Trial Protocol

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3. Summary of changes (*Page 56-57*).

Trial Protocol

The efficacy and safety of cadonilimab combined with NAB-paclitaxel, cisplatin, and capecitabine chemotherapy in recurrent or metastatic nasopharyngeal carcinoma after failure of anti-PD-1 therapy: an open labeled, phase II study

Version Number: First Version
Current Edition: September 2, 2022

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Protocol Synopsis

Study Title: The efficacy and safety of cadonilimab combined with NAB-paclitaxel, cisplatin, and capecitabine chemotherapy in recurrent or metastatic nasopharyngeal carcinoma after failure of anti-PD-1 therapy: an open labeled, phase II study
Study Objectives: To evaluate the efficacy and safety of cadonilimab combined with NAB-paclitaxel, cisplatin, and capecitabine chemotherapy in the treatment of recurrent or metastatic nasopharyngeal carcinoma after failure of anti-PD-1 therapy.
Target Subject Population: Recurrent or metastatic nasopharyngeal carcinoma patients who unfit for radiotherapy and surgery and progress from first-line of chemotherapy and anti-PD-1 systemic therapy.
Study Endpoints **Primary:** To assess objective response rate (ORR) based on the criteria of RECIST V1.1 **Secondary:** To evaluate progression-free survival (PFS), overall survival (OS), duration of response (DoR), median time to response (mTTR), and safety based on the criteria of CTCAE V5.0.
Study Design This is a Phase 2, open-label, clinical trial conducted in China to evaluate the efficacy, safety of cadonilimab combined with NAB-paclitaxel, cisplatin, and capecitabine chemotherapy in the treatment of recurrent or metastatic nasopharyngeal carcinoma after failure of anti-PD-1 therapy. This study consists of a screening period, a treatment period, and a follow-up period. **Screening Period:** All patients are under standardized management for NPC, and they need to perform a series of examinations as well as provide relevant information before the first dose to determine whether they meet the eligibility criteria. **Treatment Period:** After screened, the eligible subjects will receive cadonilimab in combination with TPC regimen every 3 weeks for a maximum of 6 cycles as induction treatment, following by cadonilimab and capecitabine every 3 weeks as maintenance treatment documented progressive disease (PD), death, intolerable toxicity, treatment duration of 24 months, or withdrawal of consent. The subject will be allowed to continue treatment if judged by the investigator to have been clinically benefited and be able to tolerate cadonilimab at the time of the first PD confirmed by imaging assessment. Subjects will receive cadonilimab for a maximum of 24 months throughout the study. The investigator and radiologists shall perform response assessments according to RECIST v1.1 criteria during the treatment period. Tumor assessments will be performed every two cycles during induction therapy phase, every three cycles during maintenance therapy phase, and three months thereafter. Subjects who discontinue drug administration due to reasons other than PD will continue to be followed for disease status until the initiation of other anti-tumor therapies, PD, withdrawal of informed consents, died or study discontinuation, whichever occurs first. During the treatment period, the safety of cadonilimab will be assessed by the investigator. AEs will

be graded as per NCI CTCAE V5.0, and judged for their relationships with the study drug. Depending on the severity and causality of the AE, the investigator will take a series of measures and concomitant therapies to ensure the safety of the subjects.

Follow-up Period:

Regardless of the cause of the study's treatment interruption, patients should be reviewed approximately one month after the last treatment cycle and all emerging adverse events recorded. A survival follow-up visit will be performed every 3 months after the last dose to obtain information on survival and subsequent tumor treatment after discontinuation until 36 months after study entry or subject death, withdrawal of consent, or end of study, whichever occurs first.

Treatment Regimen:

Cadonilimab was intravenously given at dose of 10 mg/kg, administered as a 120-minutes (± 10 min) infusion on day 1. The TPC regimen consisted of NAB-paclitaxel at a dose of 200 mg/m^2, administered over 30 minutes infusion on day 1, followed by cisplatin at a dose of 60 mg/m^2 on day 1; And capecitabine at a dose of 1000 mg/m^2, taken orally twice a day on days 1 to 14, for each cycle.

Number of Trial Patients:

25 patients will be enrolled

Statistical Analysis Plan

Sample Size Estimation:

The null hypothesis was an ORR of ≤20% for R/M NPC patients failed to at least one prior line of anti-PD1 therapy, and the alternate hypothesis was an ORR ≥ 45% for the treatment of this trial. In the first stage, 10 patients will be accrued. If there are 2 or fewer responders in these 10 patients, enrollment will discontinue. Otherwise, 12 additional patients will be accrued for a total of 22 patients. If there were more than 7 patients with PR or CR, then the treatment regimen was considered a success. With an estimated 10% shedding rate, a total of 25 patients should be finally included.

Analysis of Efficacy:

The primary endpoint of this study is ORR per RECIST v1.1. ORR analysis will be performed based on the FAS, using the Clopper Pearson method to estimate 95% confidence intervals (CIs). Time to event endpoints (DoR, PFS, and OS) will be analyzed using the Kaplan-Meier method. Measured and evaluated values of target lesions, non-target lesions, and new lesions are recorded according to RECIST v.1.1.

