Informed Consent

Dear_____sir/madam:

We invite you to participate in the "SPACE-neo study: a single arm study of apatinib combined with camrelizumab and SOX regimen in neoadjuvant treatment of local advanced gastric/gastroesophageal junction adenocarcinoma" led by Prof. Xiaofeng Chen. The First Affiliated Hospital of Nanjing Medical University (Jiangsu Province Hospital). Thirty-two patients will be recruited in the study. This study has been reviewed and approved by the Ethics Committee of Nanjing Pukou District Central Hospital. The approved No. of ethic committee is 2021-SR-034. We will introduce the research to you.

You could discuss whether you want to participate in this study with family, friends or doctor. It is entirely up to you and you have plenty of time to consider it. Even if you have signed up and agreed to participate in the study, you could change your idea and withdraw from the study at any time without any reasons. If you agree to participate in the study, we will give you or your legal representative a signed and dated informed consent approved by the Ethics Committee.

Introduction: Gastric cancer ranks third in incidence and mortality among all malignancies in China. And prognosis of advanced unresectable gastric cancer is very poor.

Fluorouracil, platinum and paclitaxel were mostly used in the treatment of advanced gastric cancer in the past, and different drug combinations were carried out on this basis. However, a number of studies have shown that the treatment effect of advanced gastric cancer has not been significantly improved, and the median overall survival of patients has always been around 10–14 months. Even after the combination of bevacizumab, trastuzumab and other targeted therapy drugs, the prognosis has not been significantly improved. With the emergence of PD-1/PD-L1 inhibitors and their great progress in neoadjuvant therapy of lung cancer and melanoma, preoperative combination of PD-1/PD-L1 inhibitors may provide more options for conversion therapy of advanced unresectable gastric cancer. Recent clinical studies have presented the following challenges to the existing standard chemotherapy therapy. Firstly, immunotherapy based on immune checkpoint, combined with chemotherapy and targeted therapy may greatly improve therapeutic effect. Secondly, low dose antiangiogenic therapy could induce vascular normalization, improve local hypoxia and chemotherapy resistance, and regulate immune microenvironment to further enhance immunotherapy. Thirdly, conversion therapy has become a hot spot in clinical research, with high completion of perioperative chemotherapy and better clinical benefit than postoperative adjuvant chemotherapy. First-line apatinib combined with chemotherapy have improved the conversion rate of patients with advanced gastric cancer. Based on the abundance of primary tumor antigens and the presence of tumor-infiltrating lymphocytes, second-line or later-line therapy or perioperative immunotherapy may be more effective. These preliminary explorations are expected to improve the clinical efficacy of patients with advanced gastric cancer. Even in the descending stage of the primary cancer, the distant metastasis can be effectively controlled, and then R0 surgery can be performed to improve the prognosis.

The SPACE-neo trial aims to evaluate the safety and preliminary efficacy of low-dose apatinib combined with camrelizumab and SOX regimen in neoadjuvant treatment of locally advanced gastric/gastroesophageal junction cancer. If you are willing to participate in the study, you will receive the corresponding comprehensive treatment, and the specific administration plan is as follows.

You will receive 3 cycles of apatinib (250 mg orally daily) combined with camrelizumab (200 mg intravenously on day 1 every 3 weeks) plus SOX (S-1, 40 mg/m^2 orally twice daily for 14 days followed by 7 days off; oxaliplatin, 130 mg/m^2 intravenously on day 1 every 3 weeks) as neoadjuvant treatment.

After 2–3 cycles of neoadjuvant treatment (6–9 weeks from the beginning of treatment), imaging and endoscopy will be performed to evaluate efficacy and surgical feasibility.

Notably, oral apatinib will be used only for 10 days during the last cycle before surgery to reduce the influence of apatinib on the surgery. Surgical approach will be determined by surgeon according to actual situation.

Postoperative treatment will be selected according to pathological results and current treatment guidelines.

