A prospective randomized single blind controlled study on maintenance therapy with Sintilimab after radiotherapy and chemotherapy for locally advanced head and neck tumors based on peripheral blood CD8TEX detection

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1. Introduction to research background:

Head and neck squamous cell carcinoma (HNSCC) includes cancers of the mouth, oropharynx, larynx and hypopharynx. The incidence rate ranks the sixth with a mortality rate of 40-50%. It is a serious disability and life-threatening disease. Due to the unique anatomical location, the surgical disability rate of HNSCC is high, which seriously affects the quality of life of patients. Radiation therapy is a very important local treatment for malignant tumors. Radiation therapy not only protects organ function and has cosmetic effects, but also has a long-term survival comparable to surgical treatment for early HNSCC patients receiving radiation therapy. However, over 60% of HNSCC patients are initially diagnosed as locally advanced. For patients with locally advanced stage who cannot undergo surgery, the current standard treatment regimen is synchronous radiotherapy and chemotherapy (CRT) or synchronous targeted treatment with cetuximab, followed by clinical follow-up. However, there are still relatively high rates of local recurrence or distant metastasis in patients with locally advanced head and neck tumors after radiotherapy and chemotherapy. The 3-year PFS rate is about 60%, 50% of relapses occur within 2 years after radiotherapy and chemotherapy, 20% to 30% of patients experience distant metastasis, and the overall 5-year survival rate is less than 50%. Therefore, it is necessary to further optimize the maintenance treatment plan after radiotherapy and chemotherapy, in order to improve the clinical cure rate of patients with locally advanced head and neck tumors.

Immunotherapy has achieved significant breakthroughs in recurrent and metastatic head and neck tumors. Studies on various tumor models have shown that tumor infiltration of PD-1+CD8+depleted T cells (CD8+TEX) is an important mechanism for the reduction of anti-tumor function and tumor progression in the body. Immunotherapy can reactivate T cell responses by blocking the PD-1 pathway. A

clinical study by Checkmate 141 showed that anti PD-1 monoclonal antibodies showed long-lasting efficacy in treating recurrent and metastatic HNSCC, with a nearly three fold increase in OS rate at 2 years (16.9% vs 6.0%). Therefore, in 2016, the first anti PD-1 antibody was approved by the FDA for recurrent or metastatic HNSCC that failed platinum chemotherapy. Radiation therapy can directly kill tumor cells while also reshaping the local immune microenvironment of the tumor, including the release of pro-inflammatory molecules and infiltration of immune cells. The subgroup analysis of KEYNOTE-001 and PEMBRO-RT studies found that patients who had previously undergone radiotherapy had better immunotherapy efficacy after recurrence and metastasis. However, studies on immunotherapy in locally advanced HNSCC have all failed, including the JAVELIN HEAD AND NECK 100 study comparing the efficacy of Avelumab combined with CRT treatment and Avelumab maintenance therapy with CRT standard treatment, and the GORTEC REACH study comparing the efficacy of Avelumab combined with cetuximab combined with radiotherapy and Avelumab maintenance therapy with standard treatment. Both studies used immunosynchronous therapy at the beginning of radiotherapy without adaptive screening, and the PFS of both studies showed a trend of numerical benefits but no statistical significance. Therefore, can better biomarkers be selected to screen suitable HNSCC patients for maintenance therapy after synchronous radiotherapy and chemotherapy?

At present, there are no research reports on the changes of CD8+TEX cells in the tumor immune microenvironment after radiotherapy. In our preliminary research, we found in the HNSCC mouse tumor model that the proportion and quantity of PD-1+CD8+TEX cells in the tumor and peripheral blood significantly increased with the prolongation of time after radiotherapy, and the combination of immunotherapy at the end of radiotherapy or 7 days after radiotherapy had the best therapeutic effect. We further tested the proportion of TEX in human peripheral blood and the expression level of PD1 during and after synchronous radiotherapy and chemotherapy, and found a similar trend as in the mouse model. So we speculate whether the proportion of peripheral blood CD8+TEX cells and the expression level of PD1 can be used as a suitable screening for immunotherapy. In the early stage, we retrospectively analyzed three patients who underwent immune maintenance therapy after synchronous radiotherapy and chemotherapy, and found that they have been followed up for three years, and no PFS time has been obtained. This study aims to ensure that patients receive standard treatment. By screening the proportion of CD8+TEX cells in peripheral blood and the expression level of PD1, patients with upregulation of CD8TEX in peripheral blood after radiotherapy or patients with PD1 expression levels higher than normal were randomly divided into two groups: one group received maintenance therapy for immunity, and the other group received placebo comparison to evaluate PFS time.