Analysis of Safety:

The frequencies and incidences of each AE and treatment-related parameters will be detailed in tabular form. The summary statistical results of AEs will be listed according to their seriousness (SAEs), severity and causality with the study drug, and AEs and AESIs that lead to discontinuation will also be summarized. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V5.0 and will be described using preferred terms (PTs) of the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory abnormalities and toxicity levels will be derived and summarized according to NCI CTCAE V5.0.

1. Background

1.1 Nasopharyngeal carcinoma (NPC)

Nasopharyngeal carcinoma (NPC) is a special type of head and neck tumors due to its distinct geographical, etiological and biological characteristics.1 It has a high prevalence in South China, Southeast Asia, and North Africa, and is closely linked to Epstein-Barr virus (EBV) infections.[1-3] The incidence of distant metastasis of newly diagnosed NPC patients is approximately 6-15%, and about 20% of non-metastatic NPC experience recurrent or metastasis eventually after definitive treatments.[4,5]

1.2 Treatment of recurrent/metastatic NPC

The results from recently studies have established the combination of gemcitabine plus cisplatin and PD-1 inhibitor as the standard first-line regimens for recurrent or metastatic NPC (RM-NPC) patients.[6-8] With objective response rate (ORR) of 69.5% to 87.3% though, the median progression-free survival (mPFS) was 9.2 to 21.4 months.[6-8] Under such conditions, most patients will develop disease progression within 1 to 2 years. Recent studies showed that the prognosis of these patients was poor under later line therapy, with an ORR of 22.68% to 34.3% and mPFS of 4.4 to 7.9 months.[9-11] Therefore, novel treatment options are urgently needed to improve the efficacy and prognosis for RM-NPC who failed to systemic chemotherapy and anti-PD-1 therapy.

1.3 Cadonilimab in NPC

Cadonilimab (AK104) is humanized bispecific antibody that targets to PD-1 and CTLA-4.[12] Its tetravalent and no Fc binding design contribute to its high binding activity in the tumor microenvironment and improved safety profile.[13] Recent studies have shown encouraging efficacy and manageable toxicity of cadonilimab in several different cancer types.[14-16] Cadonilimab monotherapy has shown an ORR of 30% and disease control rate (DCR) of 70%, with the median disease-free survival time of 3.71 months in patients with RM-NPC at the second line setting.[17] There is no study available to explore the role of cadonilimab in anti-PD-1 resistant RM NPC patients.

1.4 TPC regimen in NPC

Our previous study prospectively proven the superiority of TPC regimen (paclitaxel, cisplatin, and capecitabine) versus cisplatin and fluorouracil (PF) as induction treatment for patients with stage IVA NPC in NPC patients.[18] Besides, after achieved disease control from TPC regimen, capecitabine maintenance therapy significantly improved PFS for patients with newly diagnosed

metastatic NPC with tolerable toxicities.[19] These results suggest the promising application prospect of TPC regimen in RM-NPC patients.

In this phase 2 trial, we firstly assessed the efficacy and safety of cadonilimab plus TPC chemotherapy as the second-line treatment in patients with RM-NPC who failed to the first line of systemic chemotherapy and anti-PD-1 therapy.

2. Objectives

2.1 Primary Objectives

To assess objective response rate (ORR) of cadonilimab in combination with the TPC (NAB-paclitaxel, cisplatin and capecitabine) chemotherapy regimen for the treatment of recurrent/advanced nasopharyngeal carcinoma after failure of first line systemic chemotherapy and anti-PD-1 therapy based on the criteria of RECIST V1.1.

Primary endpoints will be analyzed based on the FAS. For the analysis of the primary endpoints, IRC-assessed ORR and its 95% confidence interval (Clopper-Pearson method) will be estimated.

2.2 Secondary Objectives

To evaluate progression-free survival (PFS), overall survival (OS), duration of response (DoR), median time to response (mTTR), and safety evaluation (Treatment-related adverse events are assessed according to NCI-CTCAE V5.0; Appendix I) of cadonilimab in combination with the TPC (NAB-paclitaxel, cisplatin and capecitabine) chemotherapy regimen for the treatment of recurrent/advanced nasopharyngeal carcinoma treated with PD-1 blockade.

3. Trial Scheme

Ten patients were enrolled in the first stage. If there are 2 or fewer responders in these 10 patients, enrollment will discontinue. Otherwise, 12 additional patients will be accrued for a total of 22 patients. If there were more than 7 patients with PR or CR, then the treatment regimen was considered a success. With an estimated 10% shedding rate, a total of 25 patients should be finally included.

4. Patients Enrollment

4.1 Eligibility Criteria

1) Pathologically confirmed diagnosis of non-keratinizing carcinoma of the nasopharynx (differentiated or undifferentiated).
2) Confirmed diagnosis of metastatic or recurrent nasopharyngeal carcinoma that is not amenable to radical local treatment.
3) Patients must have progressed to first line systemic chemotherapy and anti-PD-1 therapy.
4) Age ≥ 18 years and ≤ 70 years.
5) ECOG score (Appendix II) of 0-1 and have an expected survival more than 3 months.
6) At least one measurable lesion (according to RECIST 1.1), lesions that have received radiotherapy and have clearly progressed on imaging and are measurable may be considered as target lesions.
7) Adequate organ function: Hemoglobin (HGB) ≥ 85 g/L, white blood cells (WBC) ≥ 3×10E9 /L, platelets (PLT) ≥ 75×10E9 /L. Total bilirubin (TBIL) < 1.5 × upper limit of normal (ULN), alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) < 2.5 times the upper limit of normal (ULN); If the patient has liver metastases, ALT or AST<5 × ULN. Creatinine level ≤1.5 × ULN.
8) Voluntarily participate in this study and sign informed consent.
9) Fertile female subjects and male subjects with fertile sexual partners must agree to apply reliable contraceptive methods (e.g. condoms, contraceptive pills used regularly as prescribed, etc.) for 6 months from screening until 6 months after the last treatment.

