Informed Consent

Title: Toripalimab Plus Induction Chemotherapy Followed by Radiation Therapy Combined With Omega-3 for Locally Advanced Nasopharyngeal Carcinoma: A Phase II, Single Arm Clinical Trial

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Abbreviations of subjects:_____

Subject ID (SID):_____

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Notice Page Dear Patient (Subject):

Hello! Your doctor has confirmed the diagnosis of nasopharyngeal carcinoma. We are inviting you to participate in a Phase II single-arm clinical trial: A sequential radiotherapy combination therapy with trilaciclib plus induction chemotherapy and OMEGA-3 treatment for locally advanced nasopharyngeal carcinoma. The study will enroll a total of 30 participants. The protocol has been reviewed and approved by the Clinical Research Ethics Committee at Guangdong Medical University Affiliated Hospital for clinical implementation.

Before deciding to participate in this study, please read the following information carefully. It will help you understand the purpose of the research, its procedures and duration, as well as the potential benefits, risks, and discomforts you might experience. If needed, you may discuss with family members or friends, or consult a doctor for clarification to make an informed decision.

I. Research Background and Purpose

Nasopharyngeal carcinoma (NPC) is a malignant tumor originating from the nasopharyngeal mucosa, with a unique geographical distribution pattern, mainly affecting populations in southern China and Southeast Asia. At present, the standard treatment regimen for high-risk locally advanced nasopharyngeal carcinoma is induction chemotherapy followed by synchronous radiotherapy and chemotherapy. However, this treatment regimen has a high incidence of adverse reactions in patients, with a rate of about 15% -25%. Therefore, it is necessary to further explore treatment methods that increase efficacy and minimize toxic side effects on the basis of induction chemotherapy followed by synchronous radiotherapy and chemotherapy.

With the rise of immunotherapy, it has become the first-line treatment for advanced nasopharyngeal carcinoma, and there have been related explorations in locally advanced nasopharyngeal carcinoma. Programmed cell death receptor 1 (PD-1) inhibitor therapy has been proven to have significant efficacy in tumor immunotherapy. Multiple studies have confirmed that combining anti-PD-1 therapy with chemotherapy as a first-line treatment can significantly prolong the progression free survival (PFS) of nasopharyngeal carcinoma patients. Triprolizumab is a PD-1 inhibitor independently developed in China. Recently, a phase II clinical trial titled "Neoadjuvant and adjuvant toripalimab for locally advanced nasopharyngeal carcinoma: a randomized, single center, double blinded, placebo controlled, phase 2 trial" showed that the 2-year

progression free survival rate (92.0% [95% CI 86.7-97.3]) of the trastuzumab group was higher than that of the placebo group (74.0% [61.8-86.2]), confirming its effectiveness. Meanwhile, Omega-3 has clear anti-inflammatory and anti-tumor mechanisms, and some studies have shown that Omega-3 can alleviate adverse reactions of radiotherapy and chemotherapy and improve the efficacy of anti-tumor treatment. Based on this, this study proposes an innovative approach: to eliminate traditional synchronous chemotherapy in the treatment of high-risk locally advanced NPC, and instead use a combination of concurrent radiation therapy with trastuzumab, immunotherapy, and omega-3 to improve treatment efficacy and reduce adverse reactions.

This study will elucidate the efficacy and adverse reactions of the combination of Omega-3 and Triprolizumab in the treatment of locally advanced nasopharyngeal carcinoma with radiotherapy and chemotherapy.

II. Research Process

① Study Participants: Patients aged 18-65 years with locally advanced nasopharyngeal carcinoma (stage III-IVa, AJCC 8th edition) diagnosed at Guangdong Medical University Affiliated Hospital. According to the treatment protocol, participants will receive a regimen of teripril 240mg for 3 cycles combined with IMRT and OMEGA -3 (6 daily doses during radiotherapy).

② Research observation indicators: 1. Main study endpoint: 2-year PFS. 2. Secondary study endpoints: ORR, OS, adverse reactions, nutritional status analysis, quality of life analysis.

③ Statistical analysis: The research data were processed by statistical software SPSS 26.0. When the above collected data were analyzed by single-factor analysis, the continuous measurement data were expressed in the form of mean ± standard deviation.