2.Research Purpose

2.1 Research Purpose:

A prospective randomized single blind controlled study on maintenance therapy with Sintilimab after radiotherapy and chemotherapy for locally advanced head and neck tumors

2.2 Main study endpoints:

Evaluation of progression free survival (PFS) and 1-year progression free survival (PFS) in two groups of patients with locally advanced head and neck tumors after radiotherapy and chemotherapy (using RECIST 1.1 criteria)

2.3 Secondary study endpoints:

Evaluation of overall survival (OS), safety and tolerability, changes in quality of life relative to baseline, and time to deterioration in maintenance therapy with Xindilimab in patients with locally advanced head and neck tumors after radiotherapy and chemotherapy (EORTC QLQ-C30 and H&N-35)

The primary safety analysis will be conducted based on subjects who experience toxicity (as defined by CTCAE standards). CTCAE version 5.0 will be used to evaluate safety through reported adverse events. The relationship between adverse events and drugs, onset time, duration of events, their resolution, and any concomitant medication will be recorded. Adverse events (AEs) will be analyzed, including but not limited to all AEs, SAEs, lethal AEs, and laboratory changes.

2.4 Exploratory study endpoint:

Explore biomarkers for predicting efficacy and adverse reactions, and obtain better guidance on the combination therapy and safety of immunotumor drugs. In order to identify novel biomarkers, we collected biological samples: 10-20ml of blood (before treatment and during efficacy evaluation) to support the analysis of cellular components (such as DNA, proteins, etc.), such as whole exome gene testing, TMB, PD-L1, MRD, etc.

3.Research design and methods:

3.1 Inclusion criteria:

(1) Male or female, age ≥ 18 years old, ≤ 75 years old.

(2) Localized advanced head and neck tumors with T3 or N+or above that have been histologically confirmed as inoperable.

(3) Patients undergoing synchronous radiotherapy and chemotherapy

(4) ECOG physical fitness status ranges from 0 to 1 point.

(5) The expected lifespan is at least 12 weeks.

(6) At least one measurable lesion

(7) Hematology examination absolute neutrophil count (ANC)>1.5 × 109/L, hemoglobin>8g/dL and platelets>100 × 109/L (based on the normal value of the clinical trial center).

(8) Prothrombin time (PT)<1.5 times the upper limit of normal value and normal thromboplastin time (APTT)<1.5 times the upper limit of normal value.

(9) Laboratory tests show that serum creatinine is less than or equal to 1.5 times the upper limit of the normal reference range (if serum creatinine increases, 24-hour urine must be collected, except for those with a 24-hour creatinine clearance rate>50ml/min).

(10) When there is no liver metastasis, ALT or AST is less than or equal to 2.5 times the upper limit of the normal reference range, and serum total bilirubin is less than or equal to 1.5 times the upper limit of the normal reference range; For patients with liver metastasis, ALT or AST is less than or equal to 5 times the upper limit of the normal reference range, and serum total bilirubin is less than or equal to 3 times the upper limit of the normal reference range.
(11) Women of childbearing age must be willing to use adequate contraceptive measures during the study drug treatment period.
(12) Signed informed consent form.
(13) At the end of radiotherapy, the proportion of peripheral blood PD1+CD8T cells is greater than 10%, or more than twice the baseline

3.2 Exclusion criteria:

(1) Active autoimmune diseases that require systemic treatment (i.e. the use of disease relieving drugs, corticosteroids, or immunosuppressants) have occurred within the past 2 years. Alternative therapies (such as thyroid hormone, insulin, or physiological corticosteroid replacement therapy for adrenal or pituitary insufficiency) are not considered systemic treatments.
(2) Diagnosed as immunodeficiency or undergoing systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first administration of the trial treatment. After consulting with the sponsor, the use of physiological doses of corticosteroids may be approved.
(3) It is known that there are other malignant tumors that are progressing or require active treatment. Excluding skin basal cell carcinoma, skin squamous cell carcinoma, or cervical carcinoma in situ that have already undergone curative treatment.
(4) Active infections that require systemic treatment.
(5) There is a possibility of confusing the trial results, obstructing the participant's full participation in the study due to medical history or evidence of illness, abnormal treatment or laboratory values, or the researcher believing that participating in the study is not in the best interest of the participant.
(6) It is known that there are mental or substance abuse disorders that may affect compliance with the trial requirements.
(7) Female subjects who are pregnant or breastfeeding, or expected to conceive during the planned trial period or 180 days after the last dose of study treatment, or male subjects whose spouses are preparing to conceive.
(8) Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibody) infection.