4.2 Exclusion Criteria

A. Pathology of keratinizing squamous cell carcinoma (WHO staging type I).
B. A history of monoclonal antibody hypersensitivity.
C. A known history of interstitial pneumonia.
D. A history of serious infection within 4 weeks before enrollment, including but not limited to complications requiring hospitalization, sepsis or severe pneumonia;
E. Patients treated with aspirin (> 325 mg/day) or dipyridamole, ticlopidine, clopidogrel, and cilostazol within 3 weeks before enrollment, or anticoagulants requiring INR monitoring (e.g., warfarin), or any blood component and cell growth factor support therapy within 1 week before enrollment.
F. Active infections requiring systemic therapy.
G. Patients with active hepatitis B (HBV-DNA ≥ 1000 IU/mL) despite treatment, except for patients with cured hepatitis C.
H. Received the last radiotherapy or antineoplastic treatment within 3 weeks before enrollment.
I. Has a known history of active tuberculosis or autoimmune diseases.

J. With HIV infection.
K. Concurrently suffering from other uncontrolled malignancies.
L. Patients presenting with abnormal function of vital organs such as heart, brain or lungs, or the presence of clinically significant hydronephrosis, ascites or pericardial effusion, or being treated with thrombolytic therapy.
M. Women who are pregnant or breastfeeding.
N. Persons with personality or psychiatric disorders, civil capacity or restricted civil capacity.
O. Currently participating in an interventional clinical study or have received other investigational drugs within 4 weeks before enrollment.

4.3 Criteria for withdrawal from protocol treatment

Patients who discontinue the trial treatment for any reason are considered to have withdrawn. Patients may withdraw from the study for the following reasons:

a) The patients or their legal representative withdraw consent.
b) Investigators believe that the termination of the treatment is beneficial to patients.
c) Poor compliance did not meet the requirements of this study.
d) The test results of the subject's β-HCG test indicated that the subject was pregnant. At the same time, pregnancy will also be reported as a serious adverse event reporting procedure.
e) Use of prohibited medications or other medications that the investigator believes will cause a toxic reaction or affect the results of the study.
f) Patients suffering from an intercurrent disease that significantly affects the assessment of clinical status or necessitates discontinuation of the drug, or both.
g) Tumor progression.
h) Appears of a second primary cancer.
i) Discontinue study therapy for more than 30 days.
j) Death

5. Treatment Plan

5.1 Pretreatment Assessment

All patients are under standardized management for NPC, and they need to perform a series of examinations as well as provide relevant information to confirm pathologic diagnosis and clinical stage before admitted into trial.

1) Medical history review.
2) Personal data collection.
3) Current medications and treatment.
4) Body examinations, include height, weight and vital signs.

5) Physical examination of head and neck region, include nasopharynx and cervical lymph nodes.
6) Physical examination of the nervous system.
7) Nasal endoscopy and lesion biopsy.
8) Complete blood count and differential, electrolytes, liver and renal function test.
9) Recurrent or metastatic biopsy specimens, blood specimens (when necessary)
10) EBV antibodies and EBV DNA testing.
11) Virological examination (completed within 14 days prior to the first dose): HBsAg (if positive, HBV-DNA is required), HBsAb, HBeAg, HBeAb, HBcAb, HCV-Ab (if positive, HCV-RNA is required), HIV-Ab.
12) Electrocardiogram and Echocardiography.
13) Imaging, including enhanced MRI or enhanced CT of the head and neck (CT is indicated only in patients with contraindication to MRI).
14) Chest CT.
15) ECT bone scan.
16) Abdominal CT/MR.
17) PET/CT is optional and is performed at the discretion of the attending physician.

5.2 Pretreatment Staging Criteria

The disease stage of subjects will be staged according to the 8th edition of the Union for International Cancer Control / American Joint Committee on Cancer (UICC/AJCC) staging system (Appendix III).

5.3 Immunotherapy and chemotherapy

5.3.1 Induction therapy phase

5.3.1.1 Cadonilimab

Cadonilimab was intravenously given at dose of 10 mg/kg, administered as a 120-minutes (± 10 min) infusion on day 1; repeat every 3 weeks.

5.3.1.2 Chemotherapy with TPC regimen

The TPC regimen consisted of NAB-paclitaxel at a dose of 200 mg/m^2, administered over 30 minutes infusion on day 1, followed by cisplatin at a dose of 60 mg/m^2 on day 1; And capecitabine

at a dose of 1000 mg/m^2, taken orally twice a day on days 1 to 14; repeat every 3 weeks.

After the infusion of cadonilimab, NAB-paclitaxel and cisplatin are successively administered intravenously after an interval of at least 30 min. Cadonilimab and TPC chemotherapy were given every 3 weeks for a maximum of 6 cycles.

5.3.2 Maintenance therapy phase

5.3.2.1 Cadonilimab

Cadonilimab was intravenously given at dose of 10 mg/kg, administered as a 120-minutes (± 10 min) infusion on day 1; repeat every 3 weeks.

