oral squamous cell carcinoma with different drug cycles, and further verify the efficacy and safety of PD-L1 inhibitor combined with chemotherapy in the treatment of locally advanced oral squamous cell carcinoma.

2. Research purpose

1. Main objective: The main purpose of this study is to explore the efficacy of adebelimab combined with chemotherapy in patients with locally advanced resectable oral squamous cell carcinoma.

2. Secondary objective: The secondary objective of this study is to explore the prognostic impact of adebelimab combined with chemotherapy on patients with locally advanced resectable oral squamous cell carcinoma.

3. Exploratory objective: The exploratory objective of this study is to explore the effectiveness of adebelimab combined with chemotherapy in the treatment of locally advanced resectable oral squamous cell carcinoma with different drug cycles. To explore the correlation between biomarkers and the efficacy of combination regimens.

3. Introduction to clinical research projects

1. Research object

A total of 70 participants will be included in this study. The selection exclusion criteria are as follows:

(1) Aged between 18 and 75 years;

(2) Patients with stage III-IVB tumors with non-oropharyngeal cancer who have pathologically confirmed head and neck squamous cell carcinoma (oral cavity, including buccal, tongue, gingival, floor of mouth, palate, and maxillary sinuses) according to the 8th edition guidelines of the American Joint Committee on Cancer (AJCC);

(3) Evaluating resectable tumors by head and neck surgeons before enrollment to rule out clinical evidence of distant metastasis;

(4) At least one measurable tumor lesion according to RECIST 1.1, the efficacy evaluation criteria for

solid tumors;

(5) The performance status of the Eastern Cooperative Oncology Group (ECOG) was 0-1;

(6) Blood routine: white blood cell count (WBC) ≥3.0×109/L; Absolute neutrophil count (ANC) ≥ 1.5×109/L; Platelets (PLT) ≥ 100×109/L; Hemoglobin level (HGB) ≥ 9.0 g/dL (no corresponding supportive care such as transfusion and leukocyte increase within 7 days);

(7) Liver function: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 times the upper limit of reference value (ULN) in patients without liver metastasis; albumin (ALB) ≥ 30 g/L;

(8) Renal function: serum creatinine ≤1.5 times ULN or creatinine clearance (CrCl) ≥ 50mL/min (using Cocroft/Galt formula); Urine protein (UPRO) < (++), or 24-hour urine protein < 1.0 g;

(9) HPV status of oropharyngeal cancer was determined using p16 IHC. If > 70% of tumor cells exhibit strong diffuse nuclei and cytoplasmic staining, the sample is considered p16 positive;

(10) Have not participated in other clinical trial projects within the past 30 days;

(11) Patients who voluntarily participate in this project and sign the informed consent form.

Exclusion Criteria:

(1) The patient has abnormal blood indicators and abnormal liver and kidney function, and cannot tolerate the course of this clinical study after multidisciplinary consultation and evaluation;

(2) The patient has previously suffered from tumors in other parts of the country, or has undergone anti-tumor treatment such as surgery, chemotherapy, and radiotherapy in the past;

(3) Unable to complete the entire clinical study due to personal, social and economic reasons;

(4) Previous serious systemic diseases that cannot be cured or controlled by drugs.

2. Study design

This study aims to explore the efficacy of PD-L1 inhibitors combined with carboplatin and nab-binding shirt alcohol in different cycles of treatment in resectable locally advanced oral squamous cell carcinoma, and to compare the differences between short-course therapy (two cycles) and long-course therapy (three cycles). This study is a single-center, randomized phase II clinical study. The study was a randomized, open-label trial in which patients were randomized to receive either short-course therapy (two cycles) or long-course therapy (three cycles) in a randomized ratio of 1:1. After enrollment, the subjects were randomly assigned to the short-course group or the long-course group, and received periodic treatment according to the standard protocol of the trial. During the study, patients should be

followed up regularly, and the tumor regression rate, tumor residual rate and psychological changes of patients in the short-course group and the long-course group should be comparatively analyzed and recorded, so as to provide preliminary research data for subsequent neoadjuvant therapy studies with different drug cycles.

3. Research time limit: August 2025 to December 2027

4. Clinical research process

(1) Signed informed consent.

(2) Conduct enrollment screening, pathological biopsy and imaging examination of clinical studies to confirm the baseline evaluation before enrollment.

