A single-arm, prospective, single-center phase II clinical study to evaluate the efficacy and safety of nimotuzumab combined with concurrent chemoradiotherapy in elderly patients with locally advanced unresectable esophageal cancer

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Catalogue

1. Protocol abstract

1.1 Summary

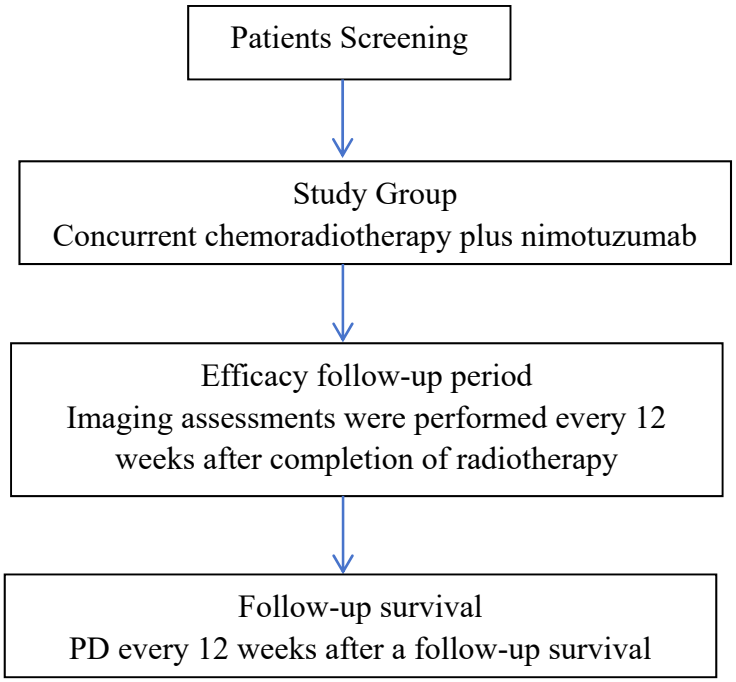
Title:	A single-arm, prospective, single-center phase II clinical study to evaluate the efficacy and safety of nimotuzumab combined with concurrent chemoradiotherapy in elderly patients with locally advanced unresectable esophageal cancer
Study overview	The mortality rate of esophageal cancer is 77%, and this rate will be even higher in elderly patients with esophageal cancer. A safe and effective treatment method is urgently needed. Currently, Nimotuzumab has been approved for esophageal cancer indications in 9 countries. We plan to conduct a single-arm, prospective, single-center Phase II clinical study to explore the efficacy and safety of Nimotuzumab in elderly patients with locally advanced esophageal cancer. The study population is elderly patients with locally advanced unresectable esophageal cancer, and 50 people are planned to be enrolled.
Purpose	To evaluate the efficacy and safety of nimotuzumab combined with concurrent chemoradiotherapy in elderly patients with locally advanced unresectable esophageal cancer.
Endpoint	Primary endpoint: progression-free survival (PFS) Secondary endpoints: objective response rate (ORR), disease control rate (DCR), local disease control rate (LDCR), overall survival (OS), 1-year OS/PFS, 2-year OS/PFS, and AE/SAE incidence.
Study population	**Inclusion criteria: All the following patients must be met to be included in this study** 1.The subjects voluntarily participated in this study, signed the informed consent, had good compliance, and cooperated with the follow-up; 2.Age 75 and above , male or female;

	3.ECOG score 0-1; 4.Esophageal cancer confirmed by histology or cytology; 5.According to the Response Evaluation Criteria for Solid Tumors (RECIST 1.1), there is at least one measurable lesion, and the measurable lesion should not have received local treatment such as radiotherapy (lesions located in the previous radiotherapy area can also be selected as target lesions if they are confirmed to have progressed and meet the RECIST1.1 criteria); 6.Patients with stage II-IVB according to AJCC (8th edition, 2018) (IVB included metastasis to the celiac trunk or supraclavicular lymph nodes only) who are not suitable for or refuse surgery can tolerate concurrent chemoradiotherapy and targeted therapy; 7.Expected survival time ≥ 12 weeks; 8.The major organs function normally, meet the following criteria: 1)Blood test: a.HBG ≥ 90 g/L; b.ANC ≥ 1.5 × 10^9/L; c.PLT ≥80×10^9/L; 2)Biochemical tests: a.ALB ≥ 30 g/L; b.ALT and AST ≤ 2.5 ULN; if there is liver metastasis, ALT and AST ≤ 5 ULN; c.TBIL≤1.5ULN; d.Plasma Cr≤1.5ULN or creatinine clearance (CCr)≥60ml/min; 9.Echocardiographic assessment: left ventricular ejection fraction (LVEF) ≥ lower limit of normal value (50%); 10.Female of childbearing age must agree to use contraceptive measures (such as intrauterine devices, birth control pills or condoms)

	during the study and within 6 months after the end of the study; the serum or urine pregnancy test is negative within 7 days before study enrollment, and they must be non-breastfeeding patients; male must agree to use contraceptive measures during the study and within 6 months after the end of the study. **Exclusion criteria: Those who meet any of the conditions will not be included in this study** 1.Received EGFR monoclonal antibody or EGFR-TKI within six months; 2.Participated in other interventional clinical trials within 30 days before screening; 3.Patients with serious concurrent diseases, such as heart failure, high-risk uncontrollable arrhythmias, severe myocardial infarction, refractory hypertension, renal failure (CKD-4 and above), thyroid dysfunction, mental illness, diabetes, severe chronic diarrhea (more than 7 bowel movements per day), or patients who are considered unsuitable to participate in this clinical study by the researchers; 4.Patients with brain metastases with symptoms or symptom control time of less than 3 months; 5.Have a history of other malignant tumors (except for cured cervical carcinoma in situ or basal cell carcinoma of the skin and other malignant tumors that have been cured for more than 5 years); 6.The presence of active infection or active infectious disease; 7.Patients with multi-segment esophageal malignant tumors or signs of esophageal fistula or perforation; 8.Patients whose tumors have invaded important blood vessels as shown by imaging or who are judged by the researchers to be very likely to invade important blood vessels and cause fatal hemorrhage during the follow-up study;

	9.Those who are allergic to the drugs or their ingredients used in this program; 10.Peripheral neuropathy or hearing loss of grade 2 or higher according to the criteria of Common Terminology for Adverse Events (NCI CTCAE V5.0); 11.Pregnant or breastfeeding women; 12.Patients with a history of psychotropic drug abuse and unable to quit or patients with mental disorders; 13.Those who are considered unsuitable to participate in this study by the researcher; 14.Those who are unwilling to participate in this study or unable to sign the informed consent.
Stage	Stage II
Center	Department of Radiation Oncology, Jiangsu Province Hospital
Study intervention	**1.Radiation Therapy** The prescription dose required that 95% PTV and PTV-nd receive 50-60 Gy /25-30 F , with a single dose range of 2.0 Gy/F, 5 days a week, external beam radiation to the chest . **2.Treatement** S-1: 40-60 mg/m ^{2} , po, D1, BID, 5 weeks; Nimotuzumab 400 mg, iv, D1, week 1; Nimotuzumab 200 mg, iv, D8, QW, Week 2-5.
Study duration	The estimated time from the start of the study to the completion of data analysis is 40 months
Visit duration	The planned enrollment period for this study is 12 months, and the time required for each subject to complete all visits are 24 months.

1.2 Study flow chart



1.3 Study schedule

Project name	**Screening/Baseline Period**	**Treatment period**					**EOT visit**	**Efficacy follow-up**	**Survival follow-up**
	-w3-w0	D1	D8	D15	D22	D29	D29	D29 to PD Date	PD date to death
Informed consent	√								
Check Inclusion and exclusion criteria	√								
Baseline and demographic data	√								
Vital signs and physical examination	◆	√	√	√	√	√	√		
ECOG PS	◆	√	√	√	√	√	√		
Quality of life[6]	◆	√	√	√	√	√	√	√	
Charlson Comorbidity Index	√								
Nutritional status	√						√		
Blood routine examination	◆	√	√	√	√	√	√	■	
Urinalysis	◆	√	√	√	√	√	√	■	
Bowel routine	◆	√	√	√	√	√	√	■	

Blood biochemistry test	◆	√	√	√	√	√	√	■	
Coagulation	◆	√	√	√	√	√	√	■	
Virological examination [1]	√								
Pregnancy test (female subjects of childbearing age)	√								
Electrocardiogram	◆	√	√	√	√	√	√	■	
Echocardiography	√								
Imaging examination[2]	√	▲			√			√	
Radiation therapy		√	√	√	√	√			
Combination medication [3]	√	√	√	√	√	√	√	√	√
Adverse event assessment[4]	√	√	√	√	√	√	√	√	√
Survival follow-up [5]		√	√	√	√	√	√	√	√

◆The examination results within 1 week can be used without repeating the measurement.

▲ The test results within 2 weeks before medication can be used without repeated measurements.

■ If there are any anomalies that have not been resolved before, evaluation will be conducted as needed

1. First, screen for HIV antibodies, five hepatitis B tests, hepatitis C antibodies, and human papillomavirus

(HPV) tests. When the test results indicate the possibility of active hepatitis B or C infection, further HBV DNA quantitative testing and HCV RNA quantitative testing are required to confirm the diagnosis;

2. The imaging assessment can be performed by esophageal angiography and chest and abdominal enhanced CT examination according to the doctor's choice (imaging examinations of the same part at different times should use the same detection technology as the baseline period). The evaluation sites are mainly the esophagus and mediastinal lymphatic drainage area, and other parts are evaluated as needed. After the screening evaluation, imaging evaluation is performed every 21 days during radiotherapy, within 1 week and 4 weeks after the end of radiotherapy, and every 12 weeks thereafter until the disease progresses or the subject is intolerant or withdraws. The examination time window is ±7 days;

3. Record the name, dosage, start and end time of combined medications and treatments, as well as the reasons for combined medications and treatments;

4. Adverse events that have occurred will be followed until they disappear, improve or stabilize and the investigators believe that no further follow-up is required, including AEs that occur within 7 days after the screening period and SAEs that occur within 30 days after the end of radiotherapy;

5. Patients will be followed up for survival every 12 weeks after PD, and can receive telephone visits, including patient survival status and tumor treatment status. The specific cause of death will be recorded in detail when it involves the following factors (primary tumor recurrence, bleeding, perforation, new lesions; recurrence or new metastatic lymph nodes within and outside the region, etc.);

6. During the efficacy follow-up period, evaluation was only performed during the first two follow-up visits.

2. Introduction

2.1 Study theoretical basis

The incidence of esophageal cancer in China ranks the first in the world, and its incidence and mortality account for more than half of the world [1]. Esophageal cancer is mainly divided into carcinoma (ESCC) and adenocarcinoma (EAC) according to pathological type, of which ESCC is the main histological type, accounting for 80% of esophageal cancer cases worldwide[2]. The incidence of ESCC is high in certain ethnic groups and certain regions, and is affected by environmental factors (drinking and smoking) and genetic factors (mutations in enzymes that metabolize alcohol)[3]. The 5-year survival rate of ESCC is only 15%-25%. China is a country with a high incidence of esophageal cancer and the main pathological type is carcinoma, accounting for 53.7% of the world's cases[4], of which about 70% are patients over 60 years old [5]. It is expected that with the aging of the population, the incidence of esophageal cancer in the elderly will further increase.