5.3.2.2 Capecitabine

Capecitabine were given at dose of 1000 mg/m^2, taken orally twice a day on days 1 to 14; repeat every 3 weeks.

Cadonilimab and capecitabine were given every 3 weeks for a maximum of 24 months. The treatment was discontinued when there were signs documented progressive disease (PD), death, intolerable toxicity, treatment duration of 24 months, or withdrawal of consent. The subject will be allowed to continue treatment if judged by the investigator to have been clinically benefited and be able to tolerate cadonilimab at the time of the first PD confirmed by imaging assessment.

5.4 Salvage therapy

Nasopharyngeal surgery, neck dissections, secondary radiotherapy, chemotherapy, or immunotherapy may be given to patients with relapse or metastasis after treatment according to guidelines of National Comprehensive Cancer Network (NCCN).

5.5 Dosage adjustment principle

Dose modification and toxicity management will be performed based on the severity of toxicities according to National Cancer Institute Common Terminology for Adverse Events Version 5.0 (NCI CTCAE V5.0) grading system. Dosage may not be reduced or discontinued if the investigator considers that the adverse reaction is unlikely to develop into a serious or life-threatening events and will not result in delay or interruption of treatment. If one agent is discontinued due to unacceptable toxicity, patients are able to continue the study with the other

agent. Dose interruptions are permitted for reasons other than toxicity, such as medical/surgical events or logistical reasons (e.g., unrelated medical events, elective surgery). The acceptable length of interruption will be at the discretion of the investigator. Reasons for dose modification or delay, the supportive measures taken, and the outcome will be documented.

5.5.1 Adjustment for Cadonilimab

In the event of ≤ Grade 2 infusion-related reactions, the infusion rate of cadonilimab may be reduced, or infusion may be interrupted until resolution of the event (up to 4 hours). If a subject experiences a Grade 3 or 4 infusion-related reaction at any time, cadonilimab treatment must be discontinued.

Adverse events related to cadonilimab may be immunologically related and may occur shortly after the first dose or several months after the last dose. For suspected immune-related AEs (irAEs), ensure adequate evaluation to confirm etiology or exclude other causes. In general, administration of cadonilimab may be continued for most of Grade 1 irAEs. For Grade 2 irAEs, treatment with cadonilimab will be discontinued until Grade 2 irAEs resolve to ≤ Grade 1. In the event of a Grade 3 irAE, cadonilimab treatment may be discontinued based on individual toxicity. In the event of a Grade 4 irAE, treatment with cadonilimab must be discontinued. Cadonilimab should be permanently discontinued if irAEs can not resolve within 12 weeks, expect for the condition that the use of corticosteroids for irAEs and glucocorticoid dose reduction process, or due to treatment of AEs that are possibly unrelated or unrelated to cadonilimab.

Grade 1 non-irAEs do not require cadonilimab adjustment. Cadonilimab should be hold until Grade 2 AEs resolves to Grade 1 or baseline level. For Grade 3 or higher AEs related to cadonilimab that do not meet treatment discontinuation criteria, cadonilimab dosing may be interrupted. The missed doses will no longer be administered thereafter. For laboratory abnormalities that are clearly not attributable to cadonilimab or are not deemed to be clinically significant will not require a dose omission. Dose reductions are not permitted.

The dose adjustment of cadonilimab is performed according to the following principles.

Table 1: Dose adjustment of cadonilimab

	Adverse events（CTC V5.0）	Treatment adjustment
Pneumonia	Grade 2	Suspend drug until recover to Grade 0-1
	Grade 3-4 or Recurrent Grade 2	Permanent withdrawal
Diarrhea and colitis	Grade 2-3	Suspend drug until recover to Grade 0-1
	Grade 4	Permanent withdrawal
Hepatitis	Grade 2	Suspend drug until recover to Grade 0-1
	Grade 3-4	Permanent withdrawal
Nephritis	Grade 2-3 elevated creatinine	Suspend drug until recover to Grade 0-1
	Grade 4 elevated creatinine	Permanent withdrawal

Endocrine disease	Grade 2-3	Suspend drug until recover to Grade 0-1
	Grade 4	Permanent withdrawal
Cutaneous AEs	Grade 3	Suspend drug until recover to Grade 0-1
	Grade 4	Permanent withdrawal
Neurological irAEs	Grade 2	Suspend drug until recover to Grade 0-1
	Grade 3-4	Permanent withdrawal
Other irAEs	Grade 3-4 elevated blood amylase or lipase Grade 2-3 pancreatitis Grade 2 myocarditis Grade 2-3 other irAEs for the first time	Suspend drug until recover to Grade 0-1
	Grade 4 pancreatitis or recurrent pancreatitis Grade 3-4 myocarditis Grade 3-4 encephalitis Grade 4 other irAEs for the first time	Permanent withdrawal
Recurrent or persistent AEs	Recurrent Grade 3-4 Grade 2 or 3 AEs did not recurrent to grade 0-1 within 12 weeks of the last treatment	Permanent withdrawal
infusion reaction	Grade 2	Slow down the drip rate or suspend the drug
	Grade 3-4	Permanent withdrawal

5.5.2 Dosage adjustment for NAB-paclitaxel

Hematologic adverse events

The hematological toxicity is assessed according to the NCI CTCAE V5.0 classification standard.