3.3 Research Design:

This study is a prospective single blind randomized controlled clinical trial of maintenance therapy with Xindilimab based on peripheral CD8TEX screening after standard radiotherapy and chemotherapy for locally advanced head and neck tumors. Synchronous radiotherapy and chemotherapy are routine standard treatments and do not require the use of immunotherapy drugs in this study. Blood samples were collected before and after radiotherapy, and participants were screened and evaluated according to the inclusion and exclusion criteria of the protocol within 28 days before randomization. Patients who

agree to participate in this study will sign an informed consent form (ICF) prior to the screening process. After completing all screening activities, eligible participants can start receiving study treatment. According to the estimated sample size, a total of 104 patients are planned to be enrolled and randomly assigned equally to the experimental group and control group. The treatment cycle for the study is 21 days. The experimental group starts treatment within one month after the end of radiotherapy and chemotherapy. On the first day of each cycle, intravenous treatment with Sintilimab is given, with a cycle of 21 days. It is expected to be administered for a total of 18 cycles, or until the disease progresses; The control group received placebo treatment. The experimental group underwent routine blood tests, liver and kidney function, myocardial enzyme spectrum, thyroid function, electrocardiogram every 2 cycles, and CT scans every 4 cycles to evaluate toxic side effects; The control group underwent the same frequency of follow-up and observation. The study started on January 1, 2024 and ended on January 1, 2027, to explore the efficacy of maintenance therapy with Xindilimab after radiotherapy and chemotherapy for locally advanced head and neck tumors.

Research plan:

Intravenous infusion of Sintilimab, D1, once every 3 weeks

3.4 Research Evaluation Plan

3.4.1 Baseline evaluation

3.4.2 Pre medication evaluation of treatment plan (starting from d1, once every 6 weeks, completed each time before administration)

Inspection items	Inspection time and related instructions
Physical examination, medical history	Medical history collection Physical examination items must include: heart rate, blood pressure, respiratory rate, body temperature, height, weight, and neurological examination Emphasis should be placed on inquiring about possible adverse reactions of Sintilimab
Peripheral blood routine	The blood routine test must include: red blood cell count (RBC), hemoglobin (Hb), white blood cell count (WBC), and white blood cell classification count (absolute neutrophil and lymphocyte counts are required), hematocrit (HCT), and platelet count (PLT).
Blood biochemical examination	The blood biochemistry items must include: blood electrolytes (K Na Ca Mg Cl HCO3- is necessary), ALT, AST, γ - GT, total bilirubin, direct bilirubin, amylase, lipase, creatinine, urea T nitrogen, serum albumin, blood glucose
thyroid function	Thyroid function items must include: T3, T4,

	fT3, fT3, TSH
urinalysis	Urine routine items must include: urine specific gravity (SG), urobilinogen (URO), occult blood (BLD), white blood cells (WBC), urine protein (PRO), urine glucose (GLU), bilirubin (BIL), ketone bodies (KET), urine red blood cells (RBC), and urine color (COL).
Electrocardiogram examination	Twelve lead electrocardiogram
Blood and tissue specimens for biomarker research	Before treatment and before each efficacy evaluation (blood samples)

3.4.3 Efficacy evaluation

Inspection items	Inspection time and related instructions
Imaging examination	Complete baseline assessment within 1 month before treatment, and treat every 3 months Chest and abdominal CT examination evaluation

3.4.4 Testing items and time after discontinuation/withdrawal from the study (once every 9 weeks since the last medication use)

Inspection items	Inspection time and related instructions
Telephone follow-up	Telephone follow-up every two months

3.5 Treatment of subjects

3.5.1 Intervention measures

Sintilimab treatment regimen

drug	Dosage	Administration frequency	Usage method	treatment cycle
Sintilimab	According to the recommended dosage in the manual	Q3W	Intravenous infusion	Cycle every 21 days, administered on the first day

The use of Sintilimab (IBI308)

The main active ingredient of IBI308 is a recombinant human monoclonal antibody against programmed cell death receptor 1, with a concentration of 10 mg/mL. This product is a clear, colorless liquid, free from foreign objects, flocculent substances, and precipitates. The excipients include 140 mmol/L mannitol, 25 mmol/L histidine, 20 mmol/L sodium citrate dihydrate, 50 mmol/L sodium chloride, 0.02 mmol/L disodium edetate (ethylenediaminetetraacetic acid disodium), 0.2 mg/mL polysorbate 80, pH 6.0.