The best treatment for locally advanced esophageal cancer is centered on radical esophagectomy. However, for some esophageal cancer patients who are not suitable for surgical treatment (such as tumor location, tumor invasion degree, age, patient's own condition, patient's willingness for treatment), concurrent chemoradiotherapy is the main treatment option.

Elderly patients are often unable to receive surgical treatment or even concurrent chemoradiotherapy due to their pre-existing medical conditions, organ dysfunction, and poor physical condition. Therefore, the prognosis of elderly patients with advanced esophageal cancer is poor. The clinical treatment of this disease is difficult, and the cure rate is low, and the recurrence, metastasis, and mortality rates are high. Therefore, it poses a serious threat to the physical and mental health and life safety of elderly patients[6]. Over the past 10 years, both domestic and foreign researchers have been exploring potential therapeutic targets for elderly patients with advanced esophageal cancer, but compared with other gastrointestinal tumors, research and development has lagged behind. At present, there is an urgent need to explore a new treatment model to improve the efficacy and improve the long-term survival and

quality of life of elderly patients.

2.2 Background

EGFR is an important prognostic factor and therapeutic target for esophageal cancer. EGFR overexpression accounts for 42.5%-85.7% of ESCC and is closely associated with high recurrence and low survival[7] [8]. Therefore, EGFR signaling molecules are regarded as biomarkers at various stages of the development of esophageal cancer[9] [10]. Monoclonal antibodies and tyrosine kinase inhibitors targeting EGFR have been developed to improve the survival rate of ESCC[8].

Nimotuzumab is a new anti-EGFR monoclonal antibody jointly developed by Biotech Pharmaceutical Co., Ltd. and Cuba. The drug was launched in China in 2008 and has been approved for marketing in 30 countries around the world, and has been approved for esophageal cancer indications in 9 countries.

A real-world study from Cuba [7] evaluated the efficacy of nimotuzumab combined with radiotherapy/chemotherapy/chemoradiotherapy in patients with locally advanced or metastatic esophageal cancer in Cuba. The study included 339 patients with locally advanced or metastatic esophageal cancer registered in the Cuban National Cancer Database between January 1, 2011 and January 1, 2015. The patients were matched by propensity score. Among them, 93 patients in the nimotuzumab group had received at least one nimotuzumab treatment, and 93 patients in the control group had not received nimotuzumab treatment. The results showed that the median OS of the nimotuzumab group was 11.9 months, which was significantly higher than that of the control group (6.5 months, $p = 0.004$); the 1-year and 2-year overall survival of the nimotuzumab group were 54.0% and 21.1%, while those of the control group were 21.9% and 0%, respectively (95% CI 0.24–0.74, $p = 0.004$). The risk of death in the nimotuzumab treatment group was 2.38 times lower than that in the control group. Another meta-analysis from China also conducted an meta-analysis of nimotuzumab combined with chemoradiotherapy for the treatment of esophageal cancer [8]. The study showed that nimotuzumab can improve the treatment efficacy and prolong the

survival of patients with esophageal cancer without increasing the incidence of adverse events. Combined chemoradiotherapy/radiotherapy can be recommended for the treatment of patients with esophageal cancer. In 2019, Zhai Yirui et al. from the Cancer Hospital Chinese Academy of Medical Sciences published a study on nimotuzumab combined with chemoradiotherapy for the treatment of unresectable local advanced esophageal cancer [9] . The study included 26 newly diagnosed patients with esophageal cancer, with a median radiotherapy dose of 60 Gy, a median total nimotuzumab dose of 1200 mg, and an effective rate of 76.9%. The median follow-up was 30.5 months, and the median survival was 28.7 months. The 2-year and 3-year overall survival were 59.4% and 38.2%; the 2-year and 3-year progression-free survival were 51.4% and 33.3%. Another study conducted a retrospective analysis of the efficacy of nimotuzumab or cetuximab combined with chemoradiotherapy in the treatment of patients with locally advanced esophageal cancer [10]. The results showed that the ORR of the nimotuzumab + CRT group was 61%, slightly higher than that of the cetuximab + CRT group (43.5%), and the disease control rate of the nimotuzumab + CRT group was significantly higher than that of the cetuximab + CRT group (P = 0.04). Other survival analyses also showed that the median PFS of the nimotuzumab + CRT group was significantly longer than that of the cetuximab + CRT group (19.6 months vs 13.0 months, p = 0.02). The 1-year and 3-year OS of the nimotuzumab + CRT group were higher than those of the cetuximab + CRT group (HR = 1.17, p = 0.23).

At present, many studies have confirmed that nimotuzumab can improve the efficacy of esophageal cancer in the elderly. Common acute toxic reactions included esophagitis, pneumonia, leukopenia, gastrointestinal reactions, and thrombocytopenia. The incidence of Grade 3-4 adverse reactions was 17.4%, and no Grade 5 toxic reactions were observed. The median overall survival (OS) was 17 months, and the progression-free survival (PFS) was 10 months. The 2-, 3-, and 5-year OS and PFS were 30.4%, 21.7%, and 19.6%, and 26.1%, 19.6%, and 19.6%, respectively. This result confirms that nimotuzumab combined with radiotherapy is a safe and effective treatment for elderly patients who cannot undergo surgery. Li Lulu [11] randomly

divided 67 patients aged 60-80 years with locally advanced esophageal cancer into an experimental group and a control group. 34 patients in the study group were treated with nimotuzumab combined with IMRT, while 33 patients in the control group were treated with IMRT alone. The results showed that the short-term response rate (ORR) of the study group and the control group were 85.2% and 63.6%, respectively, and the disease control rate (DCR) was 97.1% and 81.8%, respectively, with significant differences ($P < 0.05$). Although the 1-, 2-, and 3-year survival rates of the study group were higher than those of the control group, the difference was not statistically significant ($P > 0.05$). The adverse events of the two groups were similar, with no significant difference ($P > 0.05$). Conclusion: nimotuzumab combined with IMRT can significantly improve the ORR and DCR of patients with locally advanced esophageal cancer in the elderly, but it does not significantly improve the 1-, 2-, and 3-year survival rates of patients. In addition, JINHUA GUO [12] retrospectively analyzed the clinical data of 16 elderly patients with esophageal squamous cell carcinoma, aged > 70 years, who were treated with nimotuzumab combined with RT. The treatment efficacy was evaluated at the completion of treatment and re-evaluated 1-2 months later: 1 patient achieved complete response (CR), 10 patients achieved partial response (PR), 4 patients showed stable disease and 1 patient developed progression disease and died of radiation pneumonitis (RP) 1 month later. The overall response rate (CR + PR) was 68.8%. All 16 patients developed Grade 1-2 radiation esophagitis; no Grade 3-4 toxicity was reported. There was 1 RP-related death during the study. One patient developed a rash on the forearm. No hematological, gastrointestinal, liver, or kidney toxicity was observed. In conclusion, nimotuzumab combined with radiotherapy has good efficacy, tolerable toxicity, and high safety in the treatment of elderly patients with esophageal cancer.

The above studies provide evidence support for the treatment of EGFR-positive elderly esophageal cancer with nimotuzumab combined with chemoradiotherapy. In order to further verify the effectiveness and safety of nimotuzumab combined with concurrent chemoradiotherapy in the treatment of elderly patients with locally advanced unresectable advanced esophageal cancer, we conducted an exploratory

study on the effectiveness and safety of nimotuzumab combined with concurrent chemoradiotherapy in the treatment of elderly patients with locally advanced unresectable esophageal cancer, in order to obtain more sufficient evidence of benefits based on elderly patients, and add new evidence for the treatment of elderly esophageal cancer with nimotuzumab combined with chemoradiotherapy.

2.3 Risk/benefit assessment

2.3.1. Known potential risks

- Direct risks: From January 1, 2009 to June 1, 2020, it is estimated that approximately 117,187 patients used nimotuzumab in China. The company collected 688 adverse events reported by 459 patients. The names of adverse events were classified and summarized according to the ICH International Medical Terminology Dictionary (MedDRA) system organ class and preferred terms as shown in the appendix. Among them, there were 334 serious adverse reactions (including 180 new and serious adverse reactions, with ≥2 occurrences of bone marrow suppression, decreased platelet count, decreased white blood cell count, dyspnea, decreased neutrophil count, shortness of breath, hypersensitivity, anaphylactic shock, pruritus, anorexia, infectious pneumonia, decreased white blood cell count, decreased neutrophil count, decreased granulocyte count, decreased pancytopenia, lung inflammation, hypertension, and hematopoiesis. All serious adverse reactions did not reach the level of death or life-threatening), and 354 general adverse events (including 70 new general adverse events). According to the results of completed clinical studies and the post-marketing adverse reaction monitoring, nimotuzumab has shown good tolerability. Most adverse events are grade I, and common adverse events include nausea, vomiting, headache, fever, decreased neutrophils and white blood cells, anemia, fatigue. For the above adverse events, certain preventive measures or symptomatic treatment are taken, and most patients can be relieved after conventional treatment or on their own.

Serious adverse events mainly included hypersensitivity reactions, leukocytopenia. Demographic factors, concomitant medications, and medication dosages had no significant effect on the incidence of adverse events.

●Long-term risk: Four groups of repeated-dose toxicity studies were conducted in rats: continuous administration for 14 days, the highest dose reached 57.14 mg/kg, no animal deaths and no systemic toxicity were observed, and the NOAEL was 50 mg/kg. Once a week for 4 consecutive weeks, the highest dose was 75 mg/kg, no animal deaths and treatment-related abnormalities were observed, C_{max} and $AUC_{0\text{-}inf}$ increased with increasing doses, and there was no difference in toxic kinetic parameters between genders, and the NOAEL was 75 mg/kg/w. Three groups of repeated-dose toxicity studies were conducted in green monkeys, with continuous administration for 14 days, the highest dose was 11.4 mg/kg, or once a week for 26 consecutive weeks, the highest dose was 28.57 mg/kg, and no obvious toxicity was observed. Repeated-dose toxicity studies were conducted in cynomolgus monkeys, with once a week for 26 consecutive weeks, the highest dose was 50.00 mg/kg, and no obvious toxicity was observed. No increased clinical risks associated with long-term use of nimotuzumab have been observed in previous clinical studies.

2.3.2 Known potential benefits

●Direct potential benefits: nimotuzumab was launched in China in 2008 and has been approved for marketing in 30 countries around the world, and has been approved for esophageal cancer indications in 9 countries. Many studies have shown that nimotuzumab is effective for patients with esophageal cancer.

2.3.3 Assessment of potential risks and benefits

●The mortality rate of esophageal cancer ranks fifth among malignant tumors. The rate will be higher in elderly patients with esophageal cancer due to their

limited tolerance to treatment. A safe and effective treatment method is urgently needed to be added to the treatment plan for this population. Nimotuzumab, as a drug with proven efficacy and widely recognized safety, is expected to bring higher efficacy benefits to patients with minimal safety risks. In addition, this study will limit the population that may increase the safety risk of patients to avoid inclusion in high-risk populations. At the same time, the details of possible adverse reactions and their treatment plans will be clarified to further reduce the risk.

3. Study purpose and endpoint

Purpose	Endpoint
Main purpose	
Exploring the efficacy of nimotuzumab combined with concurrent chemoradiotherapy for elderly patients with esophageal cancer	Primary endpoint: progression-free survival (PFS)
Secondary purpose	
To explore the efficacy and safety of nimotuzumab combined with concurrent chemoradiotherapy for elderly patients with esophageal cancer	Secondary endpoints: objective response rate (ORR), disease control rate (DCR), local disease control rate (LDCR), overall survival (OS), 1-year OS/PFS, 2-year OS/PFS, and AE/SAE incidence.