Table 2: Dosage adjustment of NAB-paclitaxel for hematologic toxicity

Toxicity	Grade	Time	NAB-paclitaxel
Anemia	Any	Any	Full dosage
Neutropenia	Grade 3	Any	Full dosage
	Grade 4	First time	160 mg/m^2
		Second time	120 mg/m^2
		Third time	Stop
Neutropenic fever	Grade 3-4	First time	160 mg/m^2
		Second time	120 mg/m^2
		Third time	Stop
Thrombocytopenia	Grade 4	First time	160 mg/m^2
		Second time	120 mg/m^2

		Third time	Stop

Peripheral neuritis and extremities joint myalgia

If a patient develops one of the above symptoms, the following methods are recommended to adjust the dosage of NAB-paclitaxel according to the duration and severity of the symptoms. Symptomatic treatment with non-steroidal anti-inflammatory drugs can be given alleviate extremities joint myalgia.

Table 3: Dosage adjustment of NAB-paclitaxel for non-hematologic toxicity

Adverse events	Grade	Duration of adverse events		
		1-7 days	Over 7 days	Persistent
Pain/paresthesia/sensory disturbances, but does not affect function	1	Full dose	Full dose	160 mg/m^2
Pain/paresthesia/sensory disturbances that affect function but do not affect daily activities	2	Full dose	Full dose	120 mg/m^2
Pain/paresthesia/sensory disturbances, with functional impairment, and interference with daily activities	3	Full dose	120 mg/m^2	Stop
Pain/paresthesia/sensory disturbances resulting in loss of function or life threating	4	Stop	Stop	Stop

5.5.3 Dosage adjustment for cisplatin

Hematologic adverse events

The hematological cisplatin is assessed according to the NCI CTC AE V5.0 classification standard.

Table 4: Dosage adjustment of cisplatin for hematologic toxicity

Toxicity	Grade	Time	cisplatin
Anemia	Any	Any	Full dosage
Neutropenia	Grade 3	Any	Full dosage
	Grade 4	First time	50 mg/m2
		Second time	40 mg/m2
		Third time	Stop
Neutropenic fever	Grade 3-4	First time	50 mg/m2
		Second time	40 mg/m2
		Third time	Stop
Thrombocytopenia	Grade 4	First time	50 mg/m2
		Second time	40 mg/m2
		Third time	Stop

Other non-hematological toxicity

If other toxicity reaction less than grade 3 occur, symptomatic treatment should be given whenever possible. If grade 3 or 4 toxicity occurs, treatment should be suspended, and when toxicity reverts to grade 1 or below, cisplatin should be administered at 80% of the initial dosage for the next course of treatment

5.5.4 Dosage adjustment for capecitabine

Adverse reactions should be closely monitored during treatment and the dose should be adjusted as needed to enable patients to tolerate the treatment. Once the dose of the drug has been reduced, it should not be increased later. Dose adjustment is not recommended when grade 1 adverse events occur. Capecitabine treatment should be suspended if grade 2 or 3 adverse reactions occur. Treatment can be restarted with the original dose of capecitabine or at the dose adjusted in Table 1 once the adverse reaction has disappeared or the severity has reduced to grade 1. If grade 4 adverse reactions occur, treatment should be suspended until the adverse reactions disappear or the severity is reduced to grade 1, and then treatment should be restarted at 50% of the original dose. Missing capecitabine doses due to toxic reactions should be no longer.

Table 5: Dosage adjustment of capecitabine

NCI assessed advent events	During treatment	Dose of the next cycle (% original dose)
Grade 1	Full dose	Full dose
Grade 2		
First time	Suspended until returned to grade 0~1	100%
Second time	Suspended until returned to grade 0~1	75%
Third time	Suspended until returned to grade 0~1	50%
Grade 3		
First time	Suspended until returned to grade 0~1	75%
Second time	Suspended until returned to grade 0~1	50%
Third time	Permanent termination	
Grade 4		
First time	Permanent termination or suspended until returned to grade 0~1 if researcher believe it is in the patient's interest to continue treatment	50%
Note: patients with hand-foot syndrome would be recommended treated with topical emollient, topical corticosteroid cream, or creams containing urea		

6. Observation and Assessment During Treatment

Investigators would review all inclusion and exclusion criteria for patients to ensure that the patients meet the requirements. After that, each patient must sign the informed consent document before enrollment. The following items need to be assessed during the treatment period.

- Eastern Cooperative Oncology Group (ECOG) performance status, weight, and height.
- Vital signs measurement prior to each treatment cycle, including blood pressure, heart rate, temperature, respiratory rate
- A full physical examination prior to each treatment cycle, including the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems.
- Cardiac function tests using echocardiograms if clinical indicated.
- Acute and late toxicity assessment (including immune-related toxicity), including hematological toxicity, gastrointestinal reactions, hepatotoxicity, nephrotoxicity, mucositis, neurotoxicity, ototoxicity, etc
- Laboratory tests: routine blood tests and blood biochemistry are required for each cycle, other tests are routinely suggested but not mandated for each cycle, including coagulation function (prothrombin time, activated partial thromboplatin time [APTT], international normalized ratio [INR], thrombin time [TT], fipinogen [FIB], fibrinogen degradation products [FDP], DDimer, antithrombin III [AT III]); Urine routine (blood, glucose, ketones, protein, specific gravity, microscopic exam); Stool routine test; Thyroid function test (total triiodothyronine [T3], free triiodothyronine [free T3], total thyroxine [T4], free thyroxine [free T4], thyroid stimulating hormone); EBV-DNA loading.
- Computed tomography (CT) or magnetic resonance imaging (MRI) of chest, abdomen, and pelvis were used to evaluate the image information before the first treatment and subsequent tumor assessments. Bone scans or CT/MRI scan and nasopharynx and neck CT/MRI will also be performed if clinically indicated. Response evaluation is conducted every two cycles during induction therapy phase, every three cycles during maintenance therapy phase, and three months thereafter by the investigators with radiologists using RECIST V1.1. Per RECIST v1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. At the investigator's discretion, CT scans or MRI should be repeated at any time if progressive disease is suspected.

