Clinical Research Project
Affiliated Hospital of Guangdong Medical University

Study Protocol

Official Title (translated from Chinese)	Toripalimab Plus Induction Chemotherapy Followed by Radiation Therapy Combined With Omega-3 for Locally Advanced Nasopharyngeal Carcinoma: A Phase II, Single Arm Clinical Trial
Official Title (English)	Toripalimab Plus Induction Chemotherapy Followed by Radiation Therapy Combined With Omega-3 for Locally Advanced Nasopharyngeal Carcinoma: A Phase II, Single Arm Clinical Trial
Research Institution	Affiliated Hospital of Guangdong Medical University
Study Lead	Haiqing Luo
Version Number	2.0
Version Date	March 2, 2026
Study Period	June 2025 to December 2029
ClinicalTrials.gov Identifier	NCT07136519

Study Protocol Synopsis

Project 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		
Principal Investigator	Haiqing Luo	Contact Information	13590386289
Funding Source	Self-funded	Funding Received (×10,000)	None
Synopsis			
Study Design Type	Observational study		
Study Centers	Multicenter		
Randomization	None		
Blinding	None		
Study Type	Superiority		
Study Objectives	1. Primary objective: To determine the 2-year progression-free survival (2-year PFS) rate with toripalimab plus induction chemotherapy followed by radiation therapy combined with omega-3 for locally advanced nasopharyngeal carcinoma. 2. Secondary objectives: To evaluate the objective response rate (ORR), lipid and fatty acid profile, inflammatory factors, adverse reactions, nutritional status, and quality of life with toripalimab plus induction chemotherapy followed by radiation therapy plus omega-3 for locally advanced nasopharyngeal carcinoma.		
Study Endpoints / Observational Endpoints	1. Primary endpoint: 2-year PFS. 2. Secondary endpoints: ORR, lipid and fatty acid profile, inflammatory factors, adverse reactions, nutritional status, and quality of life.		
Study Population	Patients aged 18-70 years hospitalized at the Affiliated Hospital of Guangdong Medical University between 2025 and 2026 who have pathologically diagnosed, locally advanced nasopharyngeal carcinoma classified as 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).		
Diagnostic Criteria	Pathologically diagnosed nasopharyngeal carcinoma classified as 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).		
Inclusion Criteria	1. Aged 18-70 years on the date of signing the informed consent form. 2. Pathologically diagnosed nonkeratinizing carcinoma of the nasopharynx (differentiated or undifferentiated, corresponding to WHO type II or III). 3. Clinical stage of 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). 4. 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: ALT and AST ≤2.5 times the upper limit of normal (ULN), and total bilirubin ≤1.5 times ULN. 7. Renal function: Calculated creatinine clearance (CrCl) ≥60 mL/min, using the Cockcroft-Gault formula. 8. Thyroid-stimulating hormone (TSH) ≤1 × ULN. If abnormal, FT3 and FT4 levels should also be assessed; patients may be enrolled if FT3 and FT4 levels are normal.		

	9. International normalized ratio (INR) and activated partial thromboplastin time (APTT) ≤1.5 × ULN, unless the participant is receiving anticoagulant therapy and coagulation parameters (PT/INR and APTT) at screening are within the expected range for that therapy.
Exclusion Criteria	1. Recurrent or distantly metastatic nasopharyngeal carcinoma. 2. Histologically confirmed keratinizing squamous cell carcinoma (WHO type I). 3. Previous radiotherapy or systemic chemotherapy. 4. Pregnancy or breastfeeding, or being of childbearing potential without using effective contraception. 5. HIV positivity. 6. Previous treatment with immune checkpoint inhibitors, such as CTLA-4, PD-1, or PD-L1 inhibitors. 7. Immunodeficiency disease or a history of organ transplantation. 8. Treatment with high-dose glucocorticoids, anticancer monoclonal antibodies, or other immunosuppressants within the preceding 4 weeks. 9. Markedly impaired cardiac, hepatic, pulmonary, renal, or bone marrow function. 10. Refusal or inability to sign the informed consent form for participation in the trial. 11. A personality disorder or psychiatric illness, or lack of or limited capacity for civil conduct. 12. Hepatitis B surface antigen (HBsAg) positivity with peripheral blood hepatitis B virus DNA (HBV DNA) ≥1,000 copies/mL. 13. Patients testing positive for HCV antibodies may be enrolled only if the HCV RNA polymerase chain reaction test is negative. 14. A known history of active pulmonary tuberculosis (TB). In participants with suspected active TB, chest X-ray, sputum testing, and clinical signs and symptoms must be assessed to rule out active TB. 15. Other serious, uncontrolled medical illnesses or infections, other contraindications to treatment, or any other condition that the investigator considers may pose a risk from treatment with the study drug, interfere with evaluation of the study drug or participant safety, or interfere with interpretation of the study results.
Withdrawal Criteria	1. Radiographic disease progression assessed according to RECIST v1.1; 2. Withdrawal of consent by the patient; 3. Any medical condition that, in the investigator's judgment, could compromise the patient's safety if study treatment were continued; 4. Concomitant use of any antitumor treatment, including chemotherapy, hormonal therapy, immunotherapy, or treatment with standard or investigational anticancer agents (including Chinese herbal medicines and proprietary Chinese medicines); 5. Poor patient adherence;
Sample Size	To increase 2-year PFS from 71% to 96%, the sample size calculated using a Z test in PASS 15, with $\alpha = 0.05$ (two-sided) and $\beta = 0.10$, is 24 patients. Allowing for a 20% dropout rate, at least 30 patients must be enrolled.