The minimum packaging unit for IBI308 is a box, with each box containing one injection of Sintilimab packaged in a penicillin bottle. The packaging box is printed with the drug name, dosage form, specifications, drug code, production batch number, expiration date, storage conditions, and information about the sponsor. The label of the penicillin bottle and the packaging box have the same information printed on them, but there is no information on the dosage form, precautions, and dosage on the penicillin bottle label. All packaging boxes and penicillin bottles are labeled as "for clinical research purposes only". The finished product of Sintilimab is stored in a dark place at 2-8 ℃ and has a shelf life of 24 months. If there are quality problems such as turbidity and precipitation in the injection, it should be immediately sealed and Xinda Biopharmaceutical (Suzhou) Co., Ltd. (hereinafter referred to as "Xinda Biotech") should be notified immediately.

The intravenous infusion time of IBI308 should be within 30-60 minutes. Do not administer

through intravenous injection or single rapid intravenous injection.

The guidance for dilution of drugs before administration is as follows:

- Solution preparation and infusion
- Do not shake the medicine bottle.
- Restore the medication bottle to room temperature (25 ° C or below) before use.
- After removing the medicine bottle from the refrigerator, it can be left at room temperature (25 ° C or below) for a maximum of 24 hours before dilution.
- Before administration, the injection medication should be visually inspected for the presence of suspended particles and discoloration. This product is a clear to slightly milky, colorless to light yellow liquid with no foreign objects. If visible particles are observed, the medicine bottle should be discarded.
- Extract 2 bottles of this product injection (200mg) and transfer them to an intravenous infusion bag containing 9mg/ml (0.9%) sodium chloride solution. Prepare a final concentration range of 1.5-5.0mg/ml. Gently flip the diluent and mix well.
- From a microbiological perspective, this product must be used immediately upon dilution and should not be frozen. The stability study of this product shows that it can be stored in dark at 2-8 ° C for 24 hours, including a maximum of 6 hours under indoor light at 20-25 ° C (6 hours including administration time). After refrigeration, the medication bottle and/or intravenous infusion bag must be restored to room temperature before use. The infusion tube used during infusion must be equipped with a sterile, heat free, low protein binding infusion tube filter (pore size 0.2) μ m) . The infusion time is within 30-60 minutes.
- Do not use the same infusion tube to administer medication simultaneously with other medications.
- This product is for one-time use only. Any unused medication remaining in the medication bottle must be discarded.

Medication adjustment of Sintilimab

Throughout the entire research process, it is not allowed to adjust the dosage of Xindilimab. The principles of suspending and permanently stopping Xindilimab administration are shown in the table below.

3.5.2 信迪利单抗暂停给药和永久停药原则

Adverse events with Sintilimab	Severity	Dose adjustment
pneumonia	Grade 2	Suspend administration[a]
	Grade 3 or 4 or recurrent level 2	Permanent discontinuation of medication
Diarrhea/Colitis	Grade 2 or 3	Suspend
	Grade 4	Permanent
hepatitis	For subjects with normal baseline ALT, AST, or TBIL, level 2 AST, ALT (3-5 times ULN), or TBIL (1.5-3 times ULN) were elevated; For subjects with baseline AST, ALT, or TBIL>ULN, an increase of ≥ 50% in AST, ALT, or TBIL (meeting level 2 requirements) and a duration of<7 days is required	Suspend administration[a]