7. Exploratory analysis and translational study

7.1 Exploratory analysis

EBV DNA clearance rate.

7.2 Translational study

1) Signed informed consent is required prior to each biological sample collection.
2) Clinical specimens for the above cases whose informed consent have been signed will be collected by designated professionals, and all specimens collected will be used for subject-related scientific research only.
3) After collection, tumor tissue specimens will be collected by the principal investigator and stored in a refrigerator at -80 °C or transferred to a designated laboratory for processing and analysis.

8. Safety Evaluation

All observations relevant to the safety of the drug under study will be documented in the case report form (CRF) and the final summary report. Safety indicators are as follows: adverse events, laboratory changes (hematology, blood biochemistry), changes in vital signs (blood pressure, heart rate, respiratory rate, body temperature), and changes in electrocardiogram and chest CT.
During the treatment period, the safety of cadonilimab will be assessed by the investigator. AEs will be graded as per NCI CTCAE V5.0, and judged for their relationships with the study drug. Depending on the severity and causality of the AE, the investigator will take a series of measures and concomitant therapies to ensure the safety of the subjects.

Safety evaluation was evaluated in every cycle throughout the treatment period and 30 days after treatment discontinuation (90 days for immune-related AEs) and were graded according to the NCI CTCAE V5.0. A SAE is any life-threatening medical adverse event that occurs at a variety of drug doses:

- Causing death or endangering life. It should be noted that the term "lifethreatening" in the definition of "severe" means that at the time of the event, the patient is at risk of death. It's not a hypothetical event.
- Causing permanent or severe disability/dysfunction.
- Teratogenicity/birth defects.

- Resulting in prolonged hospital stays.
- Lead to secondary tumors.
- Other unpredictable drug related AEs

In the event of a serious adverse event, whether or not related to the study drug, the investigator shall immediately notify the Clinical Investigation Center (GCP) of the Serious Adverse Event table within 1 business day (in any case). The form must be dated and signed by the person filling it out.

All adverse events, whether or not they are thought to be drug-related, should be documented in the case report, including diagnosis, start/end time, interventions taken, discontinuation of treatment, remedies, outcomes, and other possible causes. The investigator should determine the association of all adverse events with treatment and the severity of the event. The severity of acute adverse events should be graded according to CTCAE V5.0. The most severe severity should be recorded in the CRF.

9. Follow Up

Regardless of the cause of the study's treatment interruption, patients should be reviewed approximately one month after the last treatment cycle and all emerging adverse events recorded. The patient will be evaluated for the following items during the visit:

- Physical examination includes weight, vital signs, evaluation of physical condition, general condition and toxicity;
- All abnormal laboratory test values that occurred when the patient dropped out of the study.
- Tumor evaluation

Tumor imaging should be performed whenever there is clinical suspicion of disease progression. A survival follow-up visit will be performed every 3 months after the last dose to obtain information on survival and subsequent tumor treatment after discontinuation until 36 months after study entry or subject death, withdrawal of consent, or end of study, whichever occurs first.

10. Safety Measures and Quality Control

Researchers is responsible for obtaining informed consent signed by each subject or his or her agent; carefully fill out the case report form; complete records of laboratory examinations, clinical records, and original medical records of the subjects.

A. Provide systematic learning program for every member in the research group.
B. Make monitoring plan of adverse effects and emergency plan.
C. Research plan is made by all participating centers and approved by Ethics Committee.
D. Develop all kinds of standard operation procedures related to this study.
E. Establish standardized evaluation system to unify diagnostic criteria, curative effect judging

criteria, etc.

F. Establish professional statistical plan.
G. Research staffs are trained before the study.
H. Ensure that every participating center conducts the study at the same pace.
I. Arrange quality controller, make quality control plan and check regularly.
J. Set up coordination committee, curative effect judging group and follow-up team.
K. Made records in a true, timely, complete and standardized manner.
L. Sort out the corresponding project files, which will be archived and saved after being quality control checked.
M. The management of the clinical research unit shall check the feasibility of the research carried out.

11. Data Collection and Data Management

11.1 Case Report Form (CRF)

The CRF is completed by the investigator and must be completed by each enrolled patient. After the completed CRF is reviewed by the clinical supervisor, the first copy is transferred to the data administrator for data entry and management.

