Informed Consent Form

Protocol 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

ClinicalTrials.gov Identifier: NCT07136519

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Study Institution and Department: Department of Head and Neck Oncology, Affiliated Hospital of Guangdong Medical University

Principal Investigator: Haiqing Luo, Chief Physician / Professor

Investigator Contact Number: 13729196345

Participant Initials: _____
Participant Identification Number (SID): _____

Informed Consent Form - Participant Information Sheet
Dear Patient (Potential Study Participant):

Your doctor has diagnosed you with nasopharyngeal carcinoma. We invite you to take part in a study entitled "Toripalimab Plus Induction Chemotherapy Followed by Radiation Therapy Combined With Omega-3 for Locally Advanced Nasopharyngeal Carcinoma: A Phase II, Single-Arm Clinical Trial." A total of 30 participants will be enrolled. The study protocol has been reviewed by the Clinical Research Ethics Committee of the Affiliated Hospital of Guangdong Medical University, which has approved the clinical study.

Before deciding whether to take part, please read the following information as carefully as possible. It will help you understand this study, why it is being conducted, its procedures and duration, and the possible benefits, risks, and discomforts of participation. If you wish, you may discuss it with your family and friends or ask your doctor to explain it to help you make your decision.

1. Background and Purpose of the Study

Nasopharyngeal carcinoma (NPC) is a cancer that develops in the lining of the nasopharynx, the area behind the nose. It has a distinctive geographical distribution and mainly affects populations in southern China and Southeast Asia. The current standard treatment for locally advanced NPC is induction chemotherapy followed by concurrent chemoradiotherapy. However, this treatment can cause substantial side effects, and approximately 15%-25% of patients still experience a recurrence. Better treatments with fewer side effects therefore need to be explored, building on induction chemotherapy followed by concurrent chemoradiotherapy.

With the development of immunotherapy, it has become a first-line treatment for advanced NPC and has also been investigated in locally advanced NPC. Treatment with programmed cell death protein 1 (PD-1) inhibitors is a form of cancer immunotherapy that has demonstrated substantial efficacy. Several studies have shown that combining anti-PD-1 therapy with chemotherapy as first-line treatment can significantly extend progression-free survival (PFS), the time during which the cancer does not get worse, in patients with NPC. Toripalimab is a PD-1 inhibitor developed in China. A recent phase II clinical trial of toripalimab in locoregionally advanced NPC, entitled "Neoadjuvant and adjuvant toripalimab for locoregionally advanced nasopharyngeal carcinoma: a randomised, single-centre, double-blind, placebo-controlled, phase 2 trial," reported a higher 2-year PFS rate in the toripalimab group (92.0% [95% confidence interval, 86.7-97.3]) than in the placebo group (74.0% [61.8-86.2]), demonstrating its efficacy. Omega-3 also has established anti-inflammatory and antitumor mechanisms, and some studies have shown that it can reduce the side effects of chemoradiotherapy and improve the effectiveness of anticancer treatment. On this basis, the present study proposes a new approach: omitting conventional concurrent chemotherapy in locally advanced NPC and instead using radiotherapy with concurrent toripalimab, together with immunotherapy and Omega-3, to improve treatment outcomes and reduce side effects.

This study will evaluate the efficacy and adverse reactions of Omega-3 and toripalimab combined with chemoradiotherapy for locally advanced NPC.

2. Study Procedures

Patients with nasopharyngeal carcinoma
Any T N2-3 M0 or T4 N1 M0 (AJCC 8th edition/UICC staging), or any T N2-3 M0 or T4 N1 M0 (AJCC 9th edition/UICC staging)

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Registration, screening, and signing of informed consent (n = 30)

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1. Induction treatment: toripalimab 240 mg on day 1 + albumin-bound paclitaxel 260 mg/m² on day 1 + cisplatin 80 mg/m² on day 2, every 3 weeks for 3 cycles.
2. Radiotherapy: IMRT + toripalimab 240 mg every 3 weeks for 3 cycles + Omega-3, 6 capsules once daily during radiotherapy. IMRT: GTVnx 69.96 Gy; GTVnd 69.96 Gy; CTV1 60 Gy; CTV2 54 Gy.
3. Maintenance treatment: toripalimab 240 mg every 3 weeks for 6 cycles.