Tests for One Proportion

Numeric Results for Testing One Proportion using the Z-Test with S(P0)
Alternative Hypothesis: Two-Sided (H0: P = P0 vs. H1: P ≠ P0)

Power*	n	Proportion Given H0 P0	Proportion Given H1 P1	Difference P1-P0	Target Alpha	Actual Alpha*	Reject H0 If |Z| >
0.93071	24	0.7100	0.9600	0.2500	0.0500	0.0395	1.9600

* Power and actual alpha were computed using binomial enumeration of all possible outcomes.

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Report Definitions
Power is the probability of rejecting the null hypothesis when it is false. It should be close to one.
n is the size of the sample drawn from the population. To conserve resources, it should be as small as possible.
P0 is the value of the population proportion under the null hypothesis.
P1 is the value of the population proportion under the alternative hypothesis.
P1-P0 is the difference to be detected by the study.
Alpha (significance level) is the probability of rejecting the null hypothesis when it is true. It should be small.
Target Alpha is the significance level that the study design is meant to achieve.
Actual Alpha is the significance level that is actually achieved by the design.
Reject H0 If... gives the critical value(s) for the test.

Summary Statements
A sample size of 24 achieves 93.071% power to detect a difference (P1-P0) of 0.2500 using a two-sided Z-test that uses S(P0) to estimate the standard deviation with a target significance level of 0.0500. The actual significance level achieved by this test is 0.0395. These results assume that the population proportion under the null hypothesis (P0) is 0.7100.

Dropout-Inflated Sample Size

Dropout Rate	Sample Size n	Dropout-Inflated Enrollment Sample Size n'	Expected Number of Dropouts D
20%	24	30	6

Study Interventions	Interventions in this study: ① Induction treatment: Toripalimab 240 mg on day 1 + paclitaxel (albumin-bound) 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, and CTV2 54 Gy. ③ Maintenance treatment: Toripalimab 240 mg every 3 weeks for 6 cycles.
Assessment Measures	2-year PFS, ORR, lipid and fatty acid profile, inflammatory factors, adverse reactions, nutritional status, and quality of life.
Follow-up	1. During treatment: Close clinical observation will be performed after the study protocol is initiated. The occurrence and severity of adverse events and adverse reactions will be assessed weekly according to NCI CTCAE version 5.0. Complete blood count and blood biochemistry will each be monitored every 3 weeks. Concomitant medications and adverse events, including adverse events associated with intravenous medications and chemoradiotherapy, must also be recorded during the clinical study. 2. Efficacy and safety will be assessed immediately after treatment ends. Assessments will include complete blood count, blood biochemistry, quantitative blood Epstein-Barr virus DNA, thyroid function, lipid and fatty acid profile, inflammatory factors, electronic nasopharyngoscopy, contrast-enhanced MRI of the nasopharynx and neck, chest CT, and abdominal ultrasonography or abdominal CT. Clinically

	significant abnormalities must be followed up and retested until they normalize. Short-term follow-up assessment will be performed 3 months after the end of treatment. Long-term follow-up will be performed every 3 months during the first 2 years after treatment and every 6 months thereafter. Follow-up will use records of patients' return visits to the hospital, or correspondence or telephone follow-up signed by the treating physician, to assess treatment efficacy, recovery from toxicity, and short- and long-term toxicities.
Statistical Analysis	Study data will be processed using SPSS 26.0 statistical software. In univariate analyses of the data collected as described above, continuous data will be expressed as mean ± standard deviation, and categorical data as proportions. A t test will be used for normally distributed continuous data; Pearson's chi-square test or Fisher's exact test will be used for categorical data. Clinically important covariates will be controlled during group assignment and adjusted for in statistical analyses. All statistically significant risk factors will be included in multivariable logistic regression analysis. Survival outcomes will be analyzed using the Kaplan-Meier method and the log-rank test. A P value <0.05 will be considered statistically significant.
Expected Research Outputs	1. Publication of one article in an SCI-indexed journal. 2. Training of one graduate student.