For categorical data, t-tests are employed when the measurement data follows a normal distribution. Categorical data are statistically analyzed using Pearson's chi-square test or Fisher's exact test. Significant covariates with clinical importance should be controlled during grouping and adjusted in statistical analysis. All statistically significant risk factors undergo multivariate analysis using logistic regression. Survival analysis employs Kaplan-Neyman survival methods.
Meier method and log rank test; statistically significant when P value is less than 0.05.

If you agree to participate in this study, we will communicate with you in detail about the research and ask you to provide information related to your illness, including the course of the disease, family history, previous medical visits, and test results. Each participant will be assigned a number, and we will establish a medical record and conduct regular follow-up visits.

3. Who should not participate in the study

1. Patients with recurrent and distant metastatic nasopharyngeal carcinoma.
2. Pathology was keratinizing squamous cell carcinoma (WHO type I).
3. Patients who have undergone radiotherapy or systemic chemotherapy.
4. Pregnant or lactating women who are of childbearing age and do not use effective contraception.
5. HIV positive.

6. Had other malignancies (except cured basal cell carcinoma or cervical carcinoma in situ).

7. Patients who have received immunomodulatory inhibitors (CTLA-4, PD-1, PD-L1, etc.).

8. Patients with immunodeficiency diseases and history of organ transplantation.

9. Patients treated with high doses of glucocorticoids, anticancer monoclonal antibodies, or other immunosuppressants within 4 weeks.

10. Patients with significant impairment of heart, liver, lung, kidney and bone marrow function.

11. Other investigational drugs are being used or are currently under investigation in other clinical trials.

12. Refuse or be unable to sign an informed consent form for participation in the trial.

13. Persons with personality or mental illness, without civil capacity or with limited civil capacity.

14. Hepatitis B surface antigen (HBsAg) is positive and hepatitis B virus outer peripheral blood DNA (HBV DNA) is ≥1000cps/ml.

15. Patients with positive HCV antibody test results can only be included in this study when the polymerase chain reaction test of HCV RNA is negative.

16. Patients who had any serious bleeding event of grade 3 or higher according to CTCAE v5.0 within 4 weeks prior to screening, and who were judged by the investigator to be at high risk of bleeding.

17. Venous/arterial thrombosis events occurred within 6 months prior to the start of screening, such as cerebrovascular accident (including transient ischemic attack, cerebral hemorrhage, cerebral infarction), deep vein thrombosis and pulmonary embolism.

18. Patients with hypertension that cannot be reduced to normal range by antihypertensive drugs (systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥90mmHg; average value of BP readings based on ≥2 measurements), and previous occurrence of hypertensive crisis or hypertensive encephalopathy.

19. History or current inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, or chronic diarrhea); history of previous or current gastrointestinal perforation and/or fistula.

20. A history of active tuberculosis (TB) is known. Subjects suspected of having active TB require chest X-ray, sputum, and exclusion through clinical symptoms and signs.

21. Other serious, uncontrolled medical conditions and infections or other treatment contraindications, or any condition that the investigator considers to be likely to cause risks with study drug therapy, or interfere with the evaluation of study drugs or subject safety or interpretation of study results.

IV. What will be required if I participate in the study?

1. Before you are selected for the study, your doctor will ask and record your medical history and perform tests.

You are a qualified enrollees and may voluntarily participate in the study by signing an informed consent form.

If you do not wish to participate in the study, we will treat you as you wish.

2. Other matters requiring your cooperation

You must come to the hospital at the time of follow-up as agreed with your doctor, with your medical records, test results and examination results (during the follow-up stage, your doctor may call or visit you to learn about your condition). Your follow-up is very important because your doctor will judge whether the treatment you have received is really working and give you timely guidance.

You must take the medicine as directed by your doctor and fill out your medication record in a timely and objective manner. You must return any unused medication and its packaging at each follow-up visit, along with any other medications you are taking, including those you need to continue taking for any other medical conditions.

You should not use other medications for the treatment of locally advanced nasopharyngeal carcinoma during this study. If you need to receive other treatments, please contact your physician in advance.

V. Possible benefits of participation in the research

Personal Benefits: 1. Patients with nasopharyngeal carcinoma receiving the sequential radiotherapy regimen combining teriprilimab and induction chemotherapy demonstrate improved efficacy, enhanced prognosis, and elevated quality of life. 2. Participants receive enhanced monitoring and care from leading experts in the field and accredited medical institutions involved in this clinical trial. During enrollment, treatment, and follow-up phases, patients enjoy comprehensive support including hospitalization, diagnostic procedures, therapeutic interventions, and regular checkups. Any urgent medical emergencies require immediate attention to ensure prompt resolution.