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Short-term efficacy, lipid and fatty acid profile, inflammatory status, acute toxicity, nutritional status, and quality of life assessments

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Follow-up, lipid and fatty acid profile, inflammatory status, late toxicity, nutritional status, and quality of life assessments

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Analysis, summary, and publication of the final report and articles

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Propose a new clinical treatment approach for locally advanced nasopharyngeal carcinoma

3. Who Can Take Part in the Study?

1. Age 18-70 years on the date of signing the informed consent form.

2. A pathological diagnosis of nonkeratinizing nasopharyngeal carcinoma, either differentiated or undifferentiated (WHO type II or III).

3. Clinical stage any T N2-3 M0 or T4 N1 M0 according to the AJCC 8th edition/UICC staging system, or any T N2-3 M0 or T4 N1 M0 according to the AJCC 9th edition/UICC staging system.

4. An Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.

5. Hemoglobin (HGB) ≥90 g/L, white blood cell count (WBC) ≥4.0 × 10^9/L, and platelet count (PLT) ≥100 × 10^9/L.

6. Liver function: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 times the upper limit of normal (ULN), and total bilirubin ≤1.5 times ULN.

7. Kidney function: calculated creatinine clearance (CrCl) ≥60 mL/min, using the Cockcroft-Gault formula.

8. Thyroid-stimulating hormone (TSH) ≤1 times ULN. If TSH is abnormal, free triiodothyronine (FT3) and free thyroxine (FT4) must also be assessed; enrollment is permitted if FT3 and FT4 are normal.

9. International normalized ratio (INR) and activated partial thromboplastin time (APTT) ≤1.5 times ULN, unless the participant is receiving anticoagulant treatment and the coagulation parameters (PT/INR and APTT) at screening are within the expected range for that treatment.

4. Who Should Not Take Part in the Study?

1. Patients with recurrent NPC or distant metastases.

2. Patients with a pathological diagnosis of keratinizing squamous cell carcinoma (WHO type I).

3. Patients who have previously received radiotherapy or systemic chemotherapy.

4. Pregnant or breastfeeding women, or people of reproductive potential who are not using effective contraception.

5. Patients who are HIV-positive.

6. Patients previously treated with immune checkpoint inhibitors, such as CTLA-4, PD-1, or PD-L1 inhibitors.

7. Patients with an immunodeficiency disorder or a history of organ transplantation.

8. Patients who have received high-dose glucocorticoids, anticancer monoclonal antibodies, or other immunosuppressants within the past 4 weeks.

9. Patients with markedly impaired heart, liver, lung, kidney, or bone marrow function.

10. Patients who refuse or are unable to sign the informed consent form for participation in the trial.

11. Patients with a personality disorder or mental illness, or those with no or limited legal capacity for civil acts.

12. Patients who are positive for hepatitis B surface antigen (HBsAg) and have peripheral blood hepatitis B virus DNA (HBV DNA) ≥1,000 copies/mL.

13. Patients who test positive for hepatitis C virus (HCV) antibodies may be enrolled only if the HCV RNA polymerase chain reaction test is negative.

14. Patients with a known history of active pulmonary tuberculosis (TB). For participants suspected of having active TB, chest X-ray, sputum testing, and clinical signs and symptoms must be assessed to exclude active TB.

15. Patients with other severe, uncontrolled medical conditions or infections, other contraindications to treatment, or any other condition that, in the investigator's opinion, could make treatment with the study drug risky or interfere with evaluation of the study drug, participant safety, or interpretation of the study results.

5. What Will I Need to Do If I Take Part?

1. Before you are enrolled, your doctor will ask about and record your medical history and perform a complete physical examination. This will include assessments of: (1) the head, eyes, ears, nose, and throat; (2) the cardiovascular system; (3) the skin; (4) the musculoskeletal system; (5) the respiratory system; (6) the gastrointestinal system; and (7) the nervous system, as well as relevant imaging and laboratory tests.

If you meet the eligibility criteria, you may choose to take part and sign the informed consent form.

If you do not wish to take part, we will provide treatment in accordance with your wishes.