	For subjects with normal baseline ALT, AST, or TBIL, grade 3 or 4 AST, ALT (>5x ULN), or TBIL elevation (>3x ULN); For subjects with baseline AST, ALT, or TBIL>ULN, AST, ALT, or TBIL increase ≥ 50% (meeting level 3 or 4 requirements) and duration ≥ 7 days	Permanent discontinuation of medication
nephritis	Grade 2 or Grade 3 elevated blood creatinine	Suspend administration[a]
	Grade 4 elevated blood creatinine	Permanent discontinuation
Endocrine disorders	Symptomatic grade 2 or 3 hypothyroidism Grade 2 or 3 hyperthyroidism Grade 2 or 3 pituitary inflammation Grade 2 adrenal insufficiency Grade 3 hyperglycemia or type 1 diabetes	Suspend administration[a]
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 pituitary inflammation 3rd or 4th grade adrenal insufficiency Grade 4 hyperglycemia or type 1 diabetes	Permanent discontinuation of medication
Skin adverse reactions	Grade 3	Suspend administration[a]
	Level 4, Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanent discontinuation
thrombocytopenia	Grade 3	Suspend
	Grade 4	Permanent

Other immune related adverse reactions	Level 3 or 4 elevated blood amylase or lipase Grade 2 or 3 pancreatitis Grade 2 myocarditis c Other immune related adverse reactions that occur for the first time at level 2 or 3	Suspend administration[a]
	Grade 4 pancreatitis or any level of recurrent pancreatitis Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Other immune related adverse reactions that first occurred at level 4	Permanent discontinuation of medication
Recurrent or persistent adverse reactions	Recurrent grade 3 or 4 (excluding endocrine disorders) Grade 2 or 3 adverse reactions within 12 weeks after the last administration Not improved to level 0-1 (excluding endocrine diseases) Failure of corticosteroids to decrease to ≤ 10mg/day prednisone equivalent dose within 12 weeks after the last administration	Permanent discontinuation of medication

Table: Suspension and permanent discontinuation of Sintilimab regimen

a: Resumption of medication after symptom improvement to level 0-1 or baseline level.

b: Pituitritis, adrenocortical insufficiency, thyroid insufficiency/hypothyroidism and type 1 diabetes can be re used when they are fully controlled and only need physiological hormone replacement treatment.

c: For abnormal results in Level 4 laboratory tests, the decision to terminate medication should be based on accompanying clinical symptoms/signs and the researcher's clinical judgment.

The maximum interval allowed for drug suspension is 12 weeks. If the subject cannot recover to a state where they can reuse Sintilimab within 12 weeks, they will permanently discontinue Sintilimab and enter the follow-up phase. Excluding the following two situations:

1) Due to the use of glucocorticoids in the treatment of irAE, the process of reducing glucocorticoids resulted in the suspension of Sintilimab for more than 12 weeks. In this case, it is

necessary to discuss with the medical manager of the sponsor to decide whether to continue treatment with Sintilimab. The imaging examination for evaluating the therapeutic effect is carried out according to the plan and is not affected by the suspension of medication.

2) Due to the treatment of AE unrelated to Xindilimab, Xindilimab was temporarily suspended for more than 12 weeks. In this case, it is necessary to discuss with the sponsor to decide whether to continue treatment with Sintilimab. The imaging examination for evaluating the therapeutic effect is carried out according to the plan and is not affected by the suspension of medication.

The principle of restoring Sintilimab

When resuming the use of Sintilimab, relevant AEs need to be restored to level 0-1 or baseline, with an ECOG PS score of 0-1.

Management of infusion reactions related to Sintilimab

Xindilizumab may cause severe or life-threatening infusion reactions, including severe hypersensitivity or allergic reactions. Signs and symptoms usually appear during or shortly after drug infusion, and can usually be completely resolved within 24 hours of completion of infusion. The management guidelines for infusion reactions associated with Sintilimab are shown in Table 2.

NCI CTCAE classification	Treatment	Perform pre-treatment medication during subsequent administration
Grade 1 Mild reactions; No need to interrupt infusion; No intervention required	According to the patient's medical indications, strengthen monitoring of their vital signs until the researchers believe that the subject's condition is stable.	None

Grade 2 Treatment or interruption of infusion is necessary, but symptomatic treatment (such as antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], anesthetics, intravenous infusion) should be carried out as soon as possible to quickly generate a response; Preventive medication should be taken for ≤ 24 hours	Stop infusion and monitor symptoms. Other appropriate drug treatments may include, but are not limited to: intravenous antihistamines NSAIDS Acetaminophen anesthesia According to the patient's medical indications, strengthen monitoring of their vital signs until the researchers believe that the subject's condition is stable. If the symptoms improve within one hour after stopping drug infusion, the infusion can be restarted at 50% of the original infusion rate (such as reducing from 100 mL/h to 50 mL/h). Otherwise, medication should be suspended until symptoms improve, and subjects should receive pre-treatment medication before the next planned administration. For subjects who still exhibit level 2 toxicity despite receiving sufficient pre-treatment medication, further study drug treatment should be permanently discontinued.	Subjects receiving anti PD1/PDL1 monotherapy Within 1.5 hours (± 30 minutes) prior to treatment, the following pre-treatment medications can be accepted: Oral administration of 50 mg diphenhydramine (or equivalent dose of antihistamine). Oral administration of 500-1000 mg of acetaminophen (or an equivalent dose of antipyretic).