(3) Study group and treatment: After initial screening according to the inclusion and exclusion criteria, enrollment after signing the informed consent form. This study is a single-center, randomized phase II exploratory study. Block randomization was used to generate random sequences through a central random system. The specific operation is to allocate the subjects who meet the inclusion criteria to the short-course treatment group or the long-course treatment group in a ratio of 1:1, and the randomization form is generated by an independent statistician by a third-party randomizer independent of the research team through the Interactive Web Response System (IWRS), and the subjects who meet the randomization criteria are randomized through the randomization system, and the subjects are given a unique randomization number, which is recorded in the case report form (CRF). The block length is dynamic block size to ensure that the researcher cannot predict the grouping outcome. At the same time, this study uses blinded endpoint evaluation, and during the evaluation of outcome indicators (such as imaging results, pathological results, etc.), the evaluators (such as radiologists, pathologists) do not know the grouping of the subjects. Short-course group (two cycles): Albumin-bound paclitaxel 260 mg/m2, carboplatin AUC=5, and adebelimab 1200 mg intravenously on the first day of each three-week course of treatment every three weeks. A total of two cycles were performed, and surgery was performed 21 days after the end of the second cycle, and radiotherapy and chemotherapy were performed according to the pathological stage after surgery. Patients who did not require radiotherapy were maintained with a PD-L1 inhibitor (adebelimab) as a single agent, and patients

who required chemoradiotherapy were maintained as a single agent at the same time, and the duration of medication for all patients was one year (from the time of the first dose at the initial diagnosis to the time of the last dose after surgery). Long-course group (3 cycles): Intravenous albumin-bound paclitaxel 260 mg/m2, carboplatin AUC=5, and adebelimab 1200 mg on the first day of each 3-week course every three weeks. A total of three cycles were performed, and surgery was performed 21 days after the end of the third cycle, and radiotherapy and chemotherapy were performed according to the pathological stage after surgery. Patients who did not require radiotherapy were maintained with a PD-L1 inhibitor (adebelimab) as a single agent, and patients who required chemoradiotherapy were maintained as a single agent at the same time, and the duration of medication for all patients was one year (from the time of the first dose at the initial diagnosis to the time of the last dose after surgery). All enrolled patients were given conventional medication to prevent vomiting in each cycle, while dexamethasone was given intravenous injection before each dose for allergy prevention.

(4) Visit and follow-up: During the study, you also have some corresponding responsibilities, please follow up in our hospital or telephone follow-up after each cycle of treatment, perform blood routine, liver and kidney function tests in our hospital or local hospital, and inform the researcher of the specific report. Return to our hospital for follow-up consultation 1 month after surgery and 3 months after surgery according to the doctor's instructions for clinical physical examination. 6 months after surgery and 1 year after surgery, they need to return to our hospital for MRI examination, and then return to our hospital for MRI examination at least once a year.

(5) Collection and testing of remaining samples: In this study, your doctor will collect your remaining blood during routine diagnosis and treatment, as well as some tumor tissue samples from preoperative biopsy and postoperative pathology for laboratory or genetic testing after obtaining your consent, and the use of these specimens will not affect your disease diagnosis and treatment. The results of these tests may help you better understand your disease.

(6) Other matters that require your cooperation: During the study, you are responsible for reporting to your doctor any changes in your physical and mental aspects during the study, regardless of whether such changes are related to the study. Be sure to let your doctor know about any other medications you are currently using and are being used during the study. During the study, please

do not use any other treatment-related chemotherapy or immunological drugs, and if you need other treatment, please contact your doctor in advance for formal medical guidance.

5. Alternative treatment

Participation in this study is completely voluntary, and if you do not participate or opt out at any stage of the study, you will receive alternative treatment. Alternative treatments include: surgery, chemotherapy, radiation therapy. You and your doctor can discuss specific alternative treatments before deciding whether to take part in this study.

6. Expenses related to this study

The drugs nab-azanol and carboplatin used in this study are the therapeutic drugs recommended by clinical guidelines, and imaging, tests and other examinations are routine examination items, so you need to bear the cost yourself. Participation in this study will not add an additional financial burden to you. The adebelimab used in this study has applied for the corresponding donation subsidy through the manufacturer, and the subjects in the short-course group (two cycles) pay one cycle of drug before surgery, and then use the drug for free in the second cycle; After paying for one free drug after surgery, you will receive 2 free medications, and after paying another time, you will receive free medication for 1 year (within 1 year from the first dose). Subjects in the long-course group (three cycles) paid for one cycle of medication before surgery, and then the second cycle was free of charge. After paying the drug in the third cycle, you can receive 2 doses of immune maintenance drugs after surgery, and you can get free medication for 1 year after another payment (within 1 year from the first dose).