2. If you voluntarily agree to take part, the study will proceed as follows:

The study requires a total of 30 participants. As the lead center, our hospital will enroll 30 participants who meet the screening criteria.

Enrolled patients will receive induction treatment with TP plus toripalimab: albumin-bound paclitaxel 260 mg/m² on day 1, cisplatin 80 mg/m² on day 2, and toripalimab 240 mg on day 1, once every 3 weeks for 3 cycles. This will be followed by radiotherapy with concurrent immunotherapy and Omega-3: Omega-3, 6 capsules once daily during radiotherapy, plus toripalimab 240 mg once every 3 weeks during radiotherapy for 3 cycles. Patients will then receive maintenance treatment with toripalimab 240 mg once every 3 weeks for 6 cycles.

During the observation period, your doctor will collect all information relevant to assessing treatment effectiveness and adverse reactions. This will provide a scientific basis for the final evaluation of the efficacy and safety of the study regimen. Efficacy and safety will be assessed immediately after treatment ends. Assessments will include a complete blood count, blood biochemistry, quantitative blood Epstein-Barr virus (EBV) DNA testing, thyroid function tests, lipid and fatty acid profile testing, electronic nasopharyngoscopy, contrast-enhanced MRI of the nasopharynx and neck, chest CT, and abdominal ultrasound or abdominal CT. Clinically significant abnormalities will be followed up and retested until they return to normal. A short-term follow-up assessment will be conducted 3 months after treatment ends. For long-term follow-up, you will be assessed every 3 months during the first 2 years after treatment and every 6 months thereafter. Follow-up will involve recording information from hospital return visits or using correspondence or telephone follow-up documented and signed by the treating doctor. These assessments will evaluate treatment efficacy, recovery from toxicities, and short- and long-term toxicities. Follow-up assessments will follow the disease-specific diagnosis and treatment standards. This study is expected to last 4 years.

3. Other Matters Requiring Your Cooperation

You must attend hospital visits at the times agreed with your doctor and bring your medical records, personal treatment diary card, and related materials. During follow-up, your doctor may also contact you by telephone or visit you at home to ask about your condition. Follow-up is very important because it helps your doctor determine whether the treatment is working and provide timely guidance.

You must take your medication as instructed by your doctor and complete your medication record promptly and accurately. At each follow-up visit, you must return any unused medication and its packaging. Please also bring any other medicines you are taking, including medicines that you need to continue for other medical conditions.

During the study, you must not use other medicines to treat NPC. If you need any other treatment, please contact your doctor beforehand. Prohibited concomitant medicines include the following:

1. Immunosuppressants, such as cyclosporine, tacrolimus, and sirolimus. These may interfere with the effects of toripalimab on the immune system, affect assessment of treatment efficacy, and increase the risk of adverse reactions such as infections.

2. Live vaccines. These must not be used during toripalimab treatment or for at least 30 days after stopping treatment. Toripalimab may affect the immune system's response to live vaccines, prevent effective immune protection, and increase the risk of vaccine-related adverse reactions.

3. Steroid medicines. Systemic glucocorticoids and other steroids should be avoided before immunotherapy because they may interfere with the pharmacodynamic activity and efficacy of toripalimab. However, they may be used during treatment to manage immune-related adverse reactions.

4. Traditional Chinese medicines. These contain complex ingredients; the efficacy and side effects of most have not been verified in clinical trials, and their interactions with toripalimab are unclear. Concurrent use of traditional Chinese medicines during immunotherapy is therefore generally not recommended.

Study treatment may be discontinued for reasons including, but not limited to, the following:

1. If a participant develops a serious adverse event or intolerable toxicity during the study, study participation may be stopped and the participant may be withdrawn with the approval of the principal investigator (PI).

2. If at least half of the participants develop intolerable toxicity, or if serious adverse events occur consecutively, the PI may propose early termination of the trial.