11.2 Data Entry and Modification

All information about the enrolled patients after registration will be sent to Sun Yat-sen University Cancer Center for management. We have stewards taking charge of data entry and management. Data administrators use EpiData 3.1 software to compile data entry program and carry out data entry and management. In order to ensure the accuracy of the data, two data administrators should independently conduct double input and proofreading. If there are any questions in the CRF, the data administrator will send questioned data to the investigator for verification. The investigator should answer and return the questions as soon as possible. The data administrator can modify, confirm and enter the data according to the answers of the investigator.

11.3 Data Locking

After confirming that the established database is accurate, the main researchers, data administrators, and statisticians will lock the data. The locked data file will not be modified.

12. Statistical Analysis

12.1 Endpoint Definitions

12.1.1 Primary End Point

The primary endpoint was ORR, which was defined as the objective tumor response as per the RECIST 1.1 and is obtained by dividing the number of patients whose is CR or PR by the number of patients.

12.1.2 Secondary End Points

Progression-free survival (PFS), defined as the time from treatment initiation to disease progression according to RECIST V1.1 or death from any cause, whichever occurs first. Cases in which disease progression has not yet occurred will be censored using their last tumor evaluation date;

Overall survival (OS), defined as the time from treatment initiation until death. Cases that are still alive will be censored using their last follow-up date.

Duration of response (DoR), defined as the time from the first evidence of response to disease progression or death;

Median time to response (mTTR), defined as the median time to response;

Safety evaluation, treatment-related adverse events are assessed according to CTCAE V5.0.

12.2 Sample Size and Power Calculations

A Simon's optimal two-stage design was employed with a one-sided type I error rate of 5% and power of 80%. The reported data indicated that the ORR of pembrolizumab in R/M NPC patients who received at least one prior line of platinum-based chemotherapy in NCI-9742 was 20.8%.[20] Our data suggested that ORR was 22.68% in R/M NPC patients failed to at least one prior line of anti-PD1 therapy and received chemotherapy as following treatment.[9] The null hypothesis was an ORR of $\leqslant$ 20% for R/M NPC patients failed to first line systemic chemotherapy and anti-PD-1 therapy, and the alternate hypothesis was an ORR $\geq$ 45% for the treatment of this trial. In the first stage, 10 patients will be accrued. If there are 2 or fewer responders in these 10 patients, enrollment will discontinue. Otherwise, 12 additional patients will be accrued for a total of 22 patients. If there were more than 7 patients with PR or CR, then the treatment regimen was considered a success. With an estimated 10% shedding rate, a total of 25 patients should be finally included.

12.3 Analytical Approach

Patients who received at least one dose of the study regimen were included in the protocol analysis set (intention-to-treatment (ITT) and safety set). The primary endpoint of this study is ORR per RECIST v1.1. ORR analysis will be performed based on the FAS, using the Clopper Pearson method to estimate 95% confidence intervals (CIs). Time to event endpoints (DoR, PFS, and OS) will be analyzed using the Kaplan-Meier method. Measured and evaluated values of target lesions, non-target lesions, and new lesions are recorded according to RECIST v.1.1. The frequencies and incidences of each AE and treatment-related parameters will be detailed in tabular form. The summary statistical results of AEs will be listed according to their seriousness (SAEs), severity and causality with the study drug, and AEs and AESIs that lead to discontinuation will also be summarized. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V.5.0 and will be described using preferred terms (PTs) of the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory abnormalities and toxicity levels will be derived and summarized according to NCI CTCAE V5.0. Chi-square test was used for measuring data. The statistical software was SPSS 23.0.

13. Ethical Considerations

This study must be approved by an appropriate institutional ethic committee.

An informed consent must be obtained from individual patients. Copy of the Consent Form, contact number of investigator and ethics committee will be available to patient on request.

All serious and unexpected adverse events or death related to the drugs or radiotherapy must be reported to the study coordinator immediately. Serious adverse events (SAE) to be reported include all deaths during or within 30 days of protocol treatment regardless of cause, grade 5 toxicity, life-threatening grade 4 toxicity, and/or unexpected toxicity. The Study Coordinator of respective center should complete form and fax this within 24 hours to the Principal Investigator (Dr. Yan-Qun Xiang, Tel: 020-87343359, Fax: 020-87343392), the center of clinical trials, the institutional ethic committe and Sun Yat-sen University Cancer Center. Together with the Principal Investigator, appropriate and prompt action will be taken if warranted. Reactions and deaths beyond 30 days from protocol treatment that are judged definite unrelated to treatment should not be reported.

14. Administration of Experimental Drugs

Cadonilimab was provided free of charge by Kangfang BioPharmaceuticals Co., Ltd. The management, distribution, and recovery of clinical drugs in this trial shall be the responsibility of designated researcher. The researcher must ensure that all trial drugs are used only for subjects participating in the clinical trial, that their doses and usage are in accordance with the trial scheme,

and that the remaining drugs are returned to the manufacturer. Experimental drugs should not be transferred to any non-clinical trial participant.

15. Principle center and investigator

Principle center: Sun Yat-Sen University Cancer Center
Principle Investigator: Yan-Qun Xiang
Address: Dongfeng East Road 651, Guangzhou 51006082 / 92
Telephone: 020-87343379
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Appendix I: Acute Induction Chemotherapy and Chemoradiotherapy Toxicity Graded by Common Terminology Criteria for Adverse Events (CTCAE 5.0).