4. Study design

4.1 Overall design

We plan to conduct a single-arm, prospective, single-center phase II clinical study to explore the efficacy and safety of nimotuzumab combined with concurrent chemoradiotherapy for elderly patients with locally advanced esophageal cancer. The

enrolled patients will receive nimotuzumab combined with S-1 and radiotherapy. This study includes a screening period, a treatment period, an efficacy follow-up period, and a survival follow-up period.

4.1.1 Screening period

- Definition: within 3 weeks before drug administration
- Content:

1) Sign the informed consent form;

2) Screening;

3) Demographic characteristics;

4) History of present disease;

5) Past medical history;

6) Combined treatment;

7) Body surface area (BSA);

8) Physical examination

9) Vital signs;

10) ECOG performance status: see 12.1. ECOG performance status scoring standards;

11) Nutritional status: see 12.4. Nutritional risk screening form (NRS 2002);

12) Quality of life: see 12.5. Quality of life score (QoL) of cancer patients;

13) Charlson Comorbidity Index: see 12.6. Charlson Comorbidity Index scoring criteria and calculation method;

14) Initial tumor imaging assessment:

a.Oral and intravenous contrast-enhanced CT (neck + chest + abdomen, and pelvis if necessary) is preferred;

b.Optional items include intraesophageal ultrasound, bone scan, esophageal fiber endoscopy, esophageal barium meal, PET/CT, etc.

15) Electrocardiogram (12 leads);

16) Laboratory examination of blood samples (hematology and

biochemistry);

17) Pregnancy test (female subjects of childbearing age);

18) Adverse events were observed and recorded.

4.1.2 Treatment period

- Definition: First radiotherapy day W1D1 - last radiotherapy day W5D5
- Window period: treatment ±2 days, imaging ±7 days, pre-dose items -1 day.
- Content:

1)Before WxD1 administration

a.Body surface area (BSA);

b.Physical examination

c.Vital signs;

d.ECOG performance status score;

e.Blood samples and other laboratory evaluations (hematology and clinical chemistry);

f.Electrocardiogram (12 leads);

2)Administer nimotuzumab (see 6.1.2. Dosage and administration);

3)Administer Tegafur (see 6.1.2. Dosage and Administration);

4)Administer radiation therapy (see 6.1.2. Dosage and administration);

5)Observe and record adverse events;

6)Combined treatment;

7)Imaging examination: Review every 21 days after W1D1 (such as W1D22).

4.1.3 End of treatment visit

- Definition: visit at the end date of radiotherapy
- Window period: ±3 days
- Content:

1) Physical examination and vital signs check (at the end of radiotherapy);

2) ECOG performance status;

3) QoL (assessed at the first two efficacy follow-ups);

4) Nutritional status;

5) Hematology and clinical biochemistry (at the end of radiotherapy);

6) 12-lead electrocardiogram (at the end of radiotherapy);

7) Observation and recording of adverse events (AEs occurring within 7 days after the end of radiotherapy and SAEs occurring within 30 days);

8) Blood samples and other laboratory evaluations (hematology and clinical chemistry) are required if there are previously unresolved abnormalities;

9) Combined treatment.

4.1.4 Efficacy follow-up period

●Definition: From the end date of radiotherapy (D29) to the PD date

●Frequency (except for special items): The first review is on the 28th day after completion (W9D5), and then every 12 weeks starting from W9D5 until disease progression, with a window period of ±7 days.

●Content:

1) Film degree exam;

2) Observation and recording of adverse events (AEs occurring within 7 days after the end of radiotherapy and SAEs occurring within 30 days);

3) Hematology, biochemistry, electrocardiogram (if there are previously unresolved abnormalities, blood samples and other laboratory evaluations are warranted);

4) Combined treatment.

4.1.5 Survival follow-up period:

●Definition: From PD date to death/loss to follow-up

●Frequency: Once every 12 weeks, window period ± 7 days

●Content:

1.Understand and record the subject's survival status, cause of death and time (telephone follow-up is possible);

2.Combined treatment.

4.2 Dose selection

Nimotuzumab injection is a colorless clear liquid, administered by intravenous infusion, and the administration process should last for more than 60 minutes. The BPL-IST-ESO-057 study used a 400 mg weekly dosing regimen for nimotuzumab. Considering the decreased tolerance of elderly patients, this study used a 400 mg dose for the first administration, and a 200 mg dose for subsequent treatment courses due to the poor tolerance of elderly patients.

4.3 Definition of end of study

The study is considered to be completed when the subject no longer needs to be examined or the last visit of the last subject is completed.

5. Study population

5.1 Inclusion criteria

Patients must meet all of the following criteria to be eligible for this trial:

1)The patients voluntarily participated in this study, signed the informed consent, had good compliance, and cooperated with the follow-up;

2)Age 75 and above, regardless of gender;

3)ECOG score 0-1;

4)Esophageal cancer confirmed by histology or cytology;

5)According to RECIST 1.1 (see 12.2. Response Evaluation Criteria for Solid Tumors Version 1.1 for details), there is at least one measurable lesion, and the measurable lesion should not have received local treatment such as radiotherapy (lesions located in the previous radiotherapy area can also be

selected as target lesions if they are confirmed to have progressed and meet the RECIST 1.1 criteria);

6)Patients with stage II-IVB according to AJCC (8th edition, 2018) (IVB included metastasis to the celiac trunk or supraclavicular lymph nodes only) who are not suitable for or refuse surgery can tolerate concurrent chemoradiotherapy and targeted therapy;

7)Expected survival time ≥ 12 weeks;

8)The major organs function normally, that is, they meet the following criteria:

- Blood test:
  - a.HBG ≥ 90 g/L;
  - b.ANC ≥ 1.5×10^9 /L;
  - c.PLT ≥80×10^9 /L;
- Biochemical tests:
  - a.ALB ≥ 30 g/L;
  - b.ALT and AST ≤ 2.5 ULN; if there is liver metastasis, ALT and AST ≤ 5 ULN;
  - c.TBIL≤1.5ULN;
  - d.Plasma Cr≤1.5ULN or creatinine clearance (CCr)≥60ml/min;

9)Echocardiographic assessment: left ventricular ejection fraction (LVEF) ≥ lower limit of normal value (50%);

10)Female of childbearing age must agree to use contraceptive measures (such as intrauterine devices, birth control pills or condoms) during the study and within 6 months after the end of the study; the serum or urine pregnancy test is negative within 7 days before study enrollment, and they must be non-breastfeeding patients; men must agree to use contraceptive measures during the study and within 6 months after the end of the study.

5.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from this trial:

1)Received EGFR monoclonal antibody or EGFR-TKI within six months;

2)Participated in other interventional clinical trials within 30 days before screening;

3)Patients with serious concurrent diseases, such as heart failure, high-risk uncontrollable arrhythmias, severe myocardial infarction, refractory hypertension, renal failure (CKD-4 and above), thyroid dysfunction, mental illness, diabetes, severe chronic diarrhea (more than 7 bowel movements per day), or patients who are considered unsuitable to participate in this clinical study by the researchers;

4)Patients with brain metastases with symptoms or symptom control time of less than 3 months;

5)Having a history of other malignant tumors (except for cured cervical carcinoma in situ or basal cell carcinoma of the skin and other malignant tumors that have been cured for more than 5 years);

6)The presence of active infection or active infectious disease;

7)Patients with multi-segment esophageal malignant tumors or signs of esophageal fistula or perforation;

8)Patients whose tumors have invaded important blood vessels as shown by imaging or who are judged by the researchers to be very likely to invade important blood vessels and cause fatal hemorrhage during the follow-up study;

9)Those who are allergic to the drugs or their ingredients used in this program;

10)Peripheral neuropathy or hearing loss of grade 2 or higher according to the criteria of Common Terminology for Adverse Events (NCI CTCAE V5.0);

11)Pregnant or breastfeeding women;

12)Patients with a history of psychotropic drug abuse and unable to quit or patients with mental disorders;

13)Those who are considered unsuitable to participate in this study by the researcher;

14)Those who are unwilling to participate in this study or unable to sign the informed consent.

5.3 Screening failure

Screening failure is defined as a subject who consents to participate in a clinical trial but is not randomized to receive the study intervention or enrolled in the study. Information on screening failure should include demographics, details of screening failure (eligibility criteria, and any serious adverse events).

Patients who do not meet the criteria for participating in the trial (screening failure) can undergo rescreening. The screening number of the subject in the rescreening is the same as the screening number of the initial screening.

6. Study intervention

6.1 Study intervention management

6.1.1 Description of study intervention

Intervention Name	Dosage form	Manufacturer	Specification	Administration route	Storage and stability
Nimotuzumab	Injection	Biotech Pharmaceutical Co., Ltd.	50mg/bottle (10ml)	Intravenous injection	This product should be stored and transported at 2℃-8℃ and should not be frozen. The shelf life is 24 months. After dilution with normal

					saline, this product can remain stable for 12 hours at 2℃-8℃ and 8 hours at room temperature. If stored for longer than the above time after dilution, it should not be used.
S-1	Capsule	Jiangsu Hengrui Medicine Co., Ltd./Qilu Pharmaceutical Co., Ltd.	20mg/capsule	Oral	Protect from light, seal tightly, and store at room temperature.

6.1.2 Dosage and administration

S-1: 40-60 mg/m ^{2} , po, D1, BID, 5 weeks;

Nimotuzumab 400 mg, iv, D1, week 1;

Nimotuzumab 200 mg, iv, D8, QW, Week 2-Week 5.

Radiation Therapy:

Intensity modulated radiation therapy (IMRT) technology is used to irradiate the involved field. The patient is placed in a supine position and fixed with the head, neck, shoulder or body membrane. The patient is simulated and positioned under CT. The CT image is transmitted to the treatment planning system. Combined with esophageal barium meal contrast, gastroscopy or ultrasound gastroscopy or PET-CT images, the esophageal tumor target volume (GTV) is outlined layer by layer on the enhanced CT image; the clinical target volume (CTV) is the GTV with an axial expansion of 0.6 to

0.8 cm and an upper and lower expansion of 2.0 to 3.0 cm; the planned target volume (PTV) is the CTV with an expansion of 0.5 to 0.8 cm. The metastatic lymph nodes are outlined as GTV-nd, and the GTV-nd with an expansion of 0.8 to 1.0 cm is PTV-nd. The prescription dose requires that 95% of PTV and PTV-nd receive 50 Gy /25 F , with a single dose range of 2.0 Gy/F. The target dose distribution and the dose of organs at risk are evaluated layer by layer on the cross section, and the dose-volume histogram (DVH) is combined to evaluate and optimize the treatment plan. The maximum spinal cord dose is <45 Gy, lung V20 <28%, V30 <20%, and the average lung dose Dmean ≤15 Gy. After the treatment plan is confirmed, the dose is verified on the treatment machine, and the treatment plan is executed after it is accurate.

6.2 Handling/storage/responsibilities

6.2.1 Dosage form, appearance, packaging and labeling

See 6.1.1

6.2.2 Product storage and stability

See 6.1.1

6.3 Adherence to study intervention

The study treatment will be administered in the hospital under the supervision of the investigator, so compliance can be easily monitored. The date of intravenous infusion and the exact amount of each infusion will be recorded on the CRF.

For all study drugs, if the administration is interrupted during the infusion, the clinical medical staff should assess the percentage of the drug received by the subject and record it in the CRF.