1. Rationale

1.1 Significance of the Study

Nasopharyngeal carcinoma (NPC) is a malignancy arising from the nasopharyngeal mucosa. It has a distinctive geographic distribution and primarily affects populations in southern China and Southeast Asia [1]. Under the World Health Organization classification system, NPC is divided into three histological subtypes: keratinizing carcinoma, nonkeratinizing carcinoma, and basaloid squamous cell carcinoma. Nonkeratinizing NPC is further subdivided into differentiated and undifferentiated carcinoma [2]. Notably, in endemic regions, more than 95% of NPC cases are of the nonkeratinizing undifferentiated subtype, whose aggressive biological behavior makes patients more susceptible to distant metastasis [3]. In addition, the carcinogenesis of nonkeratinizing undifferentiated NPC is closely associated with chronic latent Epstein-Barr virus (EBV) infection [4].

Because of the concealed anatomical location of the nasopharynx and the radiosensitivity of NPC, radiotherapy is the cornerstone of treatment for nonmetastatic NPC. The advent of intensity-modulated radiotherapy (IMRT) has transformed radiotherapy for NPC, enabling more precise targeting of tumors while reducing effects on adjacent tissues. In patients with early-stage NPC treated with IMRT alone, both the 5-year locoregional recurrence-free survival (LRFS) rate and the distant metastasis-free survival (DMFS) rate exceed 95% [5].

However, in patients with locally advanced NPC, the adverse features of the prevalent undifferentiated histological subtype and the advanced stage at presentation increase the risk of treatment failure. The 5-year overall survival (OS) rate in NPC patients receiving local radiotherapy alone is below 50% [6, 7]. Furthermore, as advances in diagnostic and radiotherapy techniques have greatly improved local control, distant metastasis has become the leading cause of treatment failure [8]. In recent years, extensive research has focused on combining systemic chemotherapy with radiotherapy to improve survival in patients with advanced NPC. The use of concurrent chemoradiotherapy (CCRT) combined with induction chemotherapy (IC) or adjuvant chemotherapy (AC) has also substantially improved clinical outcomes.

NPC tissues exhibit distinctive immunological features, including dense stromal immune infiltration [9], an immunosuppressive phenotype [10], and high expression of programmed death-ligand 1 (PD-L1) [11]. These features suggest that immune checkpoint inhibition may be a promising therapeutic strategy for NPC.

Three phase III clinical trials have demonstrated that adding PD-1 inhibitors to gemcitabine plus cisplatin (GP) chemotherapy as first-line treatment significantly prolongs PFS in patients with recurrent or metastatic (R/M) NPC [12-14]. PD-1 inhibitors combined with chemoradiotherapy are currently being investigated for locally advanced NPC. Several phase II trials have shown promising response rates, survival outcomes, or both when anti-PD-1 or anti-PD-L1 inhibitors are added during IC, AC, IC plus AC, or throughout treatment (objective response rates of 88.9%-94.4% and 2-year PFS rates of 69.6%-91.8%) [15-18]. To date, only one large phase III clinical trial with published data has investigated the efficacy of PD-1 inhibition in locally advanced NPC. Its results showed that adding sintilimab during GP induction chemotherapy and CCRT, and as adjuvant treatment, significantly reduced the risk of recurrence or death in high-risk patients and improved 3-year event-free survival by 10% [19]. The sintilimab group also showed significantly reduced risks of distant metastasis and locoregional recurrence (3-year DMFS, 90.3% vs. 82.8%; HR 0.57 [95% CI 0.33-0.98], p = 0.039; 3-year locoregional failure-free survival [LR-FFS], 93.4% vs. 86.8%; HR 0.52 [95% CI 0.27-0.97], p = 0.038). Notably, there was no significant difference in quality of life

between the two groups. These findings suggest that PD-1 inhibition plus chemoradiotherapy may become a new standard treatment for patients with high-risk, locally advanced NPC. Ongoing trials are also evaluating the efficacy and safety of various immune checkpoint inhibitors combined with chemoradiotherapy during the induction or adjuvant phase, or as replacements for conventional chemotherapy, in patients with locally advanced NPC. Their findings may improve current understanding of the optimal sequencing and regimens for combining immunotherapy with chemoradiotherapy in NPC management.

Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids that cannot be synthesized by the human body and are abundant in vegetable oils and fish fats. Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are important omega-3 PUFAs and are also the most extensively studied. Omega-3 PUFAs have roles in preventing cardiovascular disease, regulating inflammation, and improving nutritional status [20]. Mocellin and colleagues showed that omega-3 PUFAs can increase plasma albumin and prealbumin levels in patients with gastric cancer [21][21]. A study by Ma showed that omega-3 PUFAs can reduce CRP levels and shorten the duration of systemic inflammatory response syndrome (SIRS) [22]. A meta-analysis showed that omega-3 PUFAs can improve nutritional status after gastric cancer resection and reduce inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) [23]. In a similar trial, well-tolerated omega-3 fatty acid-enriched formulas with different omega-3/omega-6 ratios improved serum protein concentrations in hospitalized patients after head and neck cancer surgery [24]. A recent study of 37 patients after head and neck cancer surgery who consumed two to three cans of an omega-3 fatty acid- and arginine-enriched supplement daily for 12 weeks showed improvements in albumin, prealbumin, transferrin, and lymphocyte levels in the enriched-supplement group [25]. Similar benefits of formulas containing omega-3 fatty acids have also been observed in patients with head and neck or esophageal cancer receiving radiochemotherapy (RCT). A randomized controlled trial involving 37 patients tested the effects of immunonutrition comprising a diet enriched with arginine, omega-3 fatty acids, and nucleotides. The results showed significant increases in total body weight, serum albumin, and plasma antioxidant capacity in the enteral nutrition group. Functional capacity, measured by WHO performance status and the Karnofsky index, remained unchanged in the immunonutrition group but declined markedly in patients receiving standard enteral nutrition [26]. In 31 patients with nonmetastatic stage III or IV head and neck squamous cell carcinoma receiving chemoradiotherapy, another oral supplement containing amino acids, omega-3 fatty acids, ribonucleic acid, vitamins, and antioxidants was less effective in improving the proinflammatory, proangiogenic, and pro-oxidative state [27].

Early enteral nutrition containing high levels of omega-3 fatty acids can effectively reduce platelet aggregation, coagulation activity, and cytokine production. Clinically, this was manifested by reduced body temperature and significant reductions in biochemical markers such as plasma IL-8, confirming the anti-inflammatory effects of omega-3 fatty acids [28]. These responses improved when RNA and arginine were added to the formula [29]. A recent trial further examined the anti-inflammatory effects of omega-3 fatty acids in 60 patients with esophageal cancer. In the omega-3 fatty acid supplementation group, inflammation and immune function improved after surgery. Serum procalcitonin levels were significantly lower and the CD4+/CD8+ ratio significantly higher on postoperative day 6 in the omega-3 fatty acid group, but no significant differences were observed on postoperative days 1 and 3 [30]. In general, these formulas containing omega-3 fatty acids can be used safely in patients with sepsis, but there is insufficient evidence to recommend routine immunonutrition in patients undergoing esophageal cancer surgery [31]. A phase III double-blind trial of an immunomodulating nutritional formula during adjuvant chemoradiotherapy

in patients with head and neck cancer found no significant survival improvement in the formula group in the intention-to-treat (ITT) analysis 3 years after postoperative adjuvant chemoradiotherapy. However, among patients with adherence ≥75%, the immunomodulating formula group showed significantly improved 3-year OS and 3-year PFS compared with the control group ($P < 0.05$) [32].

The current standard treatment regimen for high-risk, locally advanced NPC is induction chemotherapy followed by concurrent chemoradiotherapy and then adjuvant chemotherapy. However, this regimen causes substantial adverse reactions, and some patients still experience recurrence or metastasis. With the emergence of immunotherapy, it has become a first-line treatment for advanced NPC and has also been investigated in high-risk, locally advanced NPC. Omega-3 has established anti-inflammatory and antitumor mechanisms, and some studies have shown that it can reduce adverse reactions to chemoradiotherapy and improve the efficacy of antitumor treatment. The innovation of this study is to omit concurrent chemotherapy during the concurrent chemoradiotherapy phase for high-risk, locally advanced NPC and to use concurrent immunotherapy and omega-3 instead, with the aim of improving treatment efficacy and reducing adverse reactions.

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2. Study Content

2.1 Study Objectives

Primary objective: To determine the 2-year progression-free survival (2-year PFS) rate with toripalimab plus induction chemotherapy followed by radiation therapy combined with omega-3 for locally advanced nasopharyngeal carcinoma.

Secondary objectives: To evaluate ORR, lipid and fatty acid profile, inflammatory factors, adverse reactions, nutritional status, and quality of life with toripalimab plus induction chemotherapy followed by radiation therapy combined with omega-3 for locally advanced nasopharyngeal carcinoma.

