Informed consent

Dear Sir/Madam:

We invite you to participate in the research project "A prospective, single-arm, 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 squamous cell carcinoma". This study is led by Xiaolin Ge from the Department of Radiotherapy and will be conducted in the First Affiliated Hospital of Nanjing Medical University (Jiangsu Provincial People's Hospital). The center plans to enroll 52 subjects. This study has been reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (Jiangsu Province Hospital).

EGFR is an important prognostic factor and therapeutic target for esophageal squamous cell carcinoma. EGFR overexpression accounts for 42.5%-85.7% in ESCC and is closely associated with high recurrence and low survival. Therefore, EGFR signaling molecules are regarded as biomarkers at various stages of the development of esophageal cancer. Monoclonal antibodies and tyrosine kinase inhibitors targeting EGFR have been developed to improve the survival rate of ESCC. Targeted therapeutic drugs EGFR monoclonal antibodies can achieve the purpose of anti-tumor by targeting EGFR, blocking a series of downstream signaling pathways, inhibiting tumor cell proliferation, and promoting tumor cell apoptosis.

Nimotuzumab (trade name: Taixinsheng) is a new anti-EGFR monoclonal antibody jointly developed by Bio 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 evaluated the efficacy of nimotuzumab combined with radiotherapy/chemotherapy/chemoradiotherapy in patients with locally advanced or metastatic esophageal squamous cell carcinoma in real life in Cuba. The study included 339 patients with locally advanced or metastatic esophageal cancer registered in the Cuban National Cancer Database from January 1, 2011 to January 1, 2015. They 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 survival rates 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, $p = 0.004$), and 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 in-depth analysis of nimotuzumab combined with chemoradiotherapy for the treatment of esophageal cancer. The study showed that nimotuzumab can improve the treatment efficiency and prolong the survival of patients with esophageal cancer, and does not increase the occurrence of

adverse drug reactions. Combined chemoradiotherapy/radiotherapy can be recommended for the treatment of patients with esophageal cancer. In 2019, Zhai Yirui and others from the Cancer Hospital of the Chinese Academy of Medical Sciences published a study on nimotuzumab combined with chemoradiotherapy for the treatment of unresectable local advanced esophageal squamous cell carcinoma. The study included 26 newly diagnosed patients with esophageal squamous cell carcinoma, with a median radiotherapy dose of 60Gy, a median total dose of nimotuzumab of 1200mg, 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 survival rates were 59.4% and 38.2%; the 2-year and 3-year progression-free survival rates 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 squamous cell carcinoma. 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 rates of the nimotuzumab + CRT group were higher than those of the cetuximab + CRT group (HR = 1.17, p = 0.23). The interim results of the Phase III clinical study NXCEL1311 (a randomized, controlled, double-blind study involving 201 patients with locally advanced unresectable esophageal squamous cell carcinoma) led by Chinese Academician Yu Jinming showed that nimotuzumab can effectively improve the efficacy of concurrent chemoradiotherapy, with ORRs of 93.8% vs 72% in the nimotuzumab group and placebo group, respectively (P<0.001), and CRRs of 32.5% vs 12.2%, respectively (P=0.002).