7. Possible benefits

Participating in this clinical study, your disease may be remitted, but it may not achieve the expected effect, or even disease progression; The treatment and examinations you receive may not directly benefit you, but your participation will contribute to further medical research and understanding of such diseases, and hopefully improve the diagnosis and treatment of diseases in the future.

8. Possible risks

Diagnosis and treatment of any disease can bring discomfort and unpredictable risks.

1. The study protocol causes the subject to have tumor progression and the risk of delaying surgery.

2. This study protocol has the potential to cause reversible or irreversible damage to liver and kidney function.

3. This regimen may lead to complications after immunotherapy such as immune myocarditis, immune pneumonia, and immune neuritis.

4. This study protocol may lead to post-chemotherapy reactions such as bone marrow suppression, gastrointestinal reactions, skin rashes, etc.

5. The possibility that the study protocol will lead to an increased chance of surgical complications.

6. Pregnancy risk: Since the effects of the study drug on the fetus and breastfed infants are not known, it is important that you cannot be pregnant or breastfeeding at the time of entry into the study, and you must not become pregnant during the study. You must not participate in this study if you are pregnant, trying to become pregnant, or breastfeeding. If you are a female subject of childbearing potential, the study doctor will ask you to provide a urine sample to take a pregnancy test before you start the study. If you are a female subject, of childbearing potential, must use a reliable method of contraception for the duration of the study. The study doctor will tell you which are acceptable methods of birth control. The following methods of contraception are recommended: condoms with or without spermicide (a drug that kills sperm), vaginal diaphragm or cervical cap with spermicide, or intrauterine device (a small contraceptive device installed in a woman's uterus). Emergency contraception taken after unprotected sex, such as emergency contraception, cannot be used as a conventional method of contraception. If you find a positive pregnancy test while participating in the study, you should inform the study doctor immediately. You will need to stop taking the study drug immediately and will need to agree to undergo further follow-up tests. If you are confirmed to be pregnant, the study doctor may ask you to withdraw from the study and terminate the pregnancy, and you will be responsible for the costs associated with terminating the pregnancy; If you choose to continue your pregnancy, it may result in adverse pregnancy outcomes, and you will be responsible for the consequences and costs arising therefrom. If you are a male subject: Participation in this study may damage your sperm and harm your child during the study.

This damage is currently unpredictable. If sexually active, you must agree to use medically approved contraception during the course of the study. Medically accepted contraception includes surgical contraception (e.g., vasectomy) or spermicidal condoms. Emergency contraception taken after unprotected sex, such as emergency contraception, cannot be used as a conventional method of contraception. Please inform your partner of the risks of this drug to the unborn baby. She should know that if she is pregnant, you need to tell your study doctor immediately, and she should tell her doctor immediately and agree to further follow-up tests. If your partner is confirmed to be pregnant, the study doctor may request termination of pregnancy at the expense of you and your partner; If your partner chooses to continue the pregnancy, it may result in an adverse pregnancy outcome and the consequences and costs will be borne by you and your partner.

7. The most common adverse reactions of adebelimab are proteinuria, fatigue, elevated corticotropin, increased aspartate aminotransferase, elevated thyroid-stimulating hormone, elevated hemobilirubin, elevated alanine aminotransferase, anemia, decreased appetite, and rash, which are mostly grade 1 or 2 in severity. The most common grade 3 adverse reactions > lung inflammation, increased alanine aminotransferase, increased aspartate aminotransferase, increased conjugated bilirubin, abnormal liver function, anemia, and hypokalemia. In addition, the most common adverse reactions with adebelimab in combination with chemotherapy were leukopenia, neutropenia, anemia, elevated alanine aminotransferase, thrombocytopenia, increased aspartate aminotransferase, decreased appetite, nausea, elevated Y-glutamyltransferase, fatigue, and hypothyroidism. The most common grade 3 adverse reactions > neutropenia, leukopenia, thrombocytopenia, anemia, lymphopenia, elevated alanine aminotransferase, and hypertension. Other adverse reactions can be found in the drug label for details.

9. Over-explaining the risks of medication

1. Depending on your condition, the current routine use of clinical drugs is not ideal. After fully considering the adverse reactions, contraindications, precautions, etc., and in accordance with the principles of beneficial patient health and informed consent, we believe that off-label use of this drug is your current best diagnosis and treatment plan.
2. You have the right to ask the physician or pharmacist to explain the content contained in this

informed consent form in plain language, and you have the right to ask questions to the physician and pharmacist and get an objective and scientific answer after the physician or pharmacist explains.

3. The use of this drug off-label may cause the following adverse reactions, including but not limited to: gastrointestinal symptoms, hematological symptoms, liver function damage and other adverse reactions.