2.2 Significance of the Study

Nasopharyngeal carcinoma, also known as "Canton cancer," has distinctive epidemiological characteristics, with marked differences in prevalence by region, race, and sex. Unlike other tumor types, NPC has an extremely uneven geographic distribution, one of its most prominent features. According to the International Agency for Research on Cancer, approximately 133,000 new cases of NPC occurred worldwide in 2020, accounting for 0.7% of all newly diagnosed cancers. More than 70% of new cases occurred in East and Southeast Asia, particularly southern China. In 2018, the world age-standardized incidence of NPC in China was 3 per 100,000 people, far higher than the rate of 0.4 per 100,000 in Europe. The current standard treatment for high-risk, locally advanced NPC is induction chemotherapy followed by concurrent chemoradiotherapy and then adjuvant chemotherapy. However, treatment outcomes in these patients remain relatively poor, and adverse reactions are substantial. Finding treatment regimens with greater efficacy and fewer adverse reactions is therefore an urgent priority. This phase II, single-arm clinical study will provide a preliminary evaluation of the efficacy, adverse reactions, nutritional status, and quality of life associated with toripalimab plus induction chemotherapy followed by radiation therapy combined with omega-3 for locally advanced NPC, providing new evidence to inform clinical treatment planning.

2.3 Study Endpoints (or Assessment Measures)

2.3.1 Primary Endpoint (or Primary Assessment Measure) and Definition

Two-year progression-free survival (2-year PFS): Defined as the probability over two years from the date of randomization to the first objectively documented disease progression or death from any cause, assessed according to RECIST v1.1.

2.3.2 Secondary Endpoints (or Secondary Assessment Measures) and Definitions:

(1) Objective response rate (ORR): The proportion of patients achieving a complete or partial response, assessed by an independent review committee according to RECIST v1.1 in all randomized patients with measurable disease at baseline.

(2) Lipid and fatty acid profile: A systematic analysis of parameters related to lipid metabolism and fatty acid composition, used to assess the effects of treatment on patients' lipid balance and tumor-related metabolic characteristics. This will be assessed using blood samples from all enrolled patients.

(3) Inflammatory factors: Bioactive molecules involved in inflammatory responses and immune regulation, assessed by testing peripheral blood samples from all randomized patients to reflect the effects of treatment on the tumor-associated inflammatory microenvironment.

(4) Incidence and severity of treatment-emergent adverse events, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

(5) Health-related quality of life: Assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Cancer Module (QLQ-H&N35) and Core 30 questionnaire (QLQ-C30), as presented in the patient-reported outcomes.

(6) Nutritional status: Regular measurements of body weight and other relevant measures.

3. Study Design

3.1 Overall Study Design

This is a phase II, single-arm interventional clinical study.

3.2 Expected Study Timeline and Completion Date

June 2025 to December 2029

3.3 Brief Study Flowchart

Clinical Study Flowchart

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 factors, acute toxicity, nutritional status, and quality of life assessments

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Follow-up, lipid and fatty acid profile, inflammatory factors, and late toxicity assessments

↓

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

↓

Propose a new clinical treatment approach for locally advanced nasopharyngeal carcinoma

Schedule of Study Assessments

Screening: 0-14 days before treatment. Induction chemotherapy (IC), 9 weeks: albumin-bound paclitaxel + cisplatin + toripalimab. Radiotherapy phase (IM), weeks 9-18: toripalimab + Omega-3 + IMRT.

Visit timing (days): IC1 = 0 + 21; IC2 = 21 + 21; IC3 = 42 + 21; IM1 = 63 + 21; IM2 = 84 + 21; IM3 = 105 + 21. Maintenance = maintenance treatment; Month 3 = month 3 after treatment; Follow-up = years 1-2 after treatment, once every 6 months.

Assessment	Screening	IC1	IC2	IC3	IM1	IM2	IM3	Maint.	Month 3	Follow-up
Informed consent	×									
Inclusion criteria	×									
Exclusion criteria	×									
Medical history	×									
Biopsy histopathology	×									
Nasal endoscopy	×			×			×	×	×	×
Physical examination	×	×	×	×	×	×	×	×	×	×
Complete blood count, C-reactive protein, blood biochemistry	×	×	×	×	×	×	×	×	×	×
Routine urinalysis and stool testing	×	×	×	×	×	×	×	×		
Thyroid function	×	×	×	×	×	×	×	×	×	×
Seven-cytokine panel and T-cell subsets	×	×	×	×	×	×	×	×	×	×
Fatty acid profile		×		×	×	×	×	×	×	
Quantitative EBV DNA	×	×	×	×	×	×	×	×	×	×
Electrocardiogram	×	×	×	×	×	×	×	×	×	×
Imaging	×			×			×	×	×	×
Vital signs	×	×	×	×	×	×	×	×		

Assessment	Screening	IC1	IC2	IC3	IM1	IM2	IM3	Maint.	Month 3	Follow-up
Safety assessment	×			×			×	×	×	×
Efficacy assessment				×			×	×	×	×
Adverse events and serious adverse events	Record at any time and report as required.									
Concomitant medication	×	×			×				×	×
Study termination record	Record at any time and report as required.									
Study completion record										×

× = assessment scheduled at the indicated visit or treatment phase.

4. Recruitment of Study Participants

Patients aged 18-65 years who are hospitalized at the Affiliated Hospital of Guangdong Medical University between 2025 and 2029 and have pathologically confirmed, locally advanced nasopharyngeal carcinoma staged as 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, will be selected.

4.1 Inclusion Criteria

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

2. Pathologically diagnosed nonkeratinizing nasopharyngeal carcinoma, either differentiated or undifferentiated (WHO type II or III).

3. Clinical stage of 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. ECOG performance status of 0-1.

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

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

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

8. Thyroid-stimulating hormone (TSH) ≤1 times the ULN. If TSH is abnormal, FT3 and FT4 levels should also be assessed; patients with normal FT3 and FT4 levels may be enrolled.

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

4.2 Exclusion Criteria

1. Recurrent or distantly metastatic nasopharyngeal carcinoma.

2. Pathological diagnosis of keratinizing squamous cell carcinoma (WHO type I).

3. Previous radiotherapy or systemic chemotherapy.

4. Pregnancy or breastfeeding, or being of childbearing potential without using effective contraception.

5. HIV positivity.

6. Previous treatment with immune checkpoint inhibitors, such as CTLA-4, PD-1, or PD-L1 inhibitors.

7. Immunodeficiency disorders or a history of organ transplantation.

8. Treatment with high-dose glucocorticoids, anticancer monoclonal antibodies, or other immunosuppressants within the previous 4 weeks.

9. Markedly impaired cardiac, hepatic, pulmonary, renal, or bone marrow function.

10. Refusal or inability to sign the informed consent form for trial participation.

11. Personality disorders or psychiatric disorders, or lack of or limited capacity for civil conduct.

12. Positive hepatitis B surface antigen (HBsAg) and peripheral blood hepatitis B virus DNA (HBV DNA) ≥1,000 copies/mL.

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

14. A known history of active pulmonary tuberculosis (TB). In participants suspected of having active TB, chest radiography, sputum testing, and assessment of clinical symptoms and signs are required to rule out active TB.

15. Other serious, uncontrolled medical illnesses or infections; other contraindications to treatment; or any other condition that, in the investigator's judgment, may pose a risk during treatment with the study drug or interfere with evaluation of the study drug, participant safety, or interpretation of the study results.

4.3 Duration of Study Participation

Study duration (days) = (date of last hospitalization − date of enrollment) + 1.

4.4 Recruitment Process

Start date: June 1, 2025.

(1) Recruitment plan: Identify the person responsible for recruitment and discuss responsibilities and procedures for recruiting participants.

(2) Recruitment materials: Prepare appropriate recruitment materials and submit them to the hospital ethics committee before recruiting participants.

(3) Recruitment method: Recruit participants directly during clinical care. The treating physician will make a preliminary assessment of whether a prospective participant meets the trial inclusion criteria. The volunteer will be enrolled after providing consent.

(4) Initiation of recruitment: Meet with volunteers, explain the informed consent form in detail, and ask them to provide a response during the week before the screening date. Those who agree will sign the informed consent form. Investigators should answer volunteers' questions fully and factually, without presenting information in a one-sided manner to induce participation.

(5) Completion of recruitment: The planned recruitment target is 30 participants.

4.5 Withdrawal and Discontinuation Criteria

1. Radiological disease progression according to RECIST v1.1;

2. Withdrawal of consent by the patient;

3. Any medical condition that, in the investigator's judgment, may compromise the patient's safety if study treatment is continued;

4. Concurrent use of any anticancer treatment, including chemotherapy, hormonal therapy, immunotherapy, or treatment with standard or investigational drugs for cancer, including Chinese herbal medicines and proprietary Chinese medicines;

5. Poor patient adherence.

5. Study Treatment Groups

Not applicable.

5.1 Randomization

Not applicable.

5.1.1 Method of Generating the Random Allocation Sequence

Not applicable.

5.1.2 Allocation Concealment

Not applicable.

5.1.3 Blinding and Unblinding

Not applicable.

6. Study Procedures

6.1 Study Treatment Period

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, and CTV2 54 Gy.

③ Maintenance treatment: toripalimab 240 mg every 3 weeks for 6 cycles.

6.2 Supply of Study Drugs/Treatments

Albumin-bound paclitaxel for injection: dispensed by the hospital's central pharmacy.

Cisplatin injection: dispensed by the hospital's central pharmacy.

Toripalimab injection: dispensed by the hospital's central pharmacy; participants must pay for it themselves.

Omega-3 nutritional preparation (omega-3 soft capsules): provided free of charge by this clinical research project.

6.3 Administration, Storage, and Dose Adjustments

Albumin-bound paclitaxel for injection: 260 mg/m² by intravenous infusion.

Cisplatin injection: 80 mg/m² by intravenous infusion.

Toripalimab injection: 240 mg by intravenous infusion.

Omega-3 nutritional preparation (omega-3 soft capsules): 6 capsules orally.

6.4 Concomitant Treatment and Follow-up Visits

Treatment with immune checkpoint inhibitors (such as CTLA-4, PD-1, and PD-L1 inhibitors) and other fatty acid nutritional preparations is prohibited.

6.5 Patient Adherence and Withdrawal

Specialist oncologists will provide patients with relevant education to improve adherence.

7. Sample Size Estimation

To increase the 2-year progression-free survival (2-y-PFS) rate from 71% to 96%, a Z-test was used in PASS 15 with $\alpha = 0.05$ (two-sided) and $\beta = 0.10$, yielding a calculated sample size of 24 patients. Allowing for a 20% dropout rate, at least 30 patients need to be enrolled.

8. Data Management and Statistical Analysis Plan

8.1 Data Management

(1) Data entry

Investigators will enter data from participants' original observation records into the case report forms promptly, completely, accurately, and clearly, and submit the forms to the clinical research data manager in a timely manner.

Two operators will independently enter the data on two computers using an appropriate database system. The database will then undergo two rounds of comparison. Any problems identified will be promptly communicated to the investigators for clarification. Queries and responses will be exchanged using data query forms, which will be retained for reference.

(2) Content and methods of data verification and management

Once all case report forms have been entered in duplicate and verified as accurate, the data manager will prepare a database verification report. This report will include study completion status (including a list of participants who dropped out), checks of inclusion/exclusion criteria, completeness, logical consistency, outliers, time windows, concomitant medications, and adverse events.

(3) Data archiving

After data entry and verification have been completed as required, case report forms will be archived in numerical order with a retrieval index for future reference. Electronic data files, including the database, verification programs, analysis programs, analysis results, codebook, and explanatory documents, will be stored by category. Multiple backup copies will be kept on different disks or storage media and safeguarded against damage. All original records will be retained for the periods specified by applicable requirements.

8.2 Statistical Analysis Plan

Study data will be analyzed using SPSS 26.0. In univariate analyses of the data collected above, continuous variables will be expressed as the mean ± standard deviation, and categorical variables will be expressed as proportions. A t-test will be used for normally distributed continuous variables; Pearson's chi-square test or Fisher's exact test will be used for categorical variables. Covariates of important clinical relevance will be controlled during group allocation and adjusted for in the statistical analysis. All statistically significant risk factors will be included in a multivariable logistic regression analysis. Survival outcomes will be analyzed using the Kaplan-Meier method and the log-rank test. A P value <0.05 will be considered statistically significant.

9. Study Workflow/Flowchart

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)

↓

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

↓

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.

↓

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

↓

Follow-up, lipid and fatty acid profile, inflammatory factors, and late toxicity assessments

↓

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

↓

Propose a new clinical treatment approach for locally advanced nasopharyngeal carcinoma

10. Data Confidentiality Plan

Investigators will maintain strict confidentiality regarding the trial results, protocol, and other information. All information relating to study conduct, protocol, design, results, data collection, case report forms, and informed consent forms must be stored separately and securely. Access is restricted to authorized investigators.

11. Risk-Benefit Assessment

11.1 Benefits (Individual and Societal Benefits)

Individual benefits: 1. By participating in this study, you will have the opportunity to receive an anti-PD-1 monoclonal antibody and omega-3, which may improve treatment efficacy and reduce adverse reactions in high-risk, locally advanced nasopharyngeal carcinoma. 2. You will receive closer attention and observation from the study physicians. Such clinical trials are generally conducted by experts and hospitals with substantial expertise in the field. During participation,

patients may receive more attentive care during hospitalization, examinations, treatment, and follow-up, and any condition requiring urgent intervention can be addressed promptly. However, as with any treatment, we cannot guarantee that participation in this study will produce a satisfactory outcome, and your disease may not improve with the available treatments.

Societal benefits: This study regimen offers favorable efficacy and fewer toxicities and adverse effects in high-risk, locally advanced nasopharyngeal carcinoma, providing a new treatment option for this condition.

11.2 Risks

This is an interventional study. Clinical data from hospitalized patients will be collected, and follow-up will be conducted through outpatient visits, telephone calls, WeChat, or other methods. Throughout the study, investigators will strictly follow the protocol 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." The main treatment risks are adverse reactions to toripalimab injection immunotherapy, albumin-bound paclitaxel chemotherapy, cisplatin chemotherapy, radiotherapy, and oral omega-3. The study may be implemented only after ethics committee approval. Investigators must maintain strict confidentiality regarding patient privacy, source data, study results, the protocol, and other information. Study-related information must be stored separately and securely, and no unauthorized person may access it. If a serious adverse event occurs, including death, a life-threatening event, disability or partial loss of the ability to perform activities of daily living, prolongation of hospitalization, or congenital malformation, the investigator will complete a Serious Adverse Event Report Form and report the event within 24 hours to the Department of Medical Devices and the Department of Safety Supervision of the National Medical Products Administration, the local drug regulatory authority, the implementing party, and the ethics committee. The investigator will sign and date the report. Emergencies, including particularly serious or fatal adverse events, will be reported using the fastest available means of communication. The implementing party will also promptly notify relevant participating institutions and ensure that reporting procedures meet all applicable legal and regulatory requirements.

11.3 Protection of Special Populations

Research involving vulnerable populations, such as pregnant women, requires careful consideration of risks and benefits. Review and management methods that effectively protect participants' rights and interests should be actively explored while strictly complying with relevant Chinese administrative requirements and regulations. Vulnerable populations must not be preferentially selected merely because they are easy to recruit, and they must not be used to bear research risks so that other populations can benefit from the results. Informed consent is a key safeguard for special populations and is particularly important for vulnerable groups. When members of a special population lack sufficient cognitive ability or capacity to provide or refuse consent, they may not participate in such research without the consent of a legal guardian. When recruiting vulnerable populations, the primary consideration should be whether the research helps address their diseases and health problems, and special protection should be provided throughout the study. Their rights and interests must be effectively protected through external legal and ethical oversight and the ethical self-discipline of researchers.

12. Ethical Considerations

12.1 Ethics Approval

This protocol, the written informed consent form, and materials directly related to participants must be submitted to the ethics committee. The study may formally begin only after written ethics committee approval has been obtained. Investigators must submit a study progress report to the ethics committee at least annually, if applicable. The ethics committee must be notified in writing when the study is suspended and/or completed. Investigators must promptly report all changes in study activities, such as amendments to the protocol and/or informed consent form, to the ethics committee. Such changes must not be implemented before ethics committee approval, except when necessary to eliminate an apparent and immediate hazard to participants. The ethics committee will be notified when such a situation occurs.

12.2 Informed Consent

Investigators must provide participants or their guardians with an understandable, ethics committee-approved informed consent form and sufficient time to consider participation. Participants may not be enrolled until signed written informed consent has been obtained. During participation, participants will receive all updated versions of the informed consent form and written information. Informed consent forms must be retained as essential clinical trial documents for inspection.

13. Annual Work Plan

June 1, 2025 to September 30, 2025: Collect relevant literature, determine baseline information and outcome data to be collected, and initiate recruitment.

October 1, 2025 to December 31, 2028: Screen eligible patients with nasopharyngeal carcinoma and complete enrollment of the planned sample size. Observe enrolled patients, assess their disease, collect outcome data, and follow up on prognosis according to the trial procedures designed for each group. Maintain accurate data records.

January 1, 2029 to December 31, 2029: Collect and organize trial data, conduct statistical analyses, and draft, revise, and publish the manuscript.

14. Performance Indicators

(1) Train one master's student;

(2) Publish one article in an SCI-indexed journal.

15. Prior Research Foundation and Working Conditions

When selecting cases, the research team must strictly follow the inclusion criteria and exclude patients who do not meet the eligibility requirements. Researchers must provide prospective participants with detailed information and obtain informed consent. Ethics committee and regulatory approval must be obtained to ensure compliance with ethical and regulatory requirements and to protect research participants' rights.

16. Other Matters Requiring Explanation

None.

16.1 Project Collaboration

None.

16.2 Forms of Publication and Authorship Arrangements

None.

17. Investigator Information

17.1 Principal Investigator

Name	Telephone	Email
Haiqing Luo	13729196345	hqluo@126.com

17.2 Study Team Members

Name	Institution	Degree / Professional Title	Study Responsibilities	Ethics and GCP Training	Email
Haiqing Luo	Affiliated Hospital of Guangdong Medical University	Doctoral-level postgraduate education; Associate Professor	Project Lead	Yes	hqluo@126.com
Jiong Lin	Affiliated Hospital of Guangdong Medical University	Master's-level postgraduate; Attending Physician	Project Secretary	Yes	1007489662@qq.com
Weihao Zhang	Affiliated Hospital of Guangdong Medical University	Master's-level postgraduate	Patient follow-up; manuscript preparation	No	1679655330@qq.com
Donghong Yang	Affiliated Hospital of Guangdong Medical University	Master's-level postgraduate; Associate Chief Physician	Patient follow-up	Yes	Ydh192@sina.com
Haiwen Li	Affiliated Hospital of Guangdong Medical University	Master's-level postgraduate; Attending Physician	Patient follow-up	Yes	505147279@qq.com
Tongyuan Deng	Affiliated Hospital of Guangdong Medical University	Doctoral-level postgraduate education; Physician	Patient follow-up; statistical analysis	Yes	tydeng123@163.com
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