The reason for any noncompliance should also be recorded. Inadequate compliance is defined as a subject missing more than 2 doses or follow-up visits for non-medical

reasons. In the case of inadequate compliance, the investigator and co-investigator will consider discontinuing the administration of the study drug based on the individual circumstances of the subject.

6.4 Combination therapy

For this study, prescription drugs were defined as drugs that can only be prescribed by authorized/qualified clinicians. Medications recorded in the case report form (CRF) refer to concomitant prescription drugs, over-the-counter drugs, and supplements.

7. Discontinuation of study intervention and subject discontinuation/withdrawal

7.1 Study intervention discontinuation

Suspension of study intervention does not mean suspension of the study, and subsequent study procedures should be completed in accordance with the provisions of the trial protocol. If clinically significant changes occur after enrollment (including but not limited to changes from baseline levels), the investigator will decide whether the subject management needs to be changed. Any new clinically relevant findings will be reported as adverse events (AEs).

7.1.1 Criteria for discontinuation of study intervention

In the event of any of the following circumstances, the subject must discontinue the study intervention

1)If a clinically relevant event occurs that seriously affects the safety of the subject, the investigator or sponsor considers it necessary to terminate the intervention;

2)Imaging examinations to determine disease progression;

3)The subjects received other study drugs or chemotherapy during the clinical study;

4)Lack of compliance by subjects;

5)The subject becomes pregnant during treatment;

6)Elective surgery.

7.1.2 Data collected at the time of discontinuation of the study intervention

Patients who withdraw from the study early should complete all necessary examinations and steps of the study to ensure the integrity of the study. All reasons and dates for stopping the study should be recorded in the CRF.

7.1.3 Subject discontinuation/withdrawal from study

1)Patients may request to withdraw from the study at any time.

2)Researchers may ask subjects to terminate or withdraw from the study for the following reasons:

- Pregnancy;
- Poor compliance with study interventions;
- If a clinical adverse event (AE), laboratory abnormality, or other medical condition occurs, continued participation in the study will not be in the best interest of the subject;
- Disease progression requiring discontinuation of intervention;
- The subject meets the exclusion criteria (new or previously undetected) and cannot continue to participate in the study;
- Subjects are unable to receive regularly scheduled study interventions.

3)A subject to discontinue or withdraw from the study should be recorded in the case report form (CRF). Subjects who signed informed consent and underwent randomization but did not receive the study intervention can be replaced. Subjects who signed informed consent, underwent randomization, received the study intervention, and subsequently withdrew or were withdrawn/discontinued from the study cannot be replaced.

7.2 Lost to follow-up

If a subject does not return to the study center for two consecutive scheduled visits and the study center staff cannot contact him/her, he/she will be considered lost to follow-up.

If a patient does not return to the study center for a scheduled study visit, the following actions must be taken:

- The research center attempts to contact the subject (for up to 2 visit cycle time points) to explain to the subject the importance of adhering to the visit schedule and to confirm whether the subject is willing and/or should continue to participate in the study;
- Before a subject is considered lost to follow-up, the investigator or designee will make every effort to re-contact the subject (by making three phone calls if possible and, if necessary, by sending a registered letter to the subject's most recent mailing address or locally available contact information). These attempts to contact the subject should be recorded in the subject's medical record or study files;
- If the subject still could not be contacted, he/she was considered lost to follow-up and dropped out of the study.

8. Research evaluation t and process

8.1 Efficacy evaluation

The starting point of efficacy evaluation is the time when the subject first receives treatment

8.1.1 Disease progression as the endpoint

1)The event endpoint was the time to disease progression in the subject;

2)If disease progression is confirmed but the time of disease progression

cannot be determined, the last imaging examination time of the subject without disease progression is used as the event endpoint;

3)For patients who died of any other cause before disease progression, the time of death of the subject will be used as the event endpoint;

4)For subjects who have not experienced disease progression or death (i.e., progression-free survival) at the time of analysis, the time of the last tumor assessment will be used as the event endpoint;

5)For subjects lost to follow-up, the time to the last tumor assessment without disease progression will be used as the event endpoint;

6)For subjects who only have baseline imaging examination, the time of baseline examination will be used as the event endpoint.

8.1.2 Events ending in death

1)The event endpoint was the time of subject death;

2)If the subject's death is confirmed but the time of death is not clear, the last follow-up time of the subject is taken as the event endpoint;

3)For patients who had not died at the time of analysis, the time of the last follow-up was used as the event endpoint;

4)For patients lost to follow-up, the time of the last follow-up was used as the event endpoint;

5)For patients with only survival, the time of baseline examination will be used as the end point.

8.2 Adverse events and serious adverse events

8.2.1 Definition of adverse events (AEs)

Adverse events refer to unexpected medical events related to or unrelated to the use of a drug. In this study, adverse events were judged from the subject screening period regardless of whether they were causally related to the trial drug.

8.2.1.1 Examples of adverse events include:

1)A worsening of a chronic disease or the continued presence of symptoms, including an increase in the frequency and/or intensity of symptoms;

2)New symptoms detected or diagnosed after administration of the investigational drug, even if the symptom may have existed before the start of the study;

3)Doubt caused by the interaction between the signs, symptoms or clinical sequelae；

4)Signs, symptoms, or clinical sequelae of overdose of the investigational drug or concomitant medication (overdose, by its nature, should not be reported as an AE/SAE);

When a patient dies, the cause of death is the AE, and death is the outcome of the adverse event.

8.2.1.2 Examples of adverse events do not include:

1)Medical or surgical procedures (endoscopy, appendectomy); the circumstances leading up to these procedures are AEs, not the surgical procedures themselves;

2)Situations in which adverse medical events did not occur (socially and/or recognizable to the hospital);

3)Pre-existing disease with early day-to-day fluctuations or no worsening of symptoms present or detected at study entry;

4)The disease/condition being studied, or the expected progression, signs, or symptoms of the disease/condition being studied, unless more severe than expected for the subject;

5)In principle, "lack of efficacy" or "failure to achieve the expected pharmacological effect" is not reported as an AE or SAE. However, signs, symptoms and/or clinical sequelae caused by lack of efficacy will also be reported as AEs or SAEs if they meet the definition of AEs or SAEs.

8.2.2 Definition of serious adverse event (SAE)

If the researchers or bidders think adverse events (AE) or suspected adverse reactions can lead to the following consequences, should be considered a serious: death, life-threatening adverse events, prolonged hospitalization, or hospital, affect the normal life of persistent or significant disability/disability, congenital abnormalities and/or birth defects.

Based on appropriate medical judgment, major medical events that are unlikely to result in death, be life-threatening, or require hospitalization may be considered serious adverse events when the event is likely to endanger the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples include allergic bronchospasm requiring intensive treatment in the emergency room or at home, cachexia or seizures that do not result in hospitalization, and the development of drug dependence or drug abuse.

Death (defined as Grade 5 by NCI-CTCAE Version 5.0) is generally considered the outcome of the event. If death occurs, the primary cause of death (the main cause of death) will be recorded as the SAE. "Fatal" will be recorded as the outcome of this adverse event; death should not be recorded as a separate event. Death itself will only be recorded as an SAE when the cause of death cannot be determined (e.g., sudden death, unexplained death).

8.2.3 Adverse event classification

8.2.3.1 Severity of the incident

Investigators will refer to the National Cancer Center Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 to evaluate adverse events. This standard uses descriptive terms when reporting AEs. Investigators are required to grade the severity of each adverse event. If the severity/intensity of an adverse event is not clarified in the guidelines, the investigator may make an assessment based on the general definition of 1-5 and combined with his or her best medical judgment.

The general classification is:

Grade 1: Mild;

Grade 2: Moderate;

Grade 3: Severe;

Grade 4: Life-threatening or disabling;

Grade 5: AE-related death.

8.2.3.2 Relevance to the study intervention

The clinician examining and evaluating the subjects must assess the relevance of all adverse events to the study intervention based on the timing and his/her clinical judgment. In clinical studies, the study intervention must always be a subject of suspicion.

Grading of relevance of study intervention:

1) Definitely related: There is clear evidence of a causal relationship and other possible factors can be ruled out. The clinical event (including abnormal laboratory test results) occurs in a reasonable time relationship with the administration of the study intervention and cannot be explained by concurrent illness, other drugs or chemicals. The response of withdrawing the study intervention (de-challenge) should be clinically reasonable. The event must be pharmacologically or phenomenologically clear, and if necessary, a qualified re-challenge procedure can be used;

2) Probably related: There is evidence of a causal relationship and the likelihood of other factors being influential is low. The clinical event (including laboratory abnormalities) occurred within a reasonable period of time after the study intervention was given and is unlikely to be attributed to concurrent illness, other drugs or chemicals, and is consistent with a clinically reasonable withdrawal (de-challenge) response. No re-challenge information is required to complete this definition;

3) Possibly related: There is some evidence of a causal relationship (e.g., the

event occurred within a reasonable period after administration of the trial drug). However, other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse event may be classified as "possibly related" soon after discovery, it can be recorded as requiring more information and then upgraded to "probably related" or "definitely related" depending on the circumstances;

4) Likely unrelated: The temporal relationship between the clinical event (including laboratory abnormalities) and the administration of the study intervention indicates that a causal relationship is unlikely (e.g., the event did not occur within a reasonable period after the administration of the study intervention), and other drugs, chemicals, or underlying diseases can provide a reasonable explanation (the subject's clinical condition, other concomitant treatments);

5) Definitely Unrelated: The adverse event is completely independent of the study intervention and/or there is evidence that the event is definitely related to another etiology. There must be a clear etiology documented by the clinician.

8.2.3.3 Anticipation

The investigator is responsible for determining whether an adverse event is expected or unexpected. If the nature, severity, or frequency of an adverse event is inconsistent with the risk information of the previously described research intervention (e.g., investigator's brochure, approved instructions), it is considered unexpected. The assessment of anticipation should be based on previously observed adverse events and should not be inferred from the nature of the research intervention.

8.2.4 Timing and frequency of adverse event assessment and follow-up

The occurrence of adverse events (AEs) or serious adverse events (SAEs) should be brought to the attention of the investigator during visits to the subject receiving

medical care or for review by the monitor. All adverse events that do not meet the criteria for serious adverse events will be recorded on the appropriate case report form (CRF), including local reactions and systemic reactions. Information to be collected includes description of the event, time of onset, clinician's assessment of severity (which should only be assessed by those with training and diagnostic authority), relationship to the investigational product, expected nature, and time to resolution/stabilization of the event. All adverse events occurring during the study must be recorded, regardless of whether they are related to the study intervention. All adverse events are followed up until reasonably resolved. The medical condition at the time of screening of the subject should be considered as baseline and not reported as an adverse event. However, if the subject's condition deteriorates at any time, it should be recorded as an adverse event. Changes in the severity of adverse events should be recorded to allow for an assessment of the duration of the event at each severity level. Intermittent adverse events require the time of onset and duration of each occurrence to be recorded.

From the signing of the informed consent form to 7 days (non-serious adverse events) or 30 days (serious adverse events) after the end of the trial, the investigator should record all events that need to be reported. At each visit, the researcher should ask about adverse events/serious adverse events that occurred after the last visit. Follow up the outcome information of the event until the adverse event is resolved or stabilized. All serious adverse events should be followed up until the event is resolved satisfactorily, or the investigator considers the event to be chronic, or the subject's condition is stable.