The first six patients are in the safety induction period, and the remaining patients will be extended for treatment after the safety is confirmed.

Our study is conducted in accordance with the requirements of the Good Clinical Practice (GCP) of the People's Republic of China (2003 edition) and the World Medical Association Declaration of Helsinki (2013 edition). Compensation for damage related to the study will be carried out in accordance with the relevant laws of China.

You will have regular examinations during treatment. The demographic data, history of present illness, prior cancer therapies, primary lesion surgical history, tumor history, comorbidity history, concomitant medication,

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history of drug allergy, vital signs, physical examination, Eastern Cooperative Oncology Group Performance Status (ECOG PS), blood routine, blood biochemistry and other hematological examinations, ultrasound endoscopy, thoracoabdominal enhanced computed tomography (CT) or magnetic resonance imaging (MRI) will be collected. The examination items required in this study are all those required for routine clinical use. We will do everything permitted by law to protect the privacy of your medical information.

If you have any of the following conditions, you will be excluded in this study. (I) History of acquired or congenital immunodeficiency disease, or organ transplantation. (II) Pre-existing thyroid dysfunction and failure to maintain normal thyroid function despite medical treatment. (III) Pregnancy and breastfeeding women. (IV) History of psychotropic drug abuse and cannot quit or suffering from mental disturbance. (V) Other conditions determined by researchers which are not suitable for inclusion in the study.

All therapeutic drugs may produce side effects and camrelizumab is a listed product. Common adverse events (AEs) of camrelizumab in previous clinical studies include reactive cutaneous capillary endothelial proliferation (RCCEP), anemia, fever, fatigue, hypothyroidism, proteinuria, cough, loss of appetite and so on. Common AEs of apatinib in previous clinical studies include hypertension, hand-foot syndrome (HFS), proteinuria and so on. You may have AEs similar to those mentioned above, or some unknown AEs that have not occurred so far. If you experience any discomfort or AEs during treatment, please contact investigators immediately. Camrelizumab is a drug used in the clinical treatment of malignant tumors, these AEs may occur as long as you receive this drug, even if you do not participate in the clinical study. In addition, any treatment may not be effective, and the disease may progress because of ineffective treatment or other diseases.

During treatment, the purchase policy of apatinib is buy one get one free. Camrelizumab and chemotherapy drugs are at the patient's own expense, without transportation and other expenses subsidies. If you have severe adverse events (SAEs) during the treatment which are related to the study determined by investigators, the sponsor will bear the corresponding treatment costs and financial compensation in line with the law.

You have the right to refuse participating in the study during the screening period and you also have the right to stop or withdraw from the study at any time which will not affect the doctor's care for you. If you do not participate in the study or if you drop out of the study, there are many alternative drugs such as other anti-PD-1 antibody. If you decide to withdraw from the study, please contact your doctor and you may be required to undergo examinations that are beneficial to your health.

If you have any questions concerning your personal rights and interests, please contact the Ethics Committee of our hospital at 025-58532887.

Subject's statement: I have read the introduction of this study and I am fully aware of the risks and benefits of participating in this study. I am volunteered to participate in the study. I will obtain a signed and dated copy of the informed consent form.

I agree ☐ or reject ☐ that my medical records and pathological specimens will be used in other studies other than this one.

Subject signature: _____
Date: _____month_____day_____year
Phone number: _____
Telephone of subject: _____

(If applicable) Legal representative signature: _____
_____
Date: _____month_____day_____year
Phone number: _____
Telephone: _____

Investigator's statement: I confirm that I have explained the details of the study to the patient, in particular the possible risks and benefits of participating in the study. And I have answered all questions of the subject. The subject is volunteered to participate in the study. The informed consent is made in duplicate and the investigator and the subject keep one signed informed consent.

Investigator signature: _____
Date: _____month_____day_____year
Phone number: _____
Telephone of subject: _____

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