At present, many studies have confirmed that nimotuzumab helps improve the efficacy of esophageal cancer in the elderly. Liang Jun et al. studied the safety and efficacy of nimotuzumab combined with radiotherapy in the treatment of elderly unresectable esophageal cancer. A total of 46 patients with stage II-IV esophageal squamous cell carcinoma were included, with a median age of 76.5 years. Common acute toxic reactions included esophagitis, pneumonia, leukopenia, gastrointestinal reactions, thrombocytopenia, etc. 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 randomly divided 67 patients aged 60-80 years with locally advanced esophageal squamous cell carcinoma into an experimental group and a control group. 34 patients in the experimental group were treated with nimotuzumab combined with IMRT, and 33 patients in the control group were treated with IMRT alone. The results showed that the short-term response rate (ORR) of the experimental 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 statistically significant differences (P＜0.05); although the 1-, 2-, and 3-year survival rates of the experimental group were higher than those of the control group, the difference was not statistically significant (P＞0.05); the adverse reactions of the two groups were similar, with no statistically significant difference (P＞0.05). Conclusion: Nimotuzumab combined with IMRT can significantly improve the ORR and DCR of elderly patients with locally advanced esophageal cancer, but it does not significantly improve the 1-, 2-, and 3-year survival rates of patients. In addition, JINHUA GUO retrospectively analyzed the clinical data of 16 elderly patients with esophageal squamous cell carcinoma, aged >70 years, treated with nimotuzumab combined with RT, and the treatment effect was evaluated at the completion of treatment and re-evaluated 1-2 months later: 1 patient achieved complete remission (CR), 10 patients achieved partial remission (PR), 4 patients showed stable disease, and 1 patient developed disease progression and died of radiation pneumonitis (RP) 1 month later. The overall effective 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 summary, 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 squamous cell carcinoma 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 squamous cell carcinoma, we conducted a group exploratory study on the effectiveness and safety of nimotuzumab combined with concurrent chemoradiotherapy in the treatment of elderly patients with locally advanced unresectable esophageal squamous cell carcinoma, in order to obtain more sufficient evidence of benefit based on elderly patients, and add new evidence for the treatment of elderly esophageal cancer with nimotuzumab combined with chemoradiotherapy.

Who is suitable (or not) to participate in the study? (Inform the main inclusion and exclusion criteria)

Inclusion criteria: All the following items must be met to be included in this study

1. 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;

2. The pathological type is esophageal squamous cell carcinoma;

3. Eastern Cooperative Oncology Group performance status of 0－1, age ≥ 75 years old;

4. No serious comorbidities, such as severe obstructive emphysema, hypertension, coronary heart disease, diabetes and psychiatric history, etc., and no other malignant tumors;

5. All patients had not received EGFR-targeted therapy, immunotherapy, and

chemoradiotherapy;

6. Expected survival time ⩾ 12 weeks.

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.

If you participate in the research, what do you need to do? (Mainly inform the research methods, process, steps and precautions in detail)

This study is a prospective, single-arm, open, 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 squamous cell carcinoma. The researchers used progression-free survival (PFS) as the primary endpoint.

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 are secondary study endpoints, and 52 subjects are planned to be enrolled. The subjects are elderly patients with local advanced esophageal cancer, who are expected to receive nimotuzumab combined with Segalovirus and radiotherapy. The planned enrollment time for this study is 12 months, and the time required for each subject to complete all visits is 24 months, including the screening period, treatment period, efficacy follow-up period, and survival follow-up period. The screening period is 3 weeks before administration, and the screening examination and evaluation are completed. Qualified subjects will be randomly selected to receive subsequent treatment. Treatment period: 5 weeks ± 9 days, the treatment plan is as follows: 1. Radiotherapy: The prescription dose requires 95% PTV and PTV-nd to receive 50Gy/25F, and the single dose range is 2.0Gy/F. 2. Drug treatment: S-1: 60 mg/m2, po, D1, BID, 5 weeks; Nimotuzumab 400 mg, iv, D1, week 1; Nimotuzumab 200 mg, iv, D8, QW, week 2-week 5. Efficacy follow-up period: from the end date of radiotherapy (D29) to the PD date, the first review will be conducted on the 28th day after the end (W9D5), and then W9D5 will be used as the starting date, and the review will be conducted every 12 weeks until disease progression, with a window period of ±7 days. Survival follow-up period: from the PD date to death/loss to follow-up. Once every 12 weeks, with a window period of ±7 days.

What are the benefits of participating in the research? (Objectively inform the subjects of the direct or indirect benefits and social benefits)

With this clinical study, your disease may be alleviated, but it may not achieve the expected effect, or even cause disease progression; receiving tumor tissue/blood and other biomarker tests may not benefit you directly, but your participation will help medicine further study and understand such diseases and improve the diagnosis and treatment of diseases in the future. Here, we would like to thank you for participating in scientific research and contributing to the development of medicine!