10. Study the treatment and compensation of related injuries

If an adverse event occurs that is indeed caused by the diagnostic tests and treatments required for the study drug and the study protocol, and causes harm to you, the doctor will provide you with active treatment. This study has purchased insurance, and if there is any research-related damage, the center will bear the relevant medical expenses and compensation costs in accordance with the law.

11. Confidentiality measures

The results of this clinical study are only used for scientific purposes, so your participation in the study and your personal information during the study will be confidential and will be protected in accordance with legal regulations, and your name and identity will not be disclosed, and your name will not appear in any research reports and public publications. Government management departments, hospital ethics committees, researchers, etc. have the right to access all your research materials, including clinical observation sheets, trial data, etc. according to regulations due to work needs.

12. Termination of research

You can withdraw from the study at any time without a reason while participating in the study, and your decision will not have any impact on your continued medical treatment. Your doctor may also stop you from continuing to participate in the study for the following reasons:

You did not take medication as instructed and requested by the study doctor;

Disease progression or intolerable adverse reactions, and the study doctor believes that continuing

to participate in the study will cause harm to you;

You have received treatment that is not allowed in this study;

・The research doctor, ethics committee, or government administration requested the study to be stopped.

When you withdraw from the study or the study is terminated, the study doctor will discuss follow-up treatment with you.

13. Rights

This clinical study has been reviewed and approved by the Medical Ethics Committee of Sun Yat-sen Memorial Hospital of Sun Yat-sen University, and the protocol design meets ethical requirements, which will ensure that your rights and interests are not infringed upon in this study.

Your participation in this clinical study is completely voluntary, and you may refuse to participate or withdraw at any time without discrimination or retaliation, and your medical treatment and rights will not be affected. If you withdraw from a clinical study, you should complete some appropriate medical tests at the time of withdrawal for safety reasons. If the doctor deems you unsuitable to continue participating during the study, the doctor has the right to decide to suspend your continued participation in this clinical study in order to protect your interests. In addition, you can stay informed about your research during your research. You will also be notified if we have some updates on this study so that you can decide whether to continue with the study.

During the clinical study, please notify your research doctor immediately if you experience any discomfort or worsening of your condition, and we will take appropriate medical measures in a timely manner. If you comply with study protocol regulations, the investigator will actively treat study-related adverse events that occur.

14. Detailed contact information

If you have any concerns or questions about your participation in this study, or if you experience any unusual reactions while participating in this study, or in the event of an emergency, you should contact:

Doctor: Huang Zhiquan Contact number: 13826142898

Doctor: He Yilin Contact number: 13680281880

If you have any complaints or concerns or questions about the way the study physician conducts the study, as a study subject, you can contact the Medical Ethics Committee of the Center:

Email: sysyxllwyh@163.com Contact number: 020-81332587

Informed consent form • consent signature page

Study participant statement

I have read the informed consent form carefully, the researchers have explained it to me in detail and answered my questions, and I am fully aware of the following:

（1） As a study participant, I will comply with the requirements for study participants, voluntarily participate in this study, and fully cooperate with the research staff to truthfully and objectively provide the researchers with their health status and related information before participating in this study.

（2） I agree to Sun Yat-sen Memorial Hospital's access to my medical information and research results for the purpose of scientific research. I understand that the results of this study will only be used for scientific research purposes, except for government administrations, ethics committees, researchers, etc., and my personal information participating in the research and research will be confidential and will be protected in accordance with the law.

（3） I volunteer to participate in this study and will be properly and aggressively treated if there are study-related adverse reactions in the study.

（4） My participation in this study is completely voluntary, and I can refuse to participate or withdraw from the study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

At the same time I declare:

（1） I am willing to comply with the research process;

（2） During the study, I am willing to cooperate with the doctor to see a doctor within the specified time and do corresponding examinations;

（3） This informed consent form has been received.

Study participant signature: Contact:

Signing Date:

If the study participant is a person with no or limited civil capacity (minors under 18 years of age, unconscious or for various reasons resulting from a thought disorder that prevents them from signing the informed consent form), their guardian is requested to sign here:

Signature of the guardian: Relationship with Study Participants: Contact:

Signing Date:

If the study participant/guardian is unable to read and cannot sign the informed consent form, please sign it here by an impartial witness :

Signature of an impartial witness: Contact:

Signing Date:

Statement by the researcher

I myself have fully explained and explained the purpose, research methods, operating procedures, and possible risks and potential benefits of this study to the study participants, and answered all relevant questions of the study participants satisfactorily.

Signature of the investigator (who informs the study participant): Contact:

Signing Date: