Clinical research project of Guangdong Medical University Affiliated Hospital

Research programmes

Project Name (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
Project Name (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 Unit	Affiliated Hospital of Guangdong Medical University
Research Lead	Luo Haiqing
Version Number	2.0
Version Date	June 27,2025
Duration of Study	June 2025 to December 2029

Research programme

Project Name	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 Researcher	Luo Haiqing	**contact way**	13590386289
Source of Funds	Self-financing	**Funded funds (ten thousand)**	not have
abstract			
Type of Test Design	observational study		
Research Center	Single Centre		
Randomized Grouping	NA		
Blind Method	NA		
Type of study	optimal efficiency		
Purpose of Research	1. Main Objective: This study will demonstrate the 2-year PFS rate of trypirizumab + induction chemotherapy sequential radiotherapy combined with OMEGA-3 in locally advanced nasopharyngeal carcinoma. 2. Secondary research objectives: This study will clarify the ORR, OS, adverse reactions, nutritional status analysis and quality of life analysis of local advanced nasopharyngeal carcinoma treated with trypirizumab + induction chemotherapy sequential radiotherapy + OMEGA-3.		
Study Endpoint/Observation Endpoint	1. Primary study endpoint: 2-year PFS. 2. Secondary study endpoints: ORR, OS, adverse reactions, nutritional status analysis, quality of life analysis. Exploratory endpoints:(1) to explore the correlation between		

	cytokines and patient prognosis; (2) to explore the correlation between OMEGA-6/OMEGA-3 ratio and patient efficacy; (3) to explore the correlation between immune cell changes in tumor microenvironment and anti-tumor activity of the study protocol.
Study Population	Patients aged 18 to 65 years with pathological diagnosis of nasopharyngeal carcinoma and stage anyTN2-3M0 or T4N1M0 (AJCC8th/UICC staging) were selected from those hospitalized in the Affiliated Hospital of Guangdong Medical University between 2025 and 2026.
Diagnostic Criteria	Pathological diagnosis was nasopharyngeal carcinoma with anyTN2-3M0 or T4N1M0 stage locally advanced nasopharyngeal carcinoma (AJCC8th).
Inclusion Criteria	1. Can provide written informed consent and understand and follow the research requirements and assessment schedule. 2. Age between 18 and 65 years (or the legal age specified by local laws governing the study) at the date of signing the informed consent form. 3. Pathological diagnosis was nasopharyngeal nonkeratinizing carcinoma (differentiated or undifferentiated, i.e., WHO type II or III). 4. Clinical stage is anyTN2-3M0 or T4N1M0 (AJCC8th/UICC staging). 5.ECOG score 0-1. 6. Hemoglobin (HGB) ≥ 90g/L, white blood cell (WBC) ≥ 4.0 ×109/L, platelet (PLT) ≥ 100×109/L. 7. Liver function: ALT and AST <2.5 times the upper limit of normal value (ULN), total bilirubin <2.0×UL, serum albumin ≥ 28g/L. 8. Renal function: serum creatinine <1.5×ULN or calculated

	creatinine clearance rate (CrCl) ≥60mL/min (Cockcroft-Gault formula). 9. Thyroid-stimulating hormone (TSH) ≤1×ULN (if abnormal, FT3 and FT4 levels should be examined at the same time. If FT3 and FT4 levels are normal, participants can be enrolled). 10. International Standardized Ratio (INR) and activated partial thromboplastin time (APTT) ≤1.5×ULN (unless the subject is receiving anticoagulant therapy and the coagulation parameters (PT/INR and APTT) are within the expected range for anticoagulant therapy at screening).
Exclusion criteria	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 have not taken effective contraceptive measures. 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.) therapy. 8. Patients with immunodeficiency diseases and history of organ transplantation. 9. Patients who received high doses of glucocorticoids, anticancer monoclonal antibodies, or other immunosuppressants within 4 weeks. 10. Patients with significantly impaired heart, liver, lung, kidney and bone marrow function. 11. Use of other investigational drugs or participation in other clinical trials.

	12. Refuse or be unable to sign the informed consent form for participation in the trial. 13. Persons with personality or mental illness, without capacity for civil conduct or limited capacity for civil conduct. 14. Hepatitis B surface antigen (HBsAg) positive and peripheral blood hepatitis B virus deoxyribonucleic acid (HBVDNA) ≥ 1000cps/ml. 15.HCV Patients with positive antibody test results can only be included in this study when the polymerase chain reaction of HCVRNA is negative. 16. Patients with any serious bleeding event of grade 3 or higher in CTCAEv5.0 within 4 weeks prior to screening and who are judged by the investigator to be at high risk of bleeding. 17. Venous/arterial thrombosis events occurred within 6 months prior to 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 the normal range by antihypertensive drugs (systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg; based on the average of BP readings obtained from ≥2 measurements) who have previously experienced 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. Known history of active tuberculosis (TB). Subjects suspected of having active TB should be examined for chest X-ray, sputum, and clinical symptoms and signs. 21. Other serious, uncontrolled medical conditions and infections or other contraindications for treatment, or any condition that the investigator considers to be likely to cause risks in the administration of the study drug, or to interfere with the evaluation of the study drug, the safety of the subject or the

	interpretation of the results.
Exit criteria	1. According to RECISTv1.1 criteria, it is considered as imaging disease progression; 2. The patient's written consent is revoked; 3. There are any medical conditions identified by the investigator that may endanger the safety of the patient if the patient continues to receive the study treatment; 4. Concurrent use of any anti-tumor therapy (i.e., chemotherapy, hormone therapy, immunotherapy, or standard or trial drugs [including Chinese herbal medicine and proprietary Chinese medicine] for the treatment of cancer); 5. Poor patient compliance;
Sample Capacity	To increase the 2-year PFS from 71% to 96%, we used PASS15 software and adopted the Z-test with a=0.05 (two-sided test) and β=0.10. The calculated sample size was 24 patients. Considering a 20% dropout rate, at least 30 patients were required to 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. **References** Chow, S. C., Shao, J., and Wang, H. 2008. Sample Size Calculations in Clinical Research, Second Edition. Chapman & Hall/CRC. Boca Raton, Florida. Fleiss, J. L., Levin, B., and Paik, M.C. 2003. Statistical Methods for Rates and Proportions. Third Edition. John Wiley & Sons. New York. Lachin, John M. 2000. Biostatistical Methods. John Wiley & Sons. New York. Machin, D., Campbell, M., Fayers, P., and Pinol, A. 1997. Sample Size Tables for Clinical Studies, 2nd Edition. Blackwell Science. Malden, Mass. Ryan, Thomas P. 2013. Sample Size Determination and Power. John Wiley & Sons. Hoboken, New Jersey. Zar, Jerrold H. 2010. Biostatistical Analysis (Fifth Edition). Prentice-Hall. Englewood Cliffs, New Jersey. **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
Research Factors	Interventions in this study: ① Induction therapy: Toripalimab 240mg d1 + paclitaxel (albumin-bound) 260mg/m2 d1 + cisplatin 80mg/m2 d2 Q3W X 3 cycles ② Radiotherapy: IMRT +Toripalimab 240mg Q3W X 3 cycles + omega-3 (6 tablets qd during radiotherapy) IMRT：GTVnx 69.96Gy，GTVnd 69.96Gy，CTV1 60Gy，CTV2 54Gy ③ Maintenance therapy: Toripalimab 240mg Q3W for 6 cycles
Evaluating Indicator	2-y-PFS, ORR, OS, adverse reactions, nutritional status analysis, quality of life analysis.

Follow-Up	1. During treatment: After the start of the study protocol, clinical observation should be strictly carried out. The occurrence and classification of adverse events and adverse reactions should be evaluated weekly according to NCICTCAEv5.0 version. Blood routine and blood biochemical should be monitored every 3 weeks. Concurrently, combined medication and adverse events (including adverse events of intravenous medication and chemoradiotherapy) should be recorded during the clinical study. 2. Conduct efficacy and safety evaluations after treatment completion, including 2-year progression-free survival (2y-PFS), objective response rate (ORR), complete blood count (CBC), biochemical parameters, EB virus DNA quantification, thyroid function tests, serum amylase and lipase levels, electronic nasopharyngoscopy, enhanced nasopharyngeal-neck MRI, chest X-rays or CT scans, and abdominal ultrasound or CT. If clinically significant abnormalities are detected, follow-up examinations should be repeated until normalization. Near-term follow-up evaluations should be conducted three months post-treatment, while long-term follow-ups should occur every six months after treatment initiation. Monitoring methods include recording patients' return-to-hospital review data, physician-signed mail/telephone follow-ups, etc., to assess treatment efficacy, recovery of toxic reactions, and both short-term and long-term toxicity profiles. Follow-up protocols shall adhere to the clinical guidelines for individual disease management.
Statistical Analysis	The research data were processed using SPSS26.0 statistical software. In the univariate analysis of collected data, continuous measurement data were presented as mean ± standard deviation, categorical data as frequency, and measurements with normal distribution were analyzed using t-tests. Categorical data were statistically evaluated through Pearson's chi-square test or Fisher's exact test. Significant covariates were controlled during grouping and adjusted in subsequent analyses. All statistically significant risk factors underwent multivariate analysis via logistic regression. Survival analysis utilized Kaplan-Meier method and log-rank test. Statistical significance was defined as P values <0.05.
Research Findings	1. Publish an SCI paper. 2. Train a graduate student.

1. Basis of the topic

1.1 Research significance

Nasopharyngeal carcinoma (NPC), a malignant tumor originating from the nasopharyngeal mucosa, exhibits distinct geographical distribution patterns, primarily affecting populations in southern China and Southeast Asia[1]. According to the World Health Organization's classification system, NPC is categorized into three histological subtypes: squamous cell carcinoma, non-squamous cell carcinoma, and basaloid squamous cell carcinoma. Non-squamous NPC is further subdivided into differentiated and undifferentiated subtypes[2]. Notably, over 95% of NPC cases in high-incidence regions present as non-squamous undifferentiated subtypes, which exhibit aggressive biological behavior and predispose patients to distant metastasis[3]. Additionally, the carcinogenic effects of non-squamous undifferentiated NPC are closely associated with chronic latent infections caused by Epstein-Barr virus (EBV)[4].

Given the anatomical complexity of the nasopharynx and its radio-sensitivity, radiation therapy forms the cornerstone of treatment for non-metastatic nasopharyngeal carcinoma. The advent of Intensity-Modulated Radiotherapy (IMRT) has revolutionized this approach by enabling precise tumor targeting with minimal impact on adjacent tissues. For early-stage patients receiving IMRT alone, both the 5-year local recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) rates exceed 95%[5].

However, for patients with locally advanced nasopharyngeal carcinoma, the adverse characteristics of the common undifferentiated pathological subtype and the inherent advanced stage at diagnosis increase the risk of treatment failure. The 5-year overall survival (OS) rate for nasopharyngeal carcinoma patients receiving only local radiotherapy is below 50%[6,7]. Furthermore, with significant improvements in diagnostic and radiotherapy techniques that have greatly enhanced local control rates, distant metastasis has become the primary cause of treatment failure[8]. In recent years, extensive research has focused on combining

systemic chemotherapy with radiotherapy to improve survival rates in advanced nasopharyngeal carcinoma patients. Additionally, the use of concurrent chemoradiotherapy (CCRT) combined with induction chemotherapy (IC) or adjuvant chemotherapy (AC) has significantly improved clinical outcomes.

Nasopharyngeal carcinoma tissues exhibit unique immunological features, including dense stromal immune infiltration[9], immunosuppressive characteristics[10], and high expression of programmed cell death ligand 1 (PD-L1)[11]. These features indicate that immune checkpoint inhibitors could serve as a promising therapeutic strategy for nasopharyngeal carcinoma.

Three Phase III clinical trials have demonstrated that combining PD-1 immunosuppressants with gemcitabine (GP) chemotherapy as first-line therapy can significantly extend progression-free survival (PFS)[12-14] in patients with R/M nasopharyngeal carcinoma. Current research is exploring the combination of PD-1 immunosuppressants and chemoradiotherapy for locally advanced nasopharyngeal carcinoma. Several Phase II trials have shown promising responses, survival outcomes, or both, when anti-PD-1 or anti-PD-L1 inhibitors were added during or throughout treatment regimens including IC, AC, IC+AC, or the entire course of therapy (objective response rate 88.9%-94.4%; 2-year PFS rate 69.6%-91.8%)[15-18]. To date, the only large-scale Phase III trial with published data evaluated PD-1 immunosuppressant efficacy in locally advanced nasopharyngeal carcinoma. Results indicated that adding sintilimab during GPIC, CCRT, or as adjuvant therapy significantly reduced recurrence or mortality risks in high-risk patients, with a 10% increase in 3-year event-free survival ([19]). Additionally, sintilimab-treated groups showed marked reductions in distant metastasis and local recurrence risks (3-year disease-free survival rate: 90.3% vs. 82.8%, HR0.57 [95% CI 0.33–0.98], p=0.039; 3-year local recurrence-free survival rate: 93.4% vs. 86.8%, HR0.52 [95% CI 0.27–0.97], p=0.038). Notably, no significant differences in quality of life were observed between the two groups. These findings indicate that PD-1 immunotherapy combined with

chemoradiotherapy could establish a new standard of care for high-risk patients with locally advanced nasopharyngeal carcinoma. Furthermore, ongoing clinical trials are evaluating the efficacy and safety of various immune checkpoint inhibitors (ICBs) in combination with chemoradiotherapy during induction, adjuvant phases, or as an alternative to conventional chemotherapy for locally advanced nasopharyngeal carcinoma. The results may advance our understanding of optimal sequencing and regimens for integrating immunotherapy with chemoradiotherapy in current nasopharyngeal carcinoma management.

Omega-3 polyunsaturated fatty acids (OEMG-3PUFAs) are essential fatty acids that the human body cannot synthesize, primarily found in plant oils and fish fats. DHA and EPA, two key components of OEMG-3PUFAs, have been extensively studied as the most researched types of this family. These fatty acids play a role in preventing cardiovascular diseases, regulating inflammation, and improving nutritional status[20]. Research by Mocellin et al. demonstrated that OEMG-3PUFAs can increase plasma albumin and prealbumin levels in gastric cancer patients[21][21].My research shows that omega-3PUFAs can reduce CRP levels and shorten the duration of systemicinflammatoryresponsesyndrome (SIRS) [22].Meta analysis showed that omega-3PUFAs could improve the nutritional status of patients after gastrectomy and reduce inflammatory indicators such as C-reactive protein (CRP) and interleukin 6 (IL-6) [23].In a recent study of 37 postoperative head and neck cancer patients who took two to three cans of Omega-3FA and arginine enhancement supplements daily for 12 weeks, the results showed improvements in albumin, prealbumin, transferrin, and lymphocyte levels in the enhancement group [25].In head and neck cancer and esophageal cancer patients undergoing radiochemotherapy (RCT), formulations containing Omega-3 fatty acids have demonstrated equivalent therapeutic benefits. A randomized controlled trial involving 37 patients evaluated the efficacy of an immunomodulatory diet combining arginine, omega-3 fatty acids, and nucleotide-rich nutrients. Results showed that enteral nutrition group patients

exhibited significant improvements in overall body weight, elevated albumin levels, and enhanced plasma antioxidant capacity. While functional capacity measured by WHO Performance Status and Karnofsky Index remained stable in the immunomodulatory group, it markedly declined [26] in standard enteral nutrition recipients. In 31 non-metastatic stage III/IV head and neck squamous cell carcinoma patients receiving radiochemotherapy, another oral supplement containing amino acids, omega-3 fatty acids, nucleotides, vitamins, and antioxidants demonstrated poorer efficacy in modulating pro-inflammatory, proangiogenic, and pro-oxidative states [27].[24]

Early enteral nutrition intake of large amounts of Omega-3 fatty acids can effectively reduce platelet aggregation, coagulation activity and the production of cytokines. Clinical manifestations include decreased body temperature and significantly reduced biochemical indexes such as plasma IL-8 levels, which confirm the anti-inflammatory effect of Omega-3 fatty acids [28].The above reaction was improved by adding RNA and arginine to the formula [29].In the Omega-3FA supplementation group, inflammation and immune function improved postoperatively. The Omega-3FA group showed significantly reduced serum procalcitonin levels and elevated CD4+/CD8+ cell ratio on day 6 post-surgery, though no significant differences were observed on days 1 and 3[30]. Generally, these Omega-3 fatty acid-containing formulas can be safely used in sepsis patients, but there is insufficient evidence to recommend routine immunomodulatory nutrition for esophageal cancer surgery patients[31]. A Phase III double-blind trial of immunomodulatory nutritional formula during adjuvant chemoradiotherapy for head and neck cancer patients revealed that ITT analysis over three years after adjuvant chemoradiotherapy showed no significant survival improvement in the immunomodulatory nutrition formula group.However, in patients with ≥75% compliance, compared with the control group, the immunomodulatory nutritional formula group showed a significant improvement in [32] at 3y OS and 3y PFS ($P<0.05$).

The current standard treatment for high-risk locally advanced nasopharyngeal carcinoma involves induction chemotherapy followed by concurrent chemoradiotherapy and adjuvant chemotherapy. However, this regimen causes significant adverse reactions in patients, with some still experiencing recurrence or metastasis. With the emergence of immunotherapy, it has become a first-line treatment for advanced nasopharyngeal carcinoma, particularly in high-risk locally advanced cases. Omega-3, known for its anti-inflammatory and antitumor mechanisms, has been shown to alleviate radiochemotherapy side effects and enhance therapeutic efficacy. This study innovatively removes concurrent chemotherapy during chemoradiotherapy for high-risk locally advanced nasopharyngeal carcinoma, replacing it with concurrent immunotherapy combined with Omega-3 supplementation. This approach aims to improve treatment outcomes while reducing adverse reactions in such high-risk cases.

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2. Research content

2.1 Research Purpose

The main purpose of this study was to clarify the 2-year PFS rate of

toripalimab + induction chemotherapy sequential radiotherapy combined with OMEGA-3 in locally advanced nasopharyngeal carcinoma.

Secondary objectives of the study: to clarify the ORR, OS, adverse reactions, nutritional status and quality of life analysis of local advanced nasopharyngeal carcinoma treated with toripalimab + induction chemotherapy sequential radiotherapy combined with OMEGA-3.

2.2 Research significance

Nasopharyngeal carcinoma, also known as "Guangdong cancer", exhibits unique epidemiological characteristics with significant regional, ethnic, and gender variations in prevalence. Distinct from other cancers, its geographical distribution is highly uneven, which stands out as one of its most prominent features. According to data from the International Agency for Research on Cancer (IARC), there were approximately 133,000 new cases of nasopharyngeal carcinoma globally in 2020, accounting for 0.7% of all newly detected tumors. Over 70% of these cases occurred in East and Southeast Asia, particularly in South China. In 2018, China's nasopharyngeal carcinoma incidence rate (calculated using global age-standardized methods) reached 3 per 100,000 population, far exceeding Europe's 0.4 per 100,000. The current standard treatment for high-risk locally advanced nasopharyngeal carcinoma involves induction chemotherapy followed by concurrent chemoradiotherapy and adjuvant chemotherapy. However, treatment outcomes remain suboptimal with significant adverse reactions in these patients. Therefore, developing more effective and less toxic treatment regimens has become an urgent priority. This Phase II single-arm clinical study aims to preliminarily evaluate the efficacy, adverse reactions, nutritional status analysis, and quality of life assessment of triple therapy combining toripalimab, induction chemotherapy, sequential radiotherapy, and OMEGA-3 supplementation in treating locally advanced nasopharyngeal carcinoma, providing new reference criteria for clinical practice.

2.3 Research endpoint (or evaluation indicator)

2.3.1 Main endpoint (or main evaluation indicator) and definition

2-year progression-free survival (2-year-PFS): The probability of no disease progression or death from any cause within two years from the randomized date to the first objective record of disease progression, as assessed according to

RECISTv1.1.

2.3.2 Secondary endpoints (or secondary evaluation indicators) and their definitions

(1) Overall survival (OS): The period from the random date to the date of death for any reason.

(2) Objective Response Rate (ORR): The percentage of patients achieving complete or partial remission, assessed by an independent review committee based on all randomized patients with measurable disease at baseline according to RECISTv1.1.

(3) The incidence and severity of adverse events after treatment were graded according to the common Terminology Standard for Adverse Events v5.0 of the National Cancer Institute.

(4) Health-related quality of life: assessed using the European Organization for Cancer Research and Treatment's 35-module head and neck cancer quality of life questionnaire and core 30, as shown in the patient-reported outcomes.

(5) Nutritional status analysis: regular measurement of weight, etc.

2.3.3. Exploratory endpoints:

(1) Explore the correlation analysis between cytokines and patient prognosis;

(2) Explore the correlation analysis between n6/n3 ratio and patient efficacy;

(3) Explore the correlation between immune cell changes in tumor microenvironment and anti-tumor activity

3. Research design

3.1 Overall design of the study

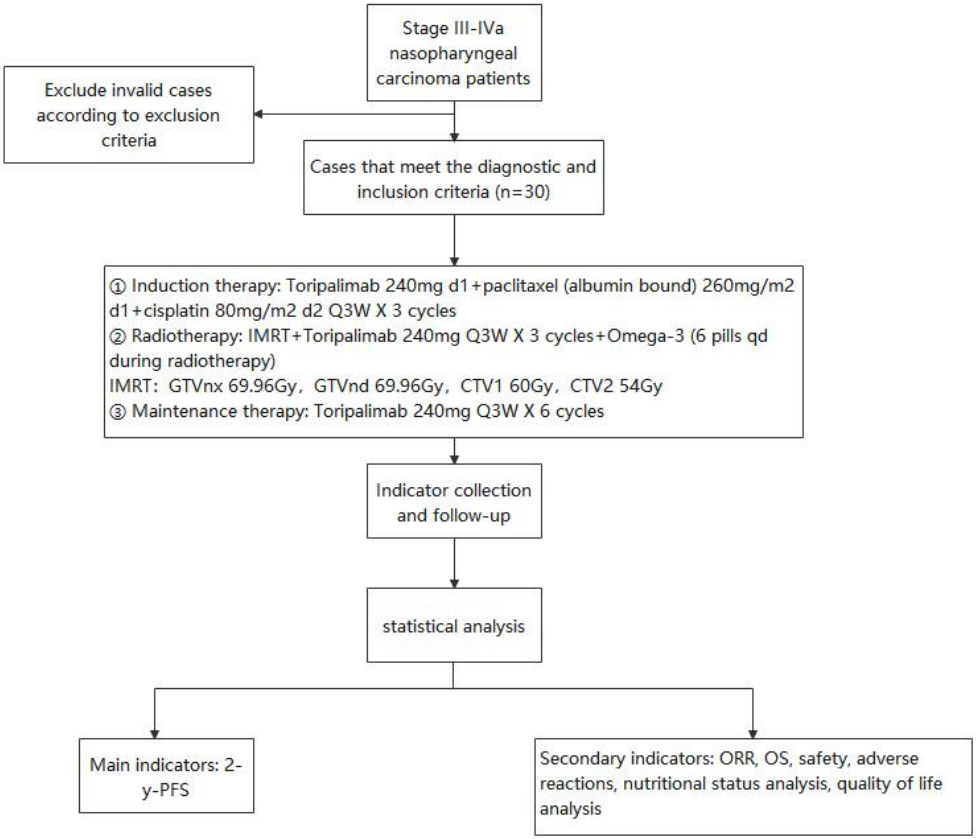
This study was a phase II, single-arm intervention clinical study

3.2 The expected schedule and completion date of the research project

June 2025 to December 2029

3.3 Brief test flow chart

Clinical research flow chart


Stage III-IVa nasopharyngeal carcinoma patients
Exclude invalid cases according to exclusion criteria
Cases that meet the diagnostic and inclusion criteria (n=30)
① Induction therapy: Toripalimab 240mg d1+paclitaxel (albumin bound) 260mg/m2 d1+cisplatin 80mg/m2 d2 Q3W X 3 cycles
② Radiotherapy: IMRT+Toripalimab 240mg Q3W X 3 cycles+Omega-3 (6 pills qd during radiotherapy)
IMRT: GTVnx 69.96Gy, GTVnd 69.96Gy, CTV1 60Gy, CTV2 54Gy
③ Maintenance therapy: Toripalimab 240mg Q3W X 6 cycles
Indicator collection and follow-up
statistical analysis
Main indicators: 2-y-PFS
Secondary indicators: ORR, OS, safety, adverse reactions, nutritional status analysis, quality of life analysis

	screening period	under treatment							After treatment	Follow-up period
	Before treatment 0-14 days	Induction chemotherapy with paclitaxel (albumin bound)+cisplatin+trastuzumab (9 weeks)			Toripalimab+OMega-3+IMRT (9-18 weeks)			Maintenance treatment	The third month	1-2 years after treatment (once every 6 months)
		1-IC(0+21天)	2-IC (21+21天)	3-IC (42+21天)	1-IM (63+21)	2-IM (84+21)	3-IM (105+21)			
Informed Consent Form	×									
Inclusion Criteria	×									
Exclusion Criteria	×									
History taking	×									
Pathological examination	×									
Nasal endoscope	×			×			×	×	×	×
Physical examination	×	×	×	×	×	×	×	×	×	×
Blood routine, blood biochemistry	×	×	×	×	×	×	×	×	×	×
Urine and stool routine	×	×	×	×	×	×	×	×		
Thyroid function and coagulation function	×	×	×	×	×	×	×	×	×	×
Quantitative examination of EB virus, DNA	×	×	×	×	×	×	×	×	×	×
electrocardiographic examination	×	×	×	×	×	×	×	×	×	×
imaging examination	×			×			×	×	×	×
vital signs	×	×	×	×	×	×	×	×		
Safety assessment	×			×			×	×	×	×
Efficacy evaluation				×			×	×	×	×
Adverse events and Serious Adverse Event Record	Record and report according to regulations at any time									
Combination therapy with medication	×	×			×				×	×
Research Suspension Record	Record and report according to regulations at any time									
Research End Record										×

4. Recruitment of research subjects

Patients aged 18 to 65 years with pathological diagnosis of nasopharyngeal carcinoma and stage anyTN2-3M0 or T4N1M0 locally advanced nasopharyngeal carcinoma (AJCC8th) were selected from those hospitalized in the Affiliated Hospital of Guangdong Medical University between 2025 and 2029.

4.1 Selection criteria:

1. Can provide written informed consent and understand and follow the research requirements and assessment schedule.
2. Age between 18 and 65 years (or the legal age specified by local laws of the study) at the date of signing the INFORMED consent form.
3. Pathological diagnosis was nasopharyngeal nonkeratinizing carcinoma (differentiated or undifferentiated, i.e., WHO type II or III).
4. Clinical stage is anyTN2-3M0 or T4N1M0 (8thAJCC/UICC staging)
5.ECOG score 0-1.
6. Hemoglobin (HGB) ≥ 90g/L, white blood cell (WBC) ≥ 4.0×109/L, platelet (PLT) ≥ 100×109/L.
7. Liver function: ALT and AST <2.5 times the upper limit of normal value (ULN), total bilirubin <2.0×UL, serum albumin ≥28g/L.
8. Renal function: serum creatinine <1.5×ULN or calculated creatinine clearance rate (CrCl) ≥60mL/min (Cockcroft-Gault formula).
9. Thyroid-stimulating hormone (TSH) ≤ 1×ULN (if abnormal, FT3 and FT4 levels should be examined at the same time. If FT3 and FT4 levels are normal, participants can be enrolled).
10. International Standardized Ratio (INR) and activated partial thromboplastin time (APTT) ≤ 1.5×ULN (unless the subject is receiving anticoagulant therapy and the coagulation parameters (PT/INR and APTT) are within the expected range for anticoagulant therapy at screening).

4.2 Exclusion criteria:

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 have not taken effective contraceptive measures.
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.) therapy.
8. Patients with immunodeficiency diseases and history of organ transplantation.
9. Patients who received high doses of glucocorticoids, anticancer monoclonal antibodies, or other immunosuppressants within 4 weeks.
10. Patients with significantly impaired heart, liver, lung, kidney and bone marrow function.
11. Use of other investigational drugs or participation in other clinical trials.
12. Refuse or be unable to sign the informed consent form for participation in the trial.
13. Persons with personality or mental illness, without capacity for civil conduct or limited capacity for civil conduct.
14. Hepatitis B surface antigen (HBsAg) positive and peripheral blood hepatitis B virus deoxyribonucleic acid (HBVDNA) ≥ 1000cps/ml.
15.HCV Patients with positive antibody test results can only be included in this study when the polymerase chain reaction of HCVRNA is negative.
16. Patients with any serious bleeding event of grade 3 or higher in CTCAEv5.0 within 4 weeks prior to screening and who are judged by the investigator to be at high risk of bleeding.
17. Venous/arterial thrombosis events occurred within 6 months prior to 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 the normal range by antihypertensive drugs (systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90mmHg; based on the average of BP readings obtained from ≥ 2 measurements) who have previously experienced 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. Known history of active tuberculosis (TB). Subjects suspected of having active TB should be examined for chest X-ray, sputum, and clinical symptoms and signs.

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

4.3 Time when the subjects participated in the study

Study time (days) = (last hospitalization date-enrollment date) +1

4.4 Recruitment process

Launch time: 2025.06.01

(1) Recruitment plan: Determine the person in charge of recruitment, and discuss the responsibilities and procedures of recruiting subjects.

(2) Materials for recruiting subjects: Before recruiting subjects, reasonable recruitment materials should be formulated and submitted to the hospital ethics committee.

(3) The way of recruiting subjects: Directly recruit from the clinical medical process, preliminarily determine whether they meet the inclusion criteria of the trial through the attending physician, and add them to the trial after obtaining the consent of the volunteers.

(4) Recruitment begins: Meet with volunteers, introduce the contents of the informed consent form in detail, and inform them to give a reply within one week before the screening date. If they are willing, they will sign the informed consent form. Researchers should answer volunteers' questions in detail and be realistic without unilateral inducement.

(5) Recruitment end: 30 people are expected to be recruited.

4.5 Exit and termination criteria

1. According to RECISTv1.1 criteria, it is considered as imaging disease progression;

2. The patient's written consent is revoked;

3. There are any medical conditions identified by the investigator that may endanger the safety of the patient if the patient continues to receive the study treatment;

4. Concurrent use of any anti-tumor therapy (i.e., chemotherapy, hormone therapy, immunotherapy, or standard or trial drugs [including Chinese herbal medicine and proprietary Chinese medicine] for the treatment of cancer);

5. Poor patient compliance;

5. Study treatment groups

uninvolved

5.1 Randomized grouping

uninvolved

5.1.1 Methods for generating random sequence allocation

uninvolved

5.1.2 Hidden randomization

uninvolved

5.1.3 Blind method and blind lifting

uninvolved

6. Research procedures

6.1 Research treatment period

① Induction therapy: Toripalimab 240mg d1 + paclitaxel (albumin-bound) 260mg/m2 d1 + cisplatin 80mg/m2 d2 Q3W X 3 cycles

② Radiotherapy: IMRT + Toripalimab 240mg Q3W for 3 cycles + omega-3 (6 tablets qd during radiotherapy). IMRT: GTVnx 69.96Gy, GTVnd 69.96Gy, CTV1 60Gy, CTV2 54Gy

③ Maintenance therapy: Toripalimab 240mg Q3W for 6 cycles

6.2 Supply of research-based drugs/treatment

Paclitaxel (albumin-bound) : Dispensed from the hospital central pharmacy

Cisplatin injection: dispensed from the hospital central pharmacy

Toripalimab: supplied by Shanghai Junshi Biomedical Technology Co., LTD

Omega-3 nutritional preparation (Omega-3 soft capsules): provided by this clinical research project

6.3 Administration, storage and dose adjustment

Paclitaxel (albumin-bound) : 260 mg/m2 intravenous infusion

Cisplatin injection: 80mg/m2 intravenous infusion

Toripalimab injection: 240mg intravenous infusion

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

6.4 Accompanying treatment and follow-up visits

The use of immune regulatory point (CTLA-4, PD-1, PD-L1, etc.) inhibitors and other fatty acid nutrients is prohibited

6.5 Patient compliance and withdrawal

Professional oncologists will popularize relevant knowledge to patients and improve compliance.

7. Sample size estimation

To increase the 2-year PFS from 71% to 96%, we used PASS15 software and adopted the Z-test with a=0.05 (two-sided test) and β=0.10. The calculated sample size was 24 patients. Considering the 20% dropout rate, at least 30 patients were required to be enrolled.

8. Data management and statistical analysis plan

8.1 Data management

(1) Data entry

According to the original observation records of subjects, the researchers shall load the data into the case report form in a timely, complete, correct and clear manner and submit them to the clinical research data administrator in a timely manner.

The data entry shall be carried out by two people with two machines using the corresponding database system. After that, the database shall be compared twice. If any problem is found during the process, the researchers shall be notified in time and asked to give an answer. All kinds of questions and answers exchanged between them shall be in the form of question sheet, which shall be kept for future reference.

(2) Contents and methods of data verification and management

After the double input and verification of all case report forms, the data administrator shall write a database check report, which includes the completion of the study (including the list of subjects who dropped out), selection/exclusion criteria check, integrity check, logical consistency check, outlier data check, time window check, combined medication check, adverse event check, etc.

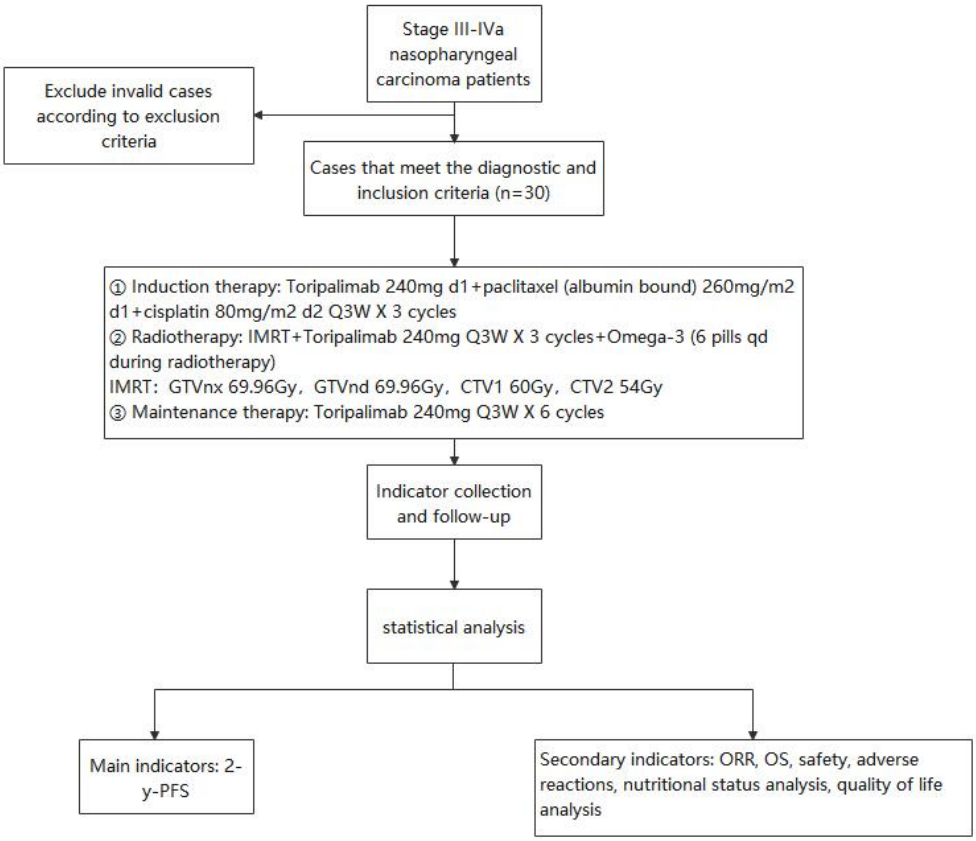
(3) Data archiving

After completing data entry and verification as required, case report forms shall be archived in numerical order with inclusion of retrieval catalogs for reference. Electronic data files — including databases, inspection procedures, analytical programs, results, coding manuals, and explanatory documents — should be categorized and stored with multiple backups on different disks or storage media to ensure proper preservation against damage. All original records must be retained for the duration specified by relevant regulations.

8.2 Statistical analysis plan

The research data were processed using SPSS26.0 statistical software. In the univariate analysis of collected data, continuous measurement data were presented as mean ± standard deviation, categorical data as frequency, and measurements with normal distribution were analyzed using t-tests. Categorical data were statistically evaluated through Pearson's chi-square test or Fisher's exact test. Significant covariates were controlled during grouping and adjusted in subsequent analyses. All statistically significant risk factors underwent multivariate analysis via logistic regression. Survival analysis utilized Kaplan-Meier method and log-rank test. Statistical significance was defined as P values <0.05.

9. Technology Roadmap



10. Data security plan

The researchers shall keep the results, protocols and other information of the trial strictly confidential. All information such as the implementation, protocol, design, results, data collection, CRF and informed consent form shall be kept separately and confidentially, and no unauthorized investigator or other personnel shall have access to them.

11. Risk/benefit assessment

11.1 Benefits (individual and societal)

Personal Benefits: [1] Cost Savings: The study will purchase relevant insurance for patients, which saves them money. For patients with limited financial means, clinical trials are the optimal choice. [2] Enhanced Care and Monitoring: Clinical trials are typically conducted by leading experts in the field and reputable hospitals. During enrollment, patients receive better care and attention during hospitalization, examinations, treatments, and follow-ups. In case of emergencies requiring urgent treatment, prompt medical intervention can

be provided.
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

11.2 risk

This intervention study involves collecting clinical data from hospitalized patients and conducting follow-up through outpatient visits, phone calls, or WeChat. Throughout the study period, researchers will strictly adhere to the protocol of "Trevirizumab + Induction Chemotherapy Sequential Radiotherapy Combined with Omega-3 Therapy for Local Advanced Nasopharyngeal Carcinoma: A Phase II, Single-Arm Clinical Study." Major treatment risks include adverse reactions from tririzumab immunotherapy, albumin-bound paclitaxel chemotherapy, cisplatin chemotherapy, radiotherapy, and oral Omega-3 supplementation. The study will only commence after approval by the ethics committee, with strict confidentiality required for patient privacy, raw data, research outcomes, and protocols. All research materials must be stored separately and exclusively, accessible only to authorized personnel. In cases of severe adverse events (including death, life-threatening conditions, disability, prolonged hospitalization, or deformities), researchers must complete the "Severe Adverse Event Report Form" and submit reports to the Medical Device Department and Safety Supervision Department of the National Medical Products Administration, local drug regulatory authorities, study implementers, and ethics committees within 72 hours, signing and noting the date. Emergency situations involving particularly severe or fatal adverse events require immediate communication via the fastest available means. Implementers must also promptly notify relevant participating institutions while ensuring compliance with all legal reporting procedures.

11.3 Protection of special groups

Research targeting vulnerable populations such as pregnant women must carefully evaluate risks and benefits. While strictly adhering to China's relevant

regulations, it is crucial to develop practical review and management protocols that effectively protect participants' rights. Priority should not be given to recruiting vulnerable groups simply because they are easier to enroll, as this could expose them to research risks while benefiting other populations through study outcomes. Informed consent remains the cornerstone of protecting special populations, particularly vulnerable groups. Individuals lacking sufficient cognitive capacity to give or withhold consent should not participate in such studies without legal guardianship authorization. When recruiting vulnerable populations, priority should be given to addressing their specific health issues, with special protections provided throughout the research process. Comprehensive safeguards must be implemented through external legal frameworks, ethical oversight, and scientists' professional ethics to ensure the rights of vulnerable groups are genuinely protected.

12. Ethical issues in research

12.1 Ethical approval

The study protocol, written informed consent forms, and all materials directly related to participants must be submitted to the ethics committee for review. The research may only commence after obtaining written approval from the ethics committee. Investigators are required to submit annual reports to the ethics committee at least once per year (if applicable). When suspending or concluding a study, investigators must notify the ethics committee in writing. All changes made during the study (such as revisions to the protocol and/or informed consent forms) must be promptly reported to the ethics committee. These modifications shall not be implemented without prior approval from the ethics committee, except when they eliminate obvious and direct risks to participants. In such cases, the ethics committee will be notified immediately.

12.2 Informed consent

Researchers must provide subjects or their guardians with an easily understandable and ethics committee-approved informed consent form, and allow sufficient time for them to consider the study. Subjects may not be

enrolled until they have signed a written informed consent form. Throughout the study, all updated versions of the consent form and written information will be provided to participants. The consent form shall be retained as an important clinical trial document for reference.

13. Annual plan

From June 01,2025 to September 30,2025: Collect relevant literature data, determine baseline data and index data, and start recruitment.

From October 01,2025 to December 31,2028: Screen eligible nasopharyngeal carcinoma cases, complete the enrollment of cases with the expected designed sample size, observe patients, assess the condition, collect indicators and follow up prognosis for the included cases according to the experimental steps designed by each group, and register the data

From January 01,2029 to December 31,2029: collect and sort out test data, conduct statistical analysis, write papers, improve papers and publish papers

14. Assessment indicators

(1) To train a master's student;

(2) Publish an SCI paper.

15. Preliminary research basis and working conditions

When selecting cases, the research team must strictly follow inclusion criteria and exclude patients who do not meet them. Researchers must provide detailed information to the patients and obtain informed consent. Approval from the ethics committee and regulatory authorities is required to ensure that the study complies with ethical and regulatory requirements and protects the rights of participants

16.Other issues that need to be explained

not have

16.1 Project cooperation

not have

16.2 Form of publication and authorship arrangement of the results

not have