What are the risks of participating in the study? (Inform all adverse reactions of the trial drugs and control drugs or the risks and countermeasures of the trial devices and trial therapies)

Anti-tumor treatment has risks. The drugs used in this study have been marketed in China. Radiotherapy is also one of the important treatment methods in the field of esophageal cancer. Compared with conventional diagnosis and treatment, it will not increase your risk. However, due to the disease itself, other existing complications or the combined use of different treatment methods, there may be adverse reactions that have not been discovered or cannot be predicted in the study. In addition, radiotherapy combined with Segafur and Nimotuzumab has not yet become a standard treatment for advanced esophageal cancer. All therapeutic drugs may have side effects, such as: common adverse reactions of Segafur include gastrointestinal reactions, bone marrow suppression, pigmentation, rash, etc.; common adverse reactions of Nimotuzumab include rash, gastrointestinal reactions, myalgia, increased creatinine, etc. The risk of venous blood draw may be pain and/or bruises. In rare cases, needle dizziness may occur and infection may occur at the acupuncture site, but it often heals on its own. We will observe the side effects/adverse reactions that may be caused

by this study by regularly checking blood routine, biochemistry, thyroid function, myocardial markers, chest CT, etc. (provide risk prevention and control guidance when necessary, such as hypoglycemia treatment, etc.). If you experience any discomfort or adverse reactions, please contact the study doctor in time. Since the drugs used in this study, such as Tegafur and Tislelizumab, are routine treatments for esophageal cancer, even if you do not participate in this clinical study, these side effects/adverse reactions may occur as long as you receive this treatment. In addition, any treatment may be ineffective, and the disease may continue to develop due to ineffective treatment or due to the combination of other diseases.

Are there any costs associated with participating in the study? (Specify compensation plan and amount)

The drugs used in this study have been marketed in China, and the related examinations are also routine examinations that have been used clinically for many years. The cost of the study drugs and related diagnosis and treatment needs to be borne by you. This study does not provide transportation expenses. If there is any damage related to the trial, corresponding treatment and compensation will be provided in accordance with relevant national regulations.

Is personal information kept confidential?

Your medical records will be kept in the hospital, and researchers, research supervisors, and ethics committees will be allowed to access your medical records. Any public report on the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical information within the scope permitted by law.

If you do not participate in this study, what other treatments are available? (Mainly to inform you of alternative treatments and potential risks and benefits)

Participation in this study is completely voluntary. If you do not participate or choose to withdraw at any stage of the study, you will receive alternative treatment. You can discuss specific alternative treatments with your doctor before deciding whether to participate in this study.

I have to take part in the research?

Participation in this study is completely voluntary. You can refuse to participate in the study or withdraw from the study at any time during the study, which will not affect the doctor's treatment of you. If you decide to withdraw from this study, please contact your doctor. You may be asked to undergo relevant examinations, which is beneficial to protecting your health.

If you have any questions regarding your personal rights, please contact our ethics committee at 025-68306360.

Subject Statement: I have read the above introduction to this study and fully understand the possible risks and benefits of participating in this study. I voluntarily participate in this study. I will

receive a copy of this informed consent form with my signature and date.

I agree □ or refuse □ the use of my medical records and clinical specimens related to this research by other research.

Subject's Signature:_____Date: _____ year ____ month ____ day

Contact number of the subject:_____Phone number:_____

(If applicable) Legal Guardian/Witness Signature:_____Date: _____ year ____ month ____ day

Legal guardian /witness contact number:_____Phone number:_____

Researcher's statement: I confirm that I have explained the details of this study to the subjects, especially the possible risks and benefits of participating in this study, and emphasized that nimotuzumab in this study is still an off-label drug, and answered all the subjects' questions. The subjects agreed to participate in this study voluntarily. This informed consent form is in duplicate, and the researcher and the subject each keep a signed informed consent form.

Study Doctor’s Signature:_____Date: _____ year ____ month ____ day

Study doctor's work phone number:_____Phone number:_____