8.2.5 Serious adverse event reporting

After receiving safety-related information from any source, researchers should immediately analyze and evaluate it, including its severity, relevance to the trial drug, etc. Suspected and unexpected serious adverse reactions should be promptly reported to the clinical trial institution and ethics committee.

8.2.6 Pregnancy report

Pregnancy that occurs during the study must be recorded and reported using the pregnancy report form. To ensure the safety of the subject, pregnancy must be reported to the principal investigator immediately and must be followed up to determine its outcome (including early termination of pregnancy) and maternal and fetal status. Pregnancy complications and termination of pregnancy for medical reasons must be reported as AEs or SAEs. Spontaneous abortion must be reported as an SAE. Any pregnancy-related SAE that occurs and comes to the attention of the investigator after the subject completes the study and is believed to be possibly related to the study drug must be reported immediately to the principal investigator. In addition, the investigator must collect information on the pregnancy of the female sexual partner of the male subject after enrollment in the study, whenever possible. Pregnancy information must be reported as described above.

9. Statistical considerations

9.1 Sample size estimation

This study is a single-arm, prospective, exploratory , single-center phase II clinical study. The sample size calculation was based on the primary study endpoint, namely, PFS assessed by the investigator.

The primary endpoint was the median PFS assessed by the investigator. Based on previous studies on radical radiotherapy for elderly esophageal cancer, the median PFS of elderly patients with locally advanced and inoperable esophageal squamous cell carcinoma after radical radiotherapy was 16 months. It was estimated that the median PFS of this study could reach 18.2 months. Using a one-sided test, $\alpha=0.05$, power=0.80, the sample size was calculated to be 41 cases. Considering the dropout rate of 20%, a total sample size of 52 subjects was required.

9.2 Analysis population

1）Full analysis set (FAS): All patients diagnosed with distant metastasis or recurrence of esophageal cancer who received trial drug treatment and had at least one post-drug efficacy follow-up data were included in the full analysis set.

2）Per-protocol set (PPS): Subjects who met the main inclusion and exclusion criteria, completed the trial drug treatment and follow-up observation according to the protocol, and had complete survival data were included in the per-protocol set.

3）Safety analysis set (SS): All subjects who received trial drug treatment and for whom at least one post-dose safety data was available were included in the safety analysis set.

9.3 Statistical Analysis

9.3.1 Statistical analysis plan

SPSS version 26.0 software was used for statistical analysis. Baseline data were analyzed according to the full analysis set, and all efficacy indicators were analyzed according to the full analysis set and the per-protocol set; safety analysis was performed using the safety analysis set.

Descriptive statistics were used to analyze all data, including demographic data, baseline, various efficacy evaluation indicators, and all safety data. Measurement data were expressed as mean ± standard deviation or median and upper and lower quartiles, and count data were expressed as frequency or percentage. Dropout was defined as any reason that caused the subject to fail to complete the follow-up required by the protocol. For exclusion, dropout cases were statistically described one by one. The anti-tumor efficacy of nimotuzumab was analyzed in the full analysis set and the per-protocol set.

9.3.2 Effectiveness Analysis

Kaplan-Meier curves were drawn to estimate the survival rate, median survival time, and hazard ratio.

9.3.3 Security analysis

1)Describe the therapeutic exposure;

2)Statistics of adverse events, the incidence and severity of serious adverse events (NCI CTCAE 5.0), and the causal relationship with the trial drug;

3)The vital signs, laboratory test values, electrocardiograms and changes relative to baseline levels of the subjects at each follow-up point will be statistically analyzed descriptively, and data that deviate from the reference value range will also be statistically analyzed;

4)Concomitant medications and concomitant therapies will be categorized and counted.

10. Supporting documents and operational considerations

10.1 Regulatory, ethical and research oversight considerations

10.1.1Informed consent

Patients must sign an informed consent form before participating in the trial. During the trial, the rights and interests of patients must be ensured, and patient information must be kept confidential in accordance with GCP requirements.

According to the Helsinki Declaration and the GCP requirements of the State Food and Drug Administration, written informed consent must be obtained before the patient enters the trial, that is, before blood samples are collected for screening assessment or any other research-related activities. The researcher is responsible for fully and comprehensively introducing the purpose of the study, the effects of the drug, possible toxic and side effects, and possible risks to the subjects or their designated

representatives, and should let the subjects know their rights, the risks and benefits to be assumed, and give the subjects a copy of relevant information. Then, give the subjects sufficient time to consider the content of this study in order to decide whether to participate. Conversational communication is a very important informed consent process. If the subject and his legal representative are illiterate, the informed consent process should be witnessed by the subject or his legal representative, who should sign the informed consent form after verbal consent, and the witness's signature should be on the same day as the subject's signature.

Each subject must obtain a written informed consent in duplicate, one copy is given to the subject and the other is retained by the researcher.

This clinical trial must comply with the Declaration of Helsinki (1996 edition), Good Clinical Practice (GCP) issued by CFDA, and related regulations. Before the start of the trial, the clinical research institution's ethics committee must be approved before the study can begin. During the clinical trial, any changes to this trial protocol must be reported to the ethics committee and filed.

10.1.2 Study suspension and termination

If there are sufficient reasonable reasons, this study may be temporarily suspended or terminated early. The party that suspends or terminates the study should notify the subjects and researchers in writing and record the reasons for the suspension or termination of the study. If the study is terminated or suspended early, the principal investigator (PI) should promptly notify the subjects and the Institutional Review Board (IRB) and provide the reasons for the termination or suspension of the study.

Circumstances that may require termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risks to subjects;
- Demonstration of effectiveness provides justification for cessation;
- Insufficient compliance with protocol requirements;

- Data are incomplete and/or insufficient for evaluation;
- Determination that the primary endpoint had been met;
- Determine that the study is invalid.

The study may proceed only if issues related to safety, protocol compliance, and data quality are addressed.

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12. Appendix

12.1 ECOG performance status scoring standard

Physical condition ECOG scoring standard Zubrod-ECOG-WHO (ZPS, 5 points)

Fitness score	Physical status
0	The ability to move is completely normal, with no difference from the ability to move before the onset of the disease
1	Able to move around freely and engage in light physical activities, including general housework or office work, but not able to engage in heavy physical activities
2	Able to move around freely and take care of oneself, but has lost the ability to work and can be out of bed and active for at least half of the day.
3	He can only partially take care of himself and spends more than half of the day in bed or in a wheelchair.
4	Bedridden and unable to take care of oneself
5	Die

12.2 Response Evaluation Criteria for Solid Tumors Version 1.1

(Response Evaluation Criteria in Solid Tumors RECIST Version 1.1)

1. Tumor measurability at baseline

1.1 Definition

At baseline, tumor lesions/nodes were categorized as measurable or non-measurable based on the following definitions:

1.1.1 Measurable lesions

Tumor lesions: There is at least one accurately measurable diameter (recorded as the maximum diameter), the minimum length of which is as follows:

- CT scan 10 mm (CT scan layer thickness is no more than 5 mm)
- Routine clinical examination instruments: 10 mm (tumor lesions that cannot be accurately measured with caliper instruments should be recorded as unmeasurable)
- Chest X-ray 20 mm
- Malignant lymph nodes: pathologically enlarged and measurable, the short diameter of a single lymph node on CT scan must be ≥15 mm (the CT scan layer thickness is recommended to be no more than 5 mm). During baseline and follow-up, only the short diameter is measured and followed up.

1.1.2 Non-measurable lesions

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph node short diameter ≥10 mm to <15 mm) and lesions that cannot be measured. Lesions that cannot be measured include: meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, skin/lung lymphangitic carcinomatosis, abdominal masses that cannot be diagnosed and followed up by imaging, and cystic lesions.

1.1.3 Special considerations for lesion measurement

Bone lesions, cystic lesions, and lesions previously treated with local therapy require special mention:

Bone lesions:

- Bone scans, PET scans, or plain radiographs are not suitable for measuring bone lesions, but can be used to confirm the presence or absence of bone lesions;
- Osteolytic lesions or mixed osteolytic/osteoblastic lesions with a definite soft tissue component that meets the above definition of measurability can be considered measurable lesions if they can be evaluated using cross-sectional imaging techniques such as CT or MRI.
- Osteogenic lesions are non-measurable lesions.

Cystic lesions:

- Lesions that meet the definition of simple cysts on radiographic imaging should not be considered malignant lesions because they are simple cysts by definition. They are neither measurable lesions nor non-measurable lesions.
- If the metastatic lesion is cystic and meets the above definition of measurability, it can be considered a measurable lesion. However, if there is a non-cystic lesion in the same patient, the non-cystic lesion should be selected as the target lesion.

Topically treated lesions:

- Lesions located in areas that have been irradiated or treated with other locoregional therapies are generally considered non-measurable unless there is clear progression of the lesion. The study protocol should describe in detail the conditions under which these lesions are considered measurable.

1.2 Description of measurement method

1.2.1 Lesion measurement

During clinical evaluation, all tumor measurements should be recorded in metric units. All baseline assessments of tumor lesion size should be completed as close to the start of treatment as possible and must be completed within 28 days (4 weeks) before the start of treatment.

1.2.2 Evaluation methods

The same techniques and methods should be used for baseline assessment and subsequent measurements of lesions. All lesions must be evaluated using imaging, except for lesions that cannot be evaluated by imaging but can only be evaluated by clinical examination.

Clinical lesions: Clinical lesions are considered measurable only when they are superficial and have a diameter of ≥10 mm (such as skin nodules). For patients with skin lesions, it is recommended to use color photos with a ruler to measure the size of the lesion for archiving. When lesions are evaluated by both imaging and clinical examination, imaging should be used as much as possible because it is more objective and can be reviewed repeatedly at the end of the study.

Chest X-ray: When tumor progression is an important research endpoint, chest CT should be used first because CT is more sensitive than X-ray, especially for new lesions. Chest X-ray is only applicable when the measured lesion has clear boundaries and the lungs are well ventilated.

CT, MRI: CT is currently the best available and repeatable method for evaluating efficacy. The definition of measurability in this guideline is based on CT scan slice thickness ≤ 5 mm. If the CT slice thickness is greater than 5 mm, the minimum measurable lesion should be twice the slice thickness. MRI is also acceptable in some cases (such as whole body scans).

Ultrasound: Ultrasound should not be used as a measurement method to measure lesion size. Ultrasound examinations are not repeatable after the measurement is completed due to their operation dependence, and the consistency of technology and measurement between different measurements cannot be guaranteed. If new lesions

are found using ultrasound during the trial, CT or MRI should be used for confirmation. If the radiation exposure of CT is considered, MRI can be used instead.

Endoscopy, laparoscopy: These techniques are not recommended for objective tumor evaluation, but they can be used to confirm CR when biopsy specimens are obtained and to confirm recurrence in trials where the endpoint is recurrence after CR or surgical resection.

Tumor markers: Tumor markers cannot be used alone to evaluate objective tumor response. However, if the marker level exceeds the upper limit of normal at baseline, it must return to normal levels to evaluate complete response. Because tumor markers vary from disease to disease, this factor must be taken into account when writing measurement standards into the protocol. Specific criteria for CA-125 response (recurrent ovarian cancer) and PSA (recurrent prostate cancer) response have been published. In addition, the International Gynecologic Cancer Organization has developed CA-125 progression criteria, which will soon be added to the objective tumor evaluation criteria for first-line ovarian cancer treatment.

Cytology/histology techniques: These techniques can be used to identify PR and CR in specific circumstances specified in the protocol (e.g., residual benign tumor tissue is often present in lesions of germ cell tumors). When effusions may be a potential side effect of a therapy (e.g., treatment with taxane compounds or angiogenesis inhibitors) and the measurable tumor meets the criteria for response or stable disease, the appearance or worsening of tumor-related effusions during treatment can be confirmed by cytology techniques to distinguish between response (or stable disease) and progressive disease.

2 Tumor response assessment

2.1 Assessment of total tumor and measurable lesions

To evaluate objective response or possible future progression, it is necessary to perform a baseline assessment of the total tumor burden of all tumor lesions as a reference for subsequent measurements. In clinical protocols with objective response

as the primary treatment endpoint, only patients with measurable lesions at baseline can be included. Measurable lesions are defined as the presence of at least one measurable lesion. For trials with disease progression (time to disease progression or degree of progression on a fixed date) as the primary treatment endpoint, the protocol inclusion criteria must clearly state whether only patients with measurable lesions are included, or whether patients without measurable lesions can also be included.

2.2 Baseline Recording of Target and Non-target Lesions

When there is more than one measurable lesion at baseline, all lesions should be recorded and measured, with a total of no more than 5 lesions (no more than 2 per organ) as target lesions representing all involved organs (that is, patients with only one or two involved organs should select a maximum of two or four target lesions as baseline measurement lesions).

Target lesions must be selected based on size (longest diameter), representative of all involved organs, and measurements must be reproducible. Sometimes when the largest lesion cannot be reproducibly measured, a reselection of the largest lesion that can be reproducibly measured is appropriate.

Lymph nodes are of particular concern because they are normal tissue and can be detected on imaging even without metastasis. Pathological lymph nodes, defined as measurable nodules or even target lesions, must meet the following criteria: a short diameter of ≥15 mm on CT. Only the short diameter is required at baseline. Radiologists often use the short diameter of a nodule to determine whether the nodule has metastatic disease. Nodule size is generally expressed in two dimensions detected by imaging (axial plane for CT and one of the axial, sagittal, or coronal planes for MRI). The short diameter is the smallest value. For example, a 20 mm × 30 mm abdominal nodule has a short diameter of 20 mm and can be considered a malignant, measurable nodule. In this example, 20 mm is the measurement of the nodule. Nodules with a diameter of ≥10 mm but <15 mm should not be considered target lesions. Nodules <10 mm do not fall into the category of pathological nodules and do

not need to be recorded or further observed.

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

All other lesions, including pathological lymph nodes, can be considered non-target lesions and do not need to be measured, but should be recorded at the baseline assessment, such as "present", "absent" or, in rare cases, "definitely progressed". Extensive target lesions can be recorded together with the target organ (such as extensive enlargement of pelvic lymph nodes or massive liver metastases).

2.3 Remission criteria

2.3.1 Target lesion assessment

Complete remission (CR): All target lesions disappear and the short diameter of all pathological lymph nodes (including target nodules and non-target nodules) must be reduced to <10 mm.

Partial response (PR): The sum of the target lesion diameters decreases by at least 30% compared with the baseline level.

Disease progression (PD): The minimum value of the sum of all target lesion diameters measured during the entire experimental study is used as a reference, and the relative increase in the sum of diameters is at least 20% (if the baseline measurement value is the smallest, the baseline value is used as a reference); in addition, the absolute value of the sum of diameters must increase by at least 5 mm (the appearance of one or more new lesions is also considered disease progression).

Stable disease (SD): The reduction in target lesions has not reached the level of PR, nor has the increase in target lesions reached the level of PD, but is somewhere in between. The minimum value of the sum of diameters can be used as a reference for

research.

2.3.2 Precautions for target lesion assessment

Lymph nodes: Even if the lymph nodes identified as target lesions are reduced to less than 10 mm, the actual short diameter value corresponding to the baseline must be recorded for each measurement (consistent with the anatomical plane at the baseline measurement). This means that if the lymph nodes are target lesions, even if the criteria for complete remission are met, it cannot be said that the lesions have disappeared, because the short diameter of normal lymph nodes is defined as <10 mm. Target lymph node lesions must be specifically recorded in a specific location on the CRF form or other recording method: for CR, all lymph node short diameters must be <10 mm; for PR, SD, and PD, the actual measurement of the target lymph node short diameter will be included in the sum of the target lesion diameters.

Target lesions too small to measure: In clinical studies, all lesions (nodular or non-nodular) recorded at baseline should have their actual measurements recorded again at subsequent evaluations, even if they are very small (e.g., 2 mm). However, sometimes they are so small that the CT scan image is very blurry and the radiologist has difficulty defining the exact value, so they may be reported as "too small to measure." In this case, it is important to record the previous value on the CRF. If the radiologist believes that the lesion may have disappeared, it should also be recorded as 0 mm. If the lesion is indeed present but is too blurry to give an accurate measurement, a default value of 5 mm can be used. (Note: This is unlikely to occur with lymph nodes, as they are generally of measurable size under normal circumstances or are often surrounded by fat tissue as in the retroperitoneum; however, if this situation occurs and a measurement cannot be given, a default value of 5 mm is also used.) The default value of 5 mm is derived from the cut thickness of the CT scan (this value does not change with different cut thickness values of CT). Since the chance of the same measurement being repeated is unlikely, providing this default value will reduce the risk of incorrect assessment. However, it needs to be reiterated that if the radiologist can give an exact numerical value for the lesion size, the actual

value must be recorded even if the lesion diameter is less than 5 mm.

Separate or coalesced lesions: When a non-nodular lesion is fragmented, the longest diameters of the separate parts are added together to calculate the sum of the diameters of the lesion. Similarly, for coalesced lesions, the planes between the coalesced parts can be distinguished and the maximum diameters of each are calculated. However, if the lesions are inseparable, the longest diameter should be the longest diameter of the entire coalesced lesion.

2.3.3 Evaluation of non-target lesions

This section defines the response criteria for non-target lesions. Although some non-target lesions are actually measurable, they do not need to be measured and only need to be qualitatively assessed at the time points specified in the protocol.

Complete remission (CR): All non-target lesions disappear and tumor markers return to normal levels. All lymph nodes are non-pathological in size (short diameter <10 mm).

Non-complete response/non-progressive disease: Presence of one or more non-target lesions and/or persistent tumor marker levels above normal levels.

Disease progression: Definite progression of existing non-target lesions. Note: The appearance of one or more new lesions is also considered disease progression.

2.3.4 Special considerations regarding the assessment of non-target lesion progression

The following is a supplementary explanation of the definition of progression of non-target lesions: When patients have measurable non-target lesions, even if the target lesions are assessed as stable or partially remitted, in order to make a clear definition of progression based on the non-target lesions, the overall deterioration of the non-target lesions must be met to the extent that treatment must be terminated. The general increase in the size of one or more non-target lesions is often not enough to meet the progression criteria. Therefore, when the target lesions are stable or partially remitted, it is almost rare to define overall tumor progression based solely on

changes in non-target lesions.

When none of the patient's non-target lesions are measurable: This situation occurs in some phase III trials when the inclusion criteria do not require the presence of measurable lesions. The overall assessment is still based on the above criteria, but because there is no measurable data on lesions in this case. The deterioration of non-target lesions is not easy to assess (by definition: all non-target lesions must be truly unmeasurable), so when the changes in non-target lesions lead to an increase in the overall disease burden equivalent to disease progression in target lesions, a clear definition of progression based on non-target lesions needs to be established for assessment. For example, it is described as an increase in tumor burden equivalent to an additional 73% increase in volume (equivalent to a 20% increase in the diameter of measurable lesions). Another example is peritoneal effusion from "trace" to "extensive"; lymphangiopathy from "local" to "widely disseminated"; or described in the protocol as "sufficient to change treatment." Examples include pleural effusion from trace to large, lymphatic involvement from the primary site to distant sites, or it may be described in the protocol as "necessary for a change in treatment." If clear progression is found, the patient should be considered to have progressive disease overall at that point. It would be desirable to have objective criteria applicable to the assessment of non-measurable disease, but the added criteria must be reliable .

2.3.5 New lesions

The appearance of new malignant lesions indicates disease progression; therefore, some evaluation of new lesions is important. There are no specific criteria for the detection of lesions on imaging; however, the finding of a new lesion should be unambiguous. For example, progression cannot be attributed to differences in imaging techniques, changes in imaging morphology, or other pathologies other than the tumor (eg, some so-called new bone lesions are simply the healing of the original lesion or the recurrence of the original lesion). This is particularly important when a patient has a partial or complete response to a baseline lesion; for example, a necrotic liver lesion may be reported on the CT report as a new cystic lesion when it is not.

Lesions detected during follow-up but not found during the baseline examination will be considered new lesions and indicate disease progression. For example, if a patient with visceral lesions during the baseline examination is found to have metastatic lesions during a CT or MRI head examination, the patient's intracranial metastatic lesions will be considered as evidence of disease progression, even if the patient did not undergo a head examination during the baseline examination.

If a new lesion is ambiguous, for example because of its small size, further treatment and follow-up evaluation are needed to confirm whether it is a new lesion. If repeat examination confirms that it is a new lesion, the time of disease progression should be calculated from the time of its initial discovery.

Lesions evaluated with FDG-PET generally require additional testing for confirmation, and it is reasonable to combine FDG-PET with additional CT results to evaluate progression (especially new suspected disease). New lesions can be confirmed with FDG-PET, according to the following procedure:

The baseline FDG-PET scan result was negative, and the subsequent follow-up FDG-PET scan was positive, indicating disease progression.

No baseline FDG-PET was performed and the follow-up FDG-PET result was positive:

If the new lesions found in the follow-up FDG-PET positive test are consistent with the results of the CT examination, it proves that the disease has progressed.

If the new lesions found in the positive results of the follow-up FDG-PET are not confirmed by the CT examination results, another CT examination is required for confirmation (if confirmed, the disease progression time is calculated from the abnormality found in the previous FDG-PET examination).

If the positive follow-up FDG-PET result is consistent with a pre-existing lesion on CT, and the lesion has not progressed on imaging, then the disease has not progressed.

2.4 Best overall efficacy evaluation

The best overall response is the best response recorded from the beginning of the trial to the end of the trial, taking into account any necessary conditions for confirmation. Sometimes the response occurs after the end of treatment, so the protocol should clarify whether the response evaluation after the end of treatment is considered in the best overall response evaluation. The protocol must clarify how any new treatment before progression affects the best response. The patient's best response depends mainly on the results of target lesions and non-target lesions and the manifestation of new lesions. In addition, it depends on the nature of the trial, protocol requirements, and outcome measurement criteria. Specifically, in non-randomized trials, the response is the primary goal, and confirmation of PR or CR is necessary to confirm which is the best overall response.

2.4.1 Time point response

Assuming that a response will occur at each specific time point for each regimen, Table A provides a summary of the overall response at each time point for the patient population with measurable disease at baseline.

If the patient has no measurable lesions (no target lesions), the evaluation can refer to Table B.

2.4.2 Assessment missing and non-assessable explanation

If a lesion cannot be imaged or measured at a particular time point, the patient is not evaluable at that time point. If only a portion of the lesions can be evaluated at an evaluation, the patient is generally considered not evaluable at that time point unless there is evidence that the missing lesions do not affect the evaluation of the efficacy response at the specified time point. This is likely to occur in the setting of progressive disease. For example, if a patient has 3 lesions totaling 50 mm at baseline, but subsequently only 2 lesions totaling 80 mm are evaluable, the patient will be evaluated as having progressive disease regardless of the impact of the missing lesions.

2.4.3 Best overall response: all time points

Once all the patient information is available, the best overall response can be determined.

Evaluation of the best overall response when the study does not require confirmation of a complete or partial efficacy response: The best efficacy response in the trial is the best response at all-time points (for example, a patient is evaluated as SD in the first cycle, PR in the second cycle, and PD in the last cycle, but his best overall response is evaluated as PR. When the best overall response is evaluated as SD, it must meet the shortest time from the baseline level specified in the protocol. If the shortest time standard is not met, even if the best overall response is evaluated as SD, it will not be recognized, and the patient's best overall response will be determined based on subsequent evaluations. For example, a patient is evaluated as SD in the first cycle and PD in the second cycle, but he does not meet the shortest time requirement for SD, and his best overall response is evaluated as PD. The same patient who is lost to follow-up after being evaluated as SD in the first cycle will be considered unevaluable.

When the study requires confirmation of complete or partial efficacy response, the best overall response assessment is: only when each subject meets the partial or complete response criteria specified in the trial and the efficacy is confirmed again at a later time point (usually four weeks later) as specifically mentioned in the protocol can a complete or partial response be declared. In this case, the best overall response is shown in the explanation of Table c.

2.4.4 Special tips for efficacy evaluation

When nodular lesions are included in the total target lesion assessment and nodules decrease in size to a “normal” size (<10 mm), they will still have a lesion size scan reported. To avoid overestimation based on increased nodule size, measurements will be recorded even if the nodule is normal. As mentioned previously, this means that a subject with a complete response will not have a score of 0 on the CRF.

If efficacy confirmation is required during the trial, repeated “unmeasurable” time

points will complicate the optimal assessment of efficacy. The analysis plan for the trial must state that these missing data/assessments can be accounted for when determining efficacy. For example, in most trials, a subject's response of PR-NE-PR can be considered to have efficacy confirmation.

When a subject experiences an overall deterioration in health that requires discontinuation of treatment, but there is no objective evidence, this should be reported as symptomatic progression. Every effort should be made to assess objective progression even after treatment has been discontinued. Symptomatic deterioration is not an assessment of objective response: it is a reason to discontinue treatment. The objective response of such subjects will be assessed by the target and non-target lesions as shown in Tables a to c.

Cases defined as early progression, early death and inevaluable are study specific and should be clearly described in each protocol (depending on the treatment interval and duration).

In some cases, it is difficult to distinguish localized disease from normal tissue. When the evaluation of complete response is based on such a definition, we recommend that a biopsy be performed before the evaluation of response to localized complete response. When some subjects have abnormal imaging results of localized disease that are thought to represent fibrosis or scarring, FDG-PET is used to confirm the response to complete response with a similar assessment criteria to biopsy. In such cases, the use of FDG-PET should be prospectively described in the protocol and supported by reports in the specialist medical literature for this setting. However, it must be recognized that the limitations of FDG-PET and biopsy, including their resolution and sensitivity, may lead to false-positive results in the evaluation of complete response.

Table a Evaluation at each time point - Subjects with target lesions (including or excluding non-target lesions)

Target lesion	Non-target lesions	New lesions	Overall remission
CR	CR	No	CR

CR	Non-CR/Non-PD	No	PR
CR	Cannot evaluate	No	PR
PR	Non-progressive or incompletely assessable	No	PR
SD	Non-progressive or incompletely assessable	No	SD
Cannot be fully evaluated	Non-progressive	No	NE
PD	Any case	Yes or no	PD
Any case	PD	Yes or no	PD
Any case	Any case	yes	PD
CR = complete remission	PR = partial response	SD = stable disease	PD = progressive disease NE = Not Evaluable

Table b Evaluation at each time point - Subjects with only non-target lesions

Non-target lesions	New lesions	Overall remission
CR	No	CR
Non-CR or non-PD	No	Non-CR or non-PD
Cannot fully evaluate	No	Cannot evaluate
Unknown PD	Yes or no	PD
Any case	yes	PD

Note: For non-target lesions, "non-CR/non-PD" refers to an efficacy that is better than SD. As SD is increasingly used as an endpoint for evaluating efficacy, the efficacy of non-CR/non-PD is formulated to address situations where no lesions can be measured.

For ambiguous progression findings (eg, very small indeterminate new lesions; cystic or necrotic changes in existing lesions), treatment can be continued until the next evaluation. If disease progression is confirmed at the next evaluation, the progression

date should be the date of the previous suspected progression.

Table c Best overall efficacy for CR and PR that needs to be confirmed

Total response at the first time point	Total response at subsequent time points	Best overall response
CR	CR	CR
CR	PR	SD, PD or PR [a]
CR	SD	If SD lasts long enough, it is SD, otherwise it should be PD
CR	PD	If SD lasts long enough, it is SD, otherwise it should be PD
CR	NE	If SD lasts long enough, it is SD, otherwise it should be NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	If SD lasts long enough, it is SD, otherwise it should be PD
PR	NE	If SD lasts long enough, it is SD, otherwise it should be NE
NE	NE	NE

Note: CR means complete remission, PR means partial remission, SD means stable disease, PD means progressive disease, and NE means not evaluable. Superscript "a": If CR actually occurs at the first time point, and any disease appears at a subsequent time point, then even if the subject's efficacy reaches the PR standard relative to the baseline, the efficacy evaluation at the subsequent time point will still be PD (because the disease will reappear after CR). The best response depends on whether SD occurs within the shortest treatment interval. However, sometimes the first evaluation is CR, but the scans at subsequent time points seem to still appear, so the subject's efficacy at the first time point should actually be PR rather than CR. In this case, the first CR judgment should be modified to PR, and the best response is PR.

2.5. Frequency of tumor re-evaluation

The frequency of tumor reassessment during treatment depends on the treatment regimen and should be consistent with the type and schedule of treatment. However, in phase II trials where the benefit of treatment is unclear, follow-up every 6 to 8 weeks (timed at the end of a cycle) is reasonable, and the length of the interval can be adjusted in special protocols or circumstances. The protocol should specify which tissue sites require baseline assessment (usually those that are most likely to be closely related to metastatic lesions of the tumor type being studied) and the frequency of re-evaluation. Under normal circumstances, target lesions and non-target lesions should be evaluated at every assessment. In some optional situations, the frequency of evaluation of certain non-target lesions can be less frequent, for example, bone scans should be repeated only when the efficacy evaluation of the target disease confirms a CR or when bone lesions are suspected to have progressed.

After treatment, re-evaluation of the tumor depends on whether the response rate or the time to a certain event (progression/death) is used as the endpoint of the clinical trial. If it is the time to a certain event (such as TTP/DFS/PFS), regular repeated evaluations specified in the protocol are required. Especially in randomized comparative trials, the scheduled evaluation should be listed in the schedule (such as 6 to 8 weeks during treatment, or 3 to 4 months after treatment) and should not be affected by other factors, such as treatment delays, dosing intervals, and any other events that may lead to imbalances in the treatment arm in the choice of disease evaluation time.

2.6. Efficacy evaluation/confirmation of remission

2.6.1. Confirmation

For non-randomized clinical studies with efficacy as the primary endpoint, the efficacy of PR and CR must be confirmed to ensure that the efficacy is not the result of evaluation error. This also allows for a reasonable interpretation of the results when historical data are available, but the efficacy in the historical data of these trials should

also have been confirmed. However, in all other cases, such as randomized trials (Phase II or Phase III) or studies with disease stabilization or disease progression as the primary endpoint, efficacy confirmation is no longer required because it has no value for the interpretation of the trial results. However, the cancellation of the requirement for efficacy confirmation will make central review to prevent bias more important, especially in non-blind experimental studies.

In the case of SD, at least one measurement met the SD criteria specified in the protocol within the shortest time interval after the start of the trial (generally no less than 6–8 weeks).

2.6.2 Total remission period

The duration of overall remission is the time from the first measurement of meeting the CR or PR (whichever is measured first) criteria to the first real documented disease relapse or progression (the minimum measurement recorded in the trial is used as a reference for disease progression). The duration of overall complete remission is the time from the first measurement of meeting the CR criteria to the first real documented disease relapse or progression.

2.6.3. Stable disease phase

It is the time from the start of treatment to disease progression (or, in randomized trials, from the time of randomization), with the smallest sum in the trial as the reference (if the baseline sum is the smallest, it is used as the reference for PD calculation). The clinical relevance of disease stabilization varies from study to study and disease to disease. If, in a particular trial, the proportion of patients who maintain a minimum stable disease duration is used as the study endpoint, the protocol should specify the minimum time interval between the two measurements used in the definition of SD.

Note: Remission, stable period, and PFS are affected by the frequency of follow-up after baseline evaluation. Defining standard follow-up frequency is beyond the scope of this guideline. Follow-up frequency should take into account many factors, such as

disease type and stage, treatment duration, and standard specifications. However, if comparisons between trials are required, the limitations of the accuracy of these measurement endpoints should be considered.

12.3 Contents of subject management

1. Subject recruitment

The requirements of the protocol should be fully reviewed, the feasibility of subject recruitment should be evaluated, and a subject recruitment plan and schedule that is in line with the actual situation of the center should be developed. If there are competing trial projects, full coordination work should be done. Potential subjects can be found and contacted through existing past patient medical records. If necessary, recruitment advertisements can be considered to expand the scope of recruitment. Recruitment advertisements must be issued after obtaining ethical approval.

2. Reception of the Subjects

We should try to create a reception environment that is conducive to the subjects' relaxation and allocate enough time for the subject reception. A hasty visit reception may lead to insufficient communication and even make the subjects feel unhappy. Therefore, it is necessary to arrange the subject reception at a relatively free time, or designate a dedicated subject reception staff, and try to keep the reception staff stable.

3. Entry/Exit Records

After the subject submits a written informed consent, the screening phase begins. After the screening meets the inclusion criteria, the subject formally enters the trial. Researchers should record the screening and inclusion information of this process. During the subject's participation in the trial, their visits and missed visits should be recorded, and after the last visit, the subject's exit record should be completed.

4. Subject guidance

During the research process, the subjects should be actively guided to comply with and cooperate with the trial process. Even if the research project has a universal subject guide, the research center needs to prepare a written guidance document to inform the subjects in detail where and who to find in the center to complete each process. Such a document will greatly reduce the workload of subject managers and researchers.

12.4 Nutritional risk screening form (NRS2002)

The total score of NRS (nutrition risk screening, NRS2002) includes the sum of three parts, namely the disease severity score + nutritional status reduction score + age score (add 1 point if over 70 years old).

1. NRS (2002) scores and definitions for reduced nutritional status:

(1) 0 points: Definition - Normal nutritional status

(2) Mild (1 point): Definition: 5% body weight loss or food intake of 50% to 75% of normal requirement within 3 months.

(3) Moderate (2 points): Definition: 5% body weight loss within 2 months or food intake in the previous week is 25% to 50% of normal requirement.

(4) Severe (3 points): Definition: 5% body weight loss within 1 month (15% body weight loss within 3 months) or BMI < 18.5 or food intake in the previous week was 0% to 25% of normal requirement.