Grade 3/4 Grade 3： Long duration (i.e. failure to respond quickly after symptomatic medication and/or brief interruption of infusion); Symptom recurrence after initial improvement; Hospitalization is required due to other clinical sequelae such as kidney damage and lung infiltration Grade 4： Endangering life; Require vasopressor medication or ventilation support	Stop infusion. Other appropriate drug treatments may include but are not limited to: adrenaline * * intravenous infusion antihistamines NSAIDS Acetaminophen anesthesia Oxygen boosting drugs Corticosteroids are used to strengthen monitoring of the patient's vital signs based on their medical indications, until researchers believe that the subject's condition is stable. Hospitalization may be required for treatment. **If an allergic reaction occurs, adrenaline should be used immediately. Subjects should permanently discontinue further study drug treatment。	No subsequent administration
Appropriate first aid equipment should be equipped in the ward and physicians should be available at all times during medication administration. For further information, please refer to the Common Terminology Standard for Adverse Events (CTCAE) version 4.03 （ http://ctep.cancer.gov ）		

3.6 Accompanying treatment

Allowing accompanying treatment

Medications that have been determined by the researchers to comply with the protocol (such as those used to treat disease-related symptoms and accompanying treatments for various AEs).

Subjects who need long-term medication due to basic diseases such as hypertension and diabetes can continue to use medication.

Allow local corticosteroid medication, such as topical use, eye drops, nasal spray, inhalation, etc.

Prohibited concomitant therapy

During the treatment period of this study, participants were prohibited from receiving the following treatments:

Biotherapy with anti-tumor effect (excluding cytokine drugs used to treat adverse events caused by chemotherapy drugs), and traditional Chinese patent medicines and simple preparations with anti-tumor effect

Drugs with immunomodulatory effects, including but not limited to non-specific immunomodulators (such as thymosin, interferon, interleukin, immunoglobulin, gamma globulin) and traditional Chinese patent medicines and simple preparations with immunomodulatory effects

Chemotherapy not specified in this plan

Live vaccine administration within 30 days prior to the first administration of Sintilimab and during the study process. Live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, rabies, BCG vaccine, typhoid fever (oral) vaccine. Allow receiving inactivated virus vaccines for seasonal influenza; However, it is not allowed to receive attenuated live influenza vaccines administered intranasally.

Corticosteroids. Allow the use of inhaled steroids as part of fixed treatment for asthma or chronic obstructive pulmonary disease (COPD). Corticosteroids allowed for handling adverse events with potential immune causes. After consulting with the sponsor, the use of physiological doses of corticosteroids can be approved.

Note: The use of prophylactic corticosteroids is allowed to avoid allergic reactions (such as pre-treatment of intravenous contrast agents or chemotherapy drugs).

According to the evaluation of the researchers, subjects who need to use any of the above treatment methods for clinical treatment should be excluded from the trial. The subjects may accept other medication treatments deemed medically necessary by the researchers. It is important for researchers to review each medication (prescription and over-the-counter) received by participants before the start of the study and during each study visit.

During each visit, the subject must be asked about any new medications they have received.

To reduce the risk of adverse drug interactions, all measures must be taken to limit the number of concomitant medications that are truly necessary.

During administration, drugs with hepatotoxicity should be avoided (i.e. drugs with hepatotoxicity are warned in the product manual). Encourage researchers to review each potential hepatotoxic drug by searching the website www.livertox.nih. gov.

3.7 This study excluded the inclusion of vulnerable groups, such as individuals with mental illness, critically ill patients, pregnant women, illiterate individuals, minors, cognitive impairment individuals, students of PI or researchers, subordinates of PI or co researchers, employees of research institutions or sponsors.