3. Disease progression during treatment.

4. Pregnancy during the study.

Participation in the study may end for reasons including, but not limited to, the following:

1. Withdrawal of informed consent.

2. Death.

3. Loss to follow-up.

4. Completion of all study assessments.

6. Possible Benefits of Taking Part

1. By taking part, you will have the opportunity to receive a PD-1 monoclonal antibody and Omega-3, which may improve treatment outcomes and reduce adverse reactions in high-risk locally advanced NPC.
2. You will receive closer attention and observation from the study doctors. Clinical trials are generally conducted by experienced experts and hospitals in the relevant field. During participation, patients may receive closer care and attention during hospitalization, examinations, treatment, and follow-up, and urgent problems can be addressed promptly. However, as with any treatment, we cannot guarantee that you will obtain a satisfactory result by taking part. Your disease may not improve with the treatments currently available.

7. Alternative Treatments

The treatment used in this study - toripalimab plus induction chemotherapy followed by radiotherapy and Omega-3 - is not the only treatment for locally advanced NPC. If this treatment is not effective for your condition, you may ask your doctor about available alternatives, such as toripalimab plus induction chemotherapy followed by radiotherapy in combination with maintenance toripalimab treatment.

8. Possible Adverse Reactions, Risks, Discomforts, and Inconveniences

If you experience any discomfort, any new change in your condition, or any unexpected event during the study, please notify your doctor promptly, whether or not it is related to the study. Your doctor will assess it and provide appropriate medical care.

Possible adverse reactions include the following:

1. Toripalimab injection: fever, upper respiratory tract infection, decreased platelet count, infusion reactions, fatigue, rash, diarrhea, abdominal pain, nephritis, pneumonitis, myocarditis, pancreatitis, eye toxicity, bone and joint disorders, thyroid dysfunction, nerve damage, and liver injury. You may experience these or similar side effects, as well as unknown side effects that have not previously been reported. The medical team will make every effort to actively treat any adverse reactions.

2. Omega-3: indigestion, nausea, vomiting, and diarrhea.

3. Albumin-bound paclitaxel: hair loss, neutropenia, peripheral neurotoxicity, abnormal electrocardiogram findings, fatigue or weakness, muscle or joint pain, increased AST, increased alkaline phosphatase, anemia, nausea, infection, diarrhea, infusion reactions, pulmonary edema, phlebitis, and air embolism.

4. Cisplatin: kidney toxicity, nausea, vomiting, decreased appetite, diarrhea, decreased white blood cell and/or platelet counts, hearing toxicity, neurotoxicity, allergic reactions, low magnesium levels, low calcium levels, muscle spasms, heart toxicity, immunosuppression, infusion reactions, pulmonary edema, phlebitis, and air embolism.

5. Intensity-modulated radiotherapy (IMRT): oral mucositis, radiation dermatitis, dry mouth, taste disturbances, radiation-related tooth decay, osteoradionecrosis, difficulty swallowing, fibrosis of the tissue beneath the skin, endocrine dysfunction, swelling of the larynx, brachial plexus neuropathy, temporal lobe necrosis, nasopharyngeal necrosis, and decreased vision.

For adverse reactions caused by chemotherapy and Omega-3, the study team will provide appropriate supportive treatment, such as treatment to increase white blood cell or platelet counts, anti-infective

treatment, fluid replacement, and medicines for vomiting or diarrhea. For adverse reactions caused by radiotherapy, the study team will provide appropriate symptomatic treatment, such as anti-inflammatory treatment, pain relief, nebulization therapy, and local care of the mucous membranes and skin.

If you experience any discomfort, any new change in your condition, or any unexpected event during the study, please notify your doctor promptly, whether or not it is related to the study. Your doctor will assess it and provide appropriate medical care.

During the study, you will need to attend hospital follow-up visits and undergo tests at the scheduled times. These will take some of your time and may cause inconvenience.

9. Costs

Participants must pay for the toripalimab injection used in this study. Omega-3 will be provided free of charge by this clinical research project. Clinical trial liability insurance has been purchased for this study. If you suffer a study-related injury as a result of participation while following the study doctor's instructions, you will receive the necessary medical treatment. The investigator has arranged liability insurance for this study. For trial-related injury, the investigator will also bear the related treatment costs and provide corresponding financial compensation, except where the injury is caused by medical malpractice. This coverage does not include injury caused by failure to follow this informed consent form, the protocol, or instructions given by study personnel during your participation. Signing this form does not waive any of your legal rights. Treatment and examination costs for other coexisting diseases are not covered for reimbursement.