Social benefits: This study protocol has better efficacy and less toxic side effects for high-risk locally advanced nasopharyngeal carcinoma, providing a new treatment plan for high-risk locally advanced nasopharyngeal carcinoma

VI. Alternatives

While existing evidence suggests that trilaciclib plus induction chemotherapy followed by radiotherapy combined with OMEGA-3 therapy demonstrates satisfactory

efficacy, this does not guarantee its effectiveness for your specific condition. The treatment protocol we employed – trilaciclib plus induction chemotherapy with radiotherapy and OMEGA-3 – is not the only option for treating locally advanced nasopharyngeal carcinoma. If this regimen proves ineffective, you may consult your physician about alternative treatment options such as combining trilaciclib with induction chemotherapy, radiotherapy, and maintenance therapy using trilaciclib.

Vii. Participate in the study of possible adverse reactions, risks and discomforts, inconveniences

If you experience any discomfort during the study, or new changes in your condition, or any accident

In any case, whether or not it is related to the study, you should inform your doctor in time, who will make a judgment and give appropriate medical treatment.

The following adverse reactions may occur:

1. Toripalimab Injection (240mg intravenous infusion, every 3 weeks): ① Anemia, elevated ALT, fatigue, increased AST, rash, fever, elevated thyroid-stimulating hormone (TSH), decreased white blood cell count, cough, itching, hypothyroidism, decreased appetite, elevated blood glucose and bilirubin levels, thrombocytopenia, elevated amylase and lipase levels, liver injury, and upper gastrointestinal bleeding. ②Immunosuppressive adverse reactions: Immune-related pneumonia, immune-related diarrhea and colitis, immune-related hepatitis, immune-related nephritis, immune-related myocarditis, immune-related myositis, and immune -related pancreatitis. ③Immunosuppressive endocrine disorders: Hyperthyroidism and hypothyroidism, hyperglycemia and type 1 diabetes, adrenal insufficiency, pituitary dysfunction, immune-related skin reactions, and immune-related neurological adverse reactions. ④Other immunosuppressive adverse reactions: Thrombocytopenia. ⑤Infusion reactions: Including fever, pulmonary edema, phlebitis, and air embolism

2. Omega-3 (Omega-3 soft capsules 6 capsules qd): ① Gastrointestinal adverse reactions: indigestion, nausea, vomiting, diarrhea, ② allergic reactions: ③ increased risk of bleeding ④ dyslipidemia

3. Albumin-bound paclitaxel: Hair loss, neutropenia, sensory neuropathy, ECG abnormalities, fatigue/weakness, muscle/joint pain, elevated AST levels, increased alkaline phosphatase, anemia, nausea, infections, and diarrhea. Infusion reactions: These include fever, pulmonary edema, phlebitis, and air embolism

4. cisplatin: ① Kidney toxicity ② Digestive system: including nausea, vomiting, loss of appetite and diarrhea. ③ Reduction of white blood cells and/or platelets ④ Ototoxicity. ⑤ Neurotoxicity ⑥ Allergic reactions ⑥ Plasma electrolyte disturbances: hypomagnesemia,

hypocalcemia, muscle spasms. ⑦ Cardiotoxicity ⑧ Immunosuppressive reactions. ⑧ Gum changes ⑨ The occurrence of secondary non-lymphocytic leukemia is associated with the use of cisplatin chemotherapy. ⑩ Vascular diseases

Changes, such as cerebral ischemia, coronary artery ischemia, peripheral vascular disorders similar to Ravnaud syndrome, have few side effects, but may be related to the use of cisplatin. @ Infusion reactions: infusion reactions include fever, pulmonary edema, phlebitis and air embolism

5. Intensity-modulated radiation therapy (IMRT): ① Oral mucositis ② Radiation dermatitis ③ Oral xerostomia ④ Taste impairment ⑤ Radiation-induced caries and radiation necrosis ⑥ Dysphagia ⑦ Subcutaneous tissue fibrosis ⑧ Endocrine dysfunction ⑨ Laryngeal edema ⑩ Brachial plexus neuropathy ⑪ Temporal lobe necrosis

In addition, you need to go to the hospital for follow-up and some tests on time during your study, which will take up some of your time and may cause you trouble or inconvenience.