(Note: If any of the three questions are met, the score will be based on that score; if several of them are met, the higher score will be used as the basis)

2. NRS (2002) scores and definitions for disease severity:

(1) 1 point: A patient with a chronic disease is hospitalized due to complications. The patient is weak but does not need to be bedridden. The protein requirement is slightly increased, but can be compensated by oral supplements;

(2) 2 points: The patient needs to stay in bed, such as after major abdominal surgery. The protein requirement increases accordingly, but most people can still recover with parenteral or enteral nutrition support;

(3) 3 points: The patient is on mechanical ventilation support in the intensive care unit. The protein requirement increases and cannot be compensated by parenteral or enteral nutrition support. However, parenteral or enteral nutrition support can significantly reduce protein breakdown and nitrogen loss.

3. Relationship between scoring results and nutritional risk:

(1) A total score ≥ 3 points (or pleural effusion, ascites, edema and serum protein < 35 g/L) indicates that the patient is malnourished or at nutritional risk, and nutritional support should be used.

(2) Total score < 3 points: Nutritional assessment will be reviewed weekly. If the result of subsequent reviews is ≥ 3 points, the nutritional support program will be initiated.

(3) If the patient is planning to undergo major abdominal surgery, the new score (2 points) will be used during the first assessment, and the need for nutritional support (≥3 points) will be determined based on the new total score.

12.5 Quality of life score (QoL) of cancer patients

In 1990, my country formulated a draft with reference to foreign indicators. The standards are as follows (scores are in brackets):

1. Appetite: ① Almost unable to eat; ② Food intake < 1/2 of normal; ③ Food intake is 1/2 of normal; ④ Food intake is slightly less; ⑤ Food intake is normal.

2. Mental state: ① Very poor; ② Poor; ③ Influenced, but sometimes better and sometimes worse; ④ Fairly good; ⑤ Normal, the same as before illness.

3. Sleep: ①Difficulty falling asleep; ②Very poor sleep; ③Poor sleep; ④Slightly poor sleep; ⑤Generally normal.

4. Fatigue: ① Often tired; ② Feeling weak; ③ Sometimes tired; ④ Sometimes slightly tired; ⑤ No feeling of fatigue.

5. Pain: ① severe pain with passive posture or pain duration for more than 6 months; ② severe pain; ③ moderate pain; ④ mild pain; ⑤ no pain.

6. Family understanding and cooperation: ① No understanding at all; ② Poor; ③ Average; ④ Family understanding and care are relatively good; ⑤ Good.

7. Understanding and cooperation from colleagues (including leaders): ① All understand and no one cares; ② Poor; ③ Average; ④ A few people understand and care; ⑤ Most people understand and care.

8. Self-understanding of cancer: ① Disappointed, completely uncooperative; ② Uneasy, reluctantly cooperating; ③ Uneasy but moderately cooperative; ④ Uneasy, but able to cooperate relatively well; ⑤ Optimistic and confident.

9. Attitude towards treatment: ① No hope for treatment; ② Half-believing and half-doubting the treatment; ③ Hope to see the effect but afraid of side effects; ④ Hope to see the effect and still able to cooperate; ⑤ Have confidence and actively cooperate.

10. Daily life: ① Bedridden; ② Able to move, but need to stay in bed most of the time; ③ Able to move, sometimes bedridden; ④ Live a normal life, unable to work; ⑤ Live and work normally.

11. Side effects of treatment: ① Severely affect daily life; ② Affect daily life; ③

No impact on daily life after symptomatic treatment; ④ No impact on daily life without symptomatic treatment; ⑤ No impact on daily life.

12. Facial expressions: divided into levels ①-⑤.

The quality of life grading currently in trial is as follows: the full score for quality of life is 60 points, extremely poor quality of life is <20 points, poor quality of life is 21-30 points, average quality of life is 31-40 points, better quality of life is 41-50 points, and good quality of life is 51-60 points.

12.6 Scoring criteria and calculation method of Charlson Comorbidity Index

1. Significance: to assess the effects of specific medical interventions and screening measures on patients' life expectancy.

2. Comorbidity score

Score	Disease		Score
1	□Coronary artery disease □Congestive heart failure □Chronic lung disease □Peptic ulcer disease □Peripheral vascular disease	□Mild liver disease □Cerebrovascular disease □Connective tissue disease □Diabetes	
2	□Dementia □Hemiplegia □Moderate to severe renal □Disease diabetes associated with organ damage	□Any tumor in five years □Leukemia □Lymphoma	
3	□Moderate to severe liver disease		
6	□Metastatic solid tumors	□Acquired Immune Deficiency Syndrome (AIDS)	
	Total score		

3. Age rating

1) Age < 50: 0 points

2) 50-59 years old: 1 point

3) 60-69 years old: 2 points

4) 70-79 years old: 3 points

4. Results Analysis

A. Calculate the Charlton index (i)

1) The sum of comorbidity index and age index = i

B. Calculate the Charlton probability (10-year survival rate)

1) Y = e (ix0.9)

2) Z=0.983Y, which is the patient's ten-year survival rate.

12.7 Quality of life score (QoL) evaluation table

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
HN1	I am able to eat the foods that I like	0	1	2	3	4
HN2	My mouth is dry	0	1	2	3	4
HN3	I have trouble breathing	0	1	2	3	4
HN4	My voice has its usual quality and strength	0	1	2	3	4
HN5	I am able to eat as much food as I want	0	1	2	3	4
HN 10	I am able to communicate with others	0	1	2	3	4
HN7	I can swallow naturally and easily	0	1	2	3	4
E1	I have difficulty swallowing solid foods	0	1	2	3	4
E2	I have difficulty swallowing soft or mashed foods	0	1	2	3	4
E3	I have difficulty swallowing liquids	0	1	2	3	4
E4	I have pain in my chest when I swallow	0	1	2	3	4
E5	I choke when I swallow	0	1	2	3	4
E6	I am able to enjoy meals with family or friends	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
E7	I wake at night because of coughing	0	1	2	3	4
ACT 11	I have pain in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4

12.8 Nutritional assessment

Subjective overall nutritional status rating scale provided by the patient

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

PG-SGA scoring worksheet

Worksheet -1 score for weight loss

One month's body weight data were used for scoring, or six months' body weight data were used if no such data were available. The following scores were used for scoring, and an additional one point was added if body weight was lost within the last two weeks.

Weight loss within 1 month	**mark**	Weight loss within 6 months
10% or more	four	**20% or more**
5~9.9%	three	**10~19.9%**
3~4.9%	2	**6~9.9%**
2~2.9%	one	**2~5.9%**
0~1.9%	**0**	**0~1.9%**

Scoring (Box 1)

Worksheet -2 Scoring Criteria for Disease and Age

classify	mark
cancer	**one**
AIDS	**one**
Pulmonary or cardiac cachexia	**one**
Bedsore, open wound or fistula	**one**
wound	**one**
Age ≥65 years old	**one**

Scoring (Box 5)

Worksheet -3 scoring of metabolic stress state

Stress state	**None (0)**	**Mild (1)**	**Moderate (2)**	Height (3)

generate heat	without	37.2~38.3℃	38.3~38.8℃	**≥38.8℃**
Duration of fever	without	<72hrs	72hrs	**>72hrs**
Glucocorticoid dosage (prednisone /d)	**without**	**<10mg**	**10~30mg**	**≥30mg**

Scoring (Box 6)

Worksheet -4 Physical Examination

	No consumption: 0	**Mild consumption: 1+**	**Moderate consumption: 2+**	Severe consumption: 3+
fat				
Orbital fat pad	0	1+	2+	**3+**
Triceps skinfold thickness	0	1+	2+	**3+**
subcostal fat	0	1+	2+	**3+**
muscle				
temporalis	0	1+	2+	**3+**
Shoulder and back	0	1+	2+	**3+**
Chest and abdomen	0	1+	2+	**3+**
arms and legs	0	1+	2+	**3+**
body fluid				
Ankle edema	0	1+	2+	**3+**
Sacral edema	0	1+	2+	**3+**
ascites	0	1+	2+	**3+**
Total consumptive Subjective evaluation	0	one	2	three

Scoring (Box 7)

Worksheet -5 PG-SGA overall rating scale

	Level a Good nutrition	**b grade Moderate or suspected malnutrition**	Class c Severe malnutrition
weight	No loss or recent increase	5% lost within 1 month (or 10% in June) or	**> 5% in 1 month (or > 10% in 6 months) or**

		Unstable or not increasing	**Unstable or not increasing**
Nutritional intake	No shortage or Recent significant improvement	Decreased exact intake	**Severe inadequate intake**
Nutrition-related symptoms	None or recent significant improvement Adequate intake	There are nutrition related symptoms Box 3	**There are nutrition related symptoms Box 3**
function	No shortage or Recent significant improvement	Moderate hypofunction or recent exacerbation Box 4	**Severe hypofunction or recent marked aggravation of Box 4**
physical examination	**No consumption or chronic consumption but recent clinical improvement**	**Mild to moderate subcutaneous fat and muscle consumption**	**Apparent signs of malnutrition Such as severe subcutaneous tissue consumption, edema**

Subjective overall nutritional status rating scale provided by the patient

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

PG-SGA history questionnaire

In the PG-SGA design, BOXs 1–4 are performed by the patient, where the scores of BOXs 1 and 3 are the accumulation of each score, and the scores of Box 2 and 4 are based on the highest score verified by the patient.

2. Weight (see sheet 1)

My weight is kg now

My height is meters

My weight was kg a month ago

My weight was kilograms six months ago

My weight in the last 2 weeks:

□ decreased (1)□ no change (0)□ increased (0)

1. Dietary intake (meal size)

How much did I eat last month compared to my normal diet: □ No change (0)

□ greater than normal (0)

□ less than normal (1)

I am eating now:

-common food but less than normal meal (1)

□ few solid foods (2)

□ Dried food (3)

□ only for nutritional additives (4)

□ Various foods are scarce (5)

4. symptom

I have had the following problems that affect my appetite for the last 2 weeks:

□ No eating problems (0)

-no appetite, don't want to eat (3)

-nausea (1)-vomiting (3)

□ constipation (1)□ diarrhea (3)

□ Oral pain (2)□ Oral dryness (1)

□ Abnormal taste or no (1) □ Food odor interference (1)

□ dysphagia (2)□ early satiety (1)

□ Pain; Location? （3）

3. Activities and functions

My overall activities last month were:

□ normal, unlimited (0)

-slightly worse than usual, but still can normal activities (1)

-most things can't do, but the time of bed or sitting less than 12 hours heart (2)

-little activity, most of the day in bed or sitting (3)

5. Illness and its relationship to nutritional needs (see worksheet 2)

All relevant diagnostics (detailed description):

Primary disease staging: I II III IV other

age

Scoring:

6. Metabolic requirements (see worksheet 3)

Scoring:

7. Physical examination (see worksheet 4)

Scoring:

Overall rating (see worksheet 2) Grade A Good Nutrition Grade B moderate or suspected malnutrition	**PG-SGA total score** **Score A+B+C+D**

Patient Name: Age: Hospitalization Number: Clinical Doctor Signature Record Date:

Recommendations for Nutrition Support

Appropriate nutritional interventions, including education and guidance for patients and their families, symptom-specific treatments such as drug intervention, and appropriate nutritional support were determined based on the overall PG-SGA score.

0-1 At this time, nutrition status was scored regularly without intervention.

2-3 A dietician, nurse or clinician shall provide education and guidance to the patients and their families, and appropriate drug intervention shall be conducted for symptoms and laboratory tests.

4-8 Need nutrition intervention and symptomatic treatment

Patients ⩾9 years old need symptomatic treatment and appropriate nutritional support

≥9 Treatment measures to improve symptoms and appropriate nutritional support are urgently needed