10. Confidentiality of Personal Information

Your complete medical records, including study medical records/case report forms (CRFs) and laboratory reports, will be kept at the hospital where you receive care. Your doctor will record laboratory and other test results in your medical records. Investigators, the ethics committee, and drug regulatory authorities will be permitted to review these records. No public report of the study results will disclose your identity. We will make every effort to protect the confidentiality of your personal medical information to the extent permitted by law.

In accordance with medical research ethics, trial data, excluding personally identifying information, will be available for public access and sharing. Such access and sharing will be limited to web-based electronic databases, with safeguards to ensure that no private personal information is disclosed.

11. How Can I Obtain More Information?

You may ask questions about this study at any time and receive answers.

If important new information becomes available during the study that may affect your willingness to continue, your doctor will inform you promptly.

12. Voluntary Participation and Withdrawal

Taking part in this study is entirely voluntary. You may refuse to take part or withdraw at any time. This will not affect your relationship with your doctor or your medical care, or result in the loss of other benefits.

Your doctor or the investigator may discontinue your participation at any time during the study if this is considered to be in your best interests.

If you withdraw for any reason, you may be asked about your use of the study medication. You may also be asked to undergo laboratory tests and a physical examination if your doctor considers them necessary.

13. Has the Study Been Approved by an Ethics Committee?

This study has been reviewed and approved by the Clinical Research Ethics Committee of the Affiliated Hospital of Guangdong Medical University. If you have questions about ethics or your rights during the study, you may contact the ethics committee by telephone: 0759-2386971.

14. What Should I Do Now?

The decision about whether to take part is yours, in consultation with your family if you wish.

Before deciding to take part, please ask your doctor any questions you may have.

Thank you for reading this information. If you decide to take part, please tell your doctor, who will make the necessary study arrangements for you. Please keep this information sheet.

Informed Consent Form - Consent and Signature Page

Clinical Study 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
Lead Institution: Affiliated Hospital of Guangdong Medical University

Collaborating Institution: The Second Affiliated Hospital of Guangdong Medical University

Statement of Consent

I have read the information above about this study and have had the opportunity to discuss it with the doctor and ask questions. All my questions have been answered to my satisfaction.

I understand the possible risks and benefits of taking part. I know that participation is voluntary, and I confirm that I have had sufficient time to consider it. I understand that:

• I may ask the doctor for more information at any time.

• I may withdraw from the study at any time without discrimination or retaliation, and my medical care and rights will not be affected.

I also understand that, if I withdraw, particularly because of the study intervention or medication, informing the doctor of changes in my condition and completing the relevant physical examinations and laboratory tests would be very helpful to the study.

If a change in my condition requires treatment with any other medicine, I will seek the doctor's advice beforehand or truthfully inform the doctor afterward.

I agree that national health authorities, drug regulatory authorities, the ethics committee, or representatives of the sponsor may review my study records.

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

I agree to take part in this study and will make every effort to follow the doctor's instructions.

Patient (Participant) Signature: _____
Date (YYYY-MM-DD): _____

Contact Telephone Number: _____

If the patient cannot sign, a legally authorized representative must sign. The relationship between the patient and the legally authorized representative must be stated. If the patient cannot read or write, an impartial witness must sign.

Signature of the Patient's (Participant's) Legally Authorized Representative (if applicable):

_____

Relationship to the Patient (Participant): _____
Date (YYYY-MM-DD): _____

Contact Telephone Number: _____

Witness Signature (if applicable): _____
Date (YYYY-MM-DD): _____

Contact Telephone Number: _____

I confirm that I have explained the details of this trial to the patient (participant), including their rights and the possible benefits and risks, and have given them a signed copy of the informed consent form.

Doctor's Signature: _____
Date (YYYY-MM-DD): _____

Doctor's Work Telephone Number: _____

I have accurately explained this document to the participant and answered their questions. The participant has indicated that they understand the study procedures and are taking part voluntarily. A fully signed copy of the informed consent form will be given to the participant to keep.

Investigator's Name (Print): _____

Investigator's Signature: _____

Contact Telephone Number: _____

Date (YYYY-MM-DD): _____