VIII. Related costs

The study uses Toripalimab Injection, which must be self-funded by participants. Omega-3 Soft Capsules are provided by this clinical research program. The study has purchased Clinical Trial Liability Insurance, but does not cover damages caused by your failure to comply with this informed consent form, study protocol, or instructions from researchers during participation. Signing this informed consent does not deprive you of any legal rights. Treatment and examinations required for concurrent comorbidities will not be covered under the free scope.

9. Confidentiality of personal information

Your medical records (including research medical records/CRF, lab reports, etc.) will be fully preserved at the hospital where you received treatment. Your doctor will document all test results and examination findings in your medical file. Researchers, the ethics committee, and drug regulatory authorities will have access to your medical records. Any public disclosure or reporting of this study's results will not reveal your personal identity. We will make every effort to protect the privacy of your medical information within legal boundaries.

In accordance with medical research ethics, except for personal privacy information, the trial data will be available to the public for inquiry and sharing, which will only be limited to online electronic databases to ensure that no personal privacy information will be leaked.

How to get more information?

You may ask any questions about this research at any time and will be answered accordingly.

If there is any important new information in the course of the study that may affect your willingness to continue the study, your doctor will inform you in a timely manner.

11. You may voluntarily choose to participate in the study or withdraw from the study

Participation in the study is entirely at your discretion. You may refuse to participate in the study or withdraw from the study at any time during the study without affecting your relationship with your physician or the loss of your medical or other interests.

At the doctor's or investigator's discretion, you may be asked to discontinue your participation in this study at any time during the course of the study.

If you withdraw from the study for any reason, you may be asked about your use of the investigational drug. You may also be asked to undergo laboratory tests and physical examinations if the physician deems it necessary.

12. Whether it has been approved by the ethics committee

This study has been reviewed and approved by the Clinical Research Ethics Committee of Guangdong Medical University Affiliated Hospital. During the research process, you can contact the ethics committee for information about ethics and your rights and interests
Tel: 0759-2386971.

XIII. What should we do now?

It is up to you (and your family) to decide whether or not to participate in this study.

Ask your doctor as many questions as possible before you decide to participate in the study.

Thank you for reading this information. If you decide to participate in this study, please tell your doctor who will arrange all research-related matters for you. Please keep this information.

Informed consent form. Consent signature page

Name of clinical study: Toripalimab Plus Induction Chemotherapy Followed by Radiation Therapy Combined With Omega-3 for Locally Advanced Nasopharyngeal Carcinoma: A Phase II, Single Arm Clinical Trial

Project undertaking unit: Affiliated Hospital of Guangdong Medical University

Project Collaborating Unit:_____

Project task book number:_____

Statement of consent

I have read the above introduction to this study and had the opportunity to discuss the study with the doctor and ask questions. All the questions I asked were answered satisfactorily.

I understand the risks and benefits of participating in this study. I know that participation is voluntary, I confirm that I have had sufficient time to consider this and I understand that:

- I can consult my doctor for more information at any time.
- I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

I am also aware that if I withdraw from the study midway, especially due to the intervention or medication, it would be beneficial for the entire study if I inform the physician of my condition changes and complete the appropriate physical examination and physical and chemical tests.

If I need to take any other medication due to changes in my condition, I will consult my doctor in advance or tell him truthfully afterwards.

I agree that the national health administration, drug regulatory authorities, ethics committees or representatives of sponsors may review my research data.

I will receive a copy of an informed consent form signed and dated.

Finally, I have decided to participate in this study and promise to follow the doctor's advice as much as possible.

Patient (subject) Signature:_____ Date:： _____

Contact Number： _____

If the patient is unable to sign, a legal representative shall sign. The relationship between the patient and the legal representative shall be explained. If the patient is illiterate, a disinterested witness shall sign.

Signature of the patient (subject) legal representative (if applicable):_____

Relationship to the patient (subject):_____ Date:： _____

contact number： _____

Signature of witness (if applicable):_____ Date:： _____

contact number： _____

I confirm that the patient (subject) has been provided with a detailed explanation of the trial, including their rights and possible benefits and risks, and that a copy of the signed informed consent form has been provided to them.

Doctor ' s signature:_____ Date:： _____

Doctor ' s office number:_____

I have accurately informed the subject of this document and answered the questions raised by the subject. The subject expressed understanding of the research process and voluntary participation in the study. A full copy of the signed informed consent form will be provided to the subject for safekeeping.

Name of researcher (regular script):_____

Researcher's signature (signature):_____

contact number： _____

Date:： _____