3.8 Data Management and Confidentiality

The data collected during the study period will be recorded in the subject's personal case report form. Each subject is assigned a unique subject number in the case report form for

identification. Any data modifications made by data entry personnel in the case report form system will be automatically recorded through the system's "audit trail" function.

The data entry personnel should fill out the case report form as soon as possible after follow-up, and any questions should be answered as soon as possible to maintain the latest data. The case report form should be completed, reviewed, and signed by the researcher as soon as possible after the last follow-up of the subjects. Each subject who has signed the ICF and passed all screening steps must have a completed case report form. If the subject did not receive treatment, the reason must be recorded in the case report form. All data outside of the case report form (laboratory tests, imaging examinations) will be integrated with the relevant data in the subject's case report form. The subject number and date of participation in the study should be recorded by the researcher in the subject's medical/research file along with the study code. Researchers should also record the following information in their medical/research records: written and oral confirmation of informed consent, clinical status of the subjects, dates of each study follow-up, dates of study drug administration, concomitant medications, copies of all relevant reports and laboratory test results, opinions on the results, and any AEs mentioned. The researcher completes electronic signatures through the system in the case report form, which indicate that the researcher has checked or reviewed the data, data questions, and research center notices on the case report form, and agrees to the relevant content. All information and other materials used by subjects and researchers must use clear and understandable vocabulary and language.

The medical records, imaging data, drug use registration form, subject code table, serious adverse event report form and other data of the subjects are kept confidential, and these materials are not disclosed to the public outside the scope permitted by relevant laws and/or regulations. The drug regulatory department, the sponsor, and their authorized supervisory personnel, as well as the ethics committee, have the right to access relevant trial data and original records with the consent of the main researchers involved in the trial.

4. Informed consent

Before participants participate in the study, the researcher is responsible for fully explaining the research purpose, methods, expected benefits, and potential hazards to the participants, in order to further obtain voluntary written consent from the participants or their guardians (if permitted by local regulations). The legal representative refers to an individual or institution who, in accordance with legal requirements and with the authorization of the subject or the law, can make consent on behalf of the subject to participate in clinical research. ICF should be written in the native language of the potential subject population.

Researchers should comply with relevant regulatory requirements, GCP, and ethical principles derived from the Helsinki Declaration to obtain written consent from participants. Before providing ICF and its revised versions to potential subjects, approval from IEC/IRB should be obtained. Researchers should ensure that each participant is informed that they can voluntarily terminate the study at any time, and that each participant has the opportunity to ask questions and have time to reflect on the information obtained.

The ICF should be obtained before the participants participate in the study and the consent form should be kept in the research center as a document. The ICF should be signed by the subject themselves or their legal representative (if permitted by local regulations), as well as the researcher's name and date. The original signed ICF should be kept at the research center and a copy of the signed consent form should be provided to the subject or their legal representative. The date of obtaining informed consent should be recorded in the medical records and original records.

If the subject or their legal representative (if permitted by local regulations) lacks reading ability, a fair witness should be present throughout the informed consent discussion process. Witnesses should sign the ICF after the subject or their legal representative agrees to participate in the study and signs the ICF (if possible). Signing the ICF indicates that the witness confirms that they have fully explained the information and any other written information in the ICF to the subject or their legal representative, that they have clearly understood the information, and that the subject or their legal representative agrees to sign the written ICF.

The following vulnerable groups with informed consent were excluded from this study, such as:

(1) Patients, especially hospitalized and mentally ill patients with serious illnesses: those who have no capacity for behavior shall have their legal guardians sign.

(2) Prisoners, pregnant women, intellectually disabled individuals, and other individuals who may be economically or educationally disadvantaged

(3) Children: must obtain an informed consent form signed by their legal guardian; When children can actually make a decision to agree to participate in the study, they must obtain their consent

(4) Students, staff members of this institution, etc.: Participating in research conducted by their management personnel shall not have any additional benefits, and shall not be forced to participate;

(5) Notes on obtaining informed consent for patients with mental/cognitive impairments:

7. Reporting of Adverse Events

7.1 Definition of Adverse Events

Adverse Event (AE) is defined as any adverse medical event that occurs in a clinical study after a subject receives treatment with a certain drug, regardless of whether it is causally related to the investigational drug. AE includes but is not limited to the following situations:

- The worsening of the original medical condition/disease (including symptoms, signs, and laboratory test abnormalities) before entering clinical trials;
- Any newly occurring adverse medical conditions (including symptoms, signs, newly

diagnosed diseases);

- Abnormal laboratory test values or results with clinical significance.

7.2 Definition of serious adverse events

Serious Adverse Event (SAE) refers to an adverse event that meets at least one of the following criteria:

- Causing death, excluding deaths caused by disease progression based on research indications.
- Life threatening (defined as "life-threatening" refers to an AE where the subject is at risk of death when it occurs, but does not include an AE that could potentially cause death if the event worsens).
- Hospitalization treatment or extended hospital stay is required, excluding the following situations:
    - ✓ Rehabilitation institutions
    - ✓ Sanatorium
    - ✓ Routine emergency room admission
    - ✓ Same day surgery (such as outpatient/same day/non bed rest surgery)

      Hospitalization treatment or prolonged hospital stay that is not related to the deterioration of AE itself is not an SAE.For example, if admitted due to an existing disease, there have been no new adverse events or worsening of the existing disease (such as in order to check for laboratory test abnormalities that have persisted since the trial); Hospitalization for management reasons (such as annual routine physical examinations); Hospitalization specified in the trial protocol during the clinical trial period (such as operating according to the requirements of the trial protocol); Selective hospitalization unrelated to the worsening of adverse events (such as elective surgery); The scheduled treatment or surgical procedure should be included in the entire trial protocol and/Or record in the baseline data of the individual subject; Admitted solely for the use of blood

products.

- Causing permanent or severe disability/loss of ability.
- Causing congenital abnormalities/birth defects.
- Other important medical events: defined as events that harm subjects or require medical intervention to prevent the occurrence of any of the above situations.

7.3 Evaluation of Adverse Events

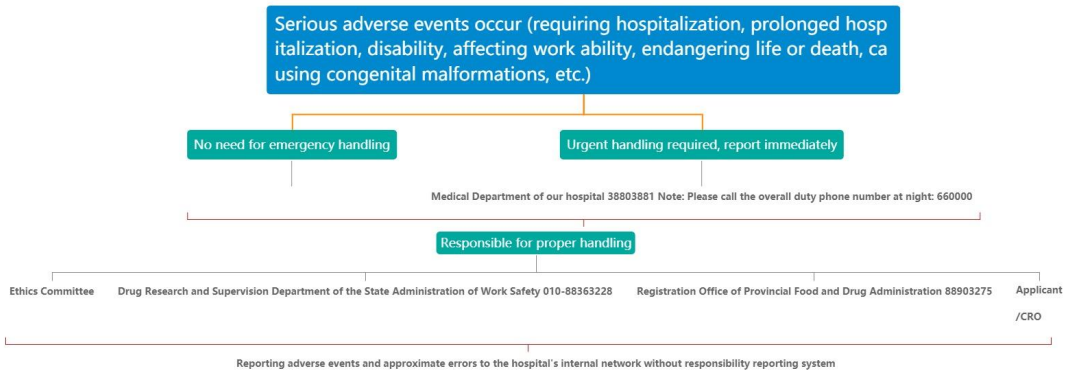
Researchers will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE) version 5.0. Any adverse events that change the CTCAE level will be recorded in the adverse event case report form/worksheet.

All adverse events, regardless of CTCAE level, must be evaluated for severity.

Various adverse events: Take timely measures to handle and record in the case report form.

Serious adverse events (SAE): Take timely measures to handle, record in the case report form, decide to stop or reduce medication by the researcher, immediately report to the ethics committee, drug clinical trial institution, and sponsor, and report to the national and provincial food and drug regulatory authorities within 24 hours. SAE must log in to the "Non Responsibility Reporting System for Adverse Events and Similar Errors within the Hospital" to report. Specific process: see the following figure

Serious adverse events occur (requiring hospitalization, prolonged hospitalization, disability, affecting work ability, endangering life or death, causing congenital malformations, etc.)


Serious adverse events occur (requiring hospitalization, prolonged hosp italization, disability, affecting work ability, endangering life or death, ca using congenital malformations, etc.)
No need for emergency handling
Urgent handling required, report immediately
Medical Department of our hospital 38803881 Note: Please call the overall duty phone number at night: 660000
Responsible for proper handling
Ethics Committee
Drug Research and Supervision Department of the State Administration of Work Safety 010-88363228
Registration Office of Provincial Food and Drug Administration 88903275
Applicant /CRO
Reporting adverse events and approximate errors to the hospital's internal network without responsibility reporting system