The CTCAE V5.0 manual can be found at the following URL:
https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

Appendix II: ECOG Performance Status and Scores

Score	ECOG Performance status*
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead
* Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655. Note: ECOG denotes Eastern Cooperative Oncology Group	

Appendix III: The 8th editions of the AJCC Staging System of Nasopharyngeal Carcinoma

Tumor stage	
Tx	Primary tumour cannot be assessed
T0	No tumour identified, but there is EBV-positive cervical node(s) involvement
T1	Nasopharynx, oropharynx, or nasal cavity without parapharyngeal extension
T2	Parapharyngeal extension, adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T3	Bony structures (skull base, cervical vertebra) and/or paranasal sinuses
T4	Intracranial extension, cranial nerve, hypopharynx, orbit, extensive soft tissue involvement (beyond the lateral surface of the lateral pterygoid muscle, parotid gland)
Node stage	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral cervical, unilateral, or bilateral retropharyngeal lymph nodes, above the caudal border of cricoid cartilage; ≤ 6 cm
N2	Bilateral metastasis in lymph node(s), ≤ 6 cm in greatest dimension, above the caudal border of cricoid cartilage
N3	> 6 cm and/or below caudal border of cricoid cartilage (regardless of laterality)
Metastasis	
M0	No distant metastasis
M1	Distant metastasis
TNM stage	
I	T1 N0 M0
II	T2 N0–1 M0, T0–1 N1 M0
III	T3 N0–2 M0, T0–2 N2 M0
IVa	T4 or N3 M0
IVb	Any T, any N, M1

Trial Protocol

An open-label, phase II study of cadonilimab (anti-PD-1 and CTLA-4 bispecific antibody) in combination with chemotherapy in anti-PD-1 resistant recurrent or metastatic nasopharyngeal carcinoma

Version Number: Final Version
Current Edition: May 15, 2023

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Protocol Synopsis

Study Title: An open-label, phase II study of cadonilimab (anti-PD-1 and CTLA-4 bispecific antibody) in combination with chemotherapy in anti-PD-1 resistant recurrent or metastatic nasopharyngeal carcinoma
Study Objectives: To evaluate the efficacy and safety of cadonilimab combined with NAB-paclitaxel, platin, and capecitabine chemotherapy in the treatment of recurrent or metastatic nasopharyngeal carcinoma patients who failed to at least one line of systemic chemotherapy and anti-PD-1 therapy.
Target Subject Population: Recurrent or metastatic nasopharyngeal carcinoma patients who unfit for radiotherapy and surgery and progress from at least one line of systemic chemotherapy and anti-PD-1 therapy.
Study Endpoints **Primary:** To assess objective response rate (ORR) based on the criteria of RECIST V1.1 **Secondary:** To evaluate progression-free survival (PFS), overall survival (OS), duration of response (DoR), median time to response (mTTR), and safety based on the criteria of CTCAE V5.0. **Exploratory:** Tumor tissue biomarkers: including but not limited to PD-L1 expression, tumor mutation burden (TMB), immune-related gene expression, and changes in tumor immune microenvironment.
Study Design This is a Phase 2, open-label, clinical trial conducted in China to evaluate the efficacy, safety of cadonilimab combined with NAB-paclitaxel, platin, and capecitabine chemotherapy in the treatment of recurrent or metastatic nasopharyngeal carcinoma after failure of at least one line of systemic chemotherapy and anti-PD-1 therapy. This study consists of a screening period, a treatment period, and a follow-up period. **Screening Period:** All patients are under standardized management for NPC, and they need to perform a series of examinations as well as provide relevant information before the first dose to determine whether they meet the eligibility criteria. **Treatment Period:** After screened, the eligible subjects will receive cadonilimab in combination with TPC regimen every 3 weeks for a maximum of 6 cycles as induction treatment, following by cadonilimab and capecitabine every 3 weeks as maintenance treatment documented progressive disease (PD), death, intolerable toxicity, treatment duration of 24 months, or withdrawal of consent. The subject will be allowed to continue treatment if judged by the investigator to have been clinically benefited and be able to tolerate cadonilimab at the time of the first PD confirmed by imaging assessment. Subjects will receive cadonilimab for a maximum of 24 months throughout the study. The investigator and radiologists shall perform response assessments according to RECIST v1.1 criteria during the treatment period. Tumor assessments will be performed every two cycles during induction therapy phase, every three cycles during maintenance therapy phase, and three

months thereafter. Subjects who discontinue drug administration due to reasons other than PD will continue to be followed for disease status until the initiation of other anti-tumor therapies, PD, withdrawal of informed consents, dead or study discontinuation, whichever occurs first.
During the treatment period, the safety of cadonilimab will be assessed by the investigator. AEs will be graded as per NCI CTCAE V5.0, and judged for their relationships with the study drug.
Depending on the severity and causality of the AE, the investigator will take a series of measures and concomitant therapies to ensure the safety of the subjects.

Follow-up Period:

Regardless of the cause of the study's treatment interruption, patients should be reviewed approximately one month after the last treatment cycle and all emerging adverse events recorded. A survival follow-up visit will be performed every 3 months after the last dose to obtain information on survival and subsequent tumor treatment after discontinuation until 36 months after study entry or subject death, withdrawal of consent, or end of study, whichever occurs first.

Treatment Regimen:

Cadonilimab was intravenously given at dose of 10 mg/kg, administered as a 120-minutes (± 10 min) infusion on day 1. The TPC regimen consisted of NAB-paclitaxel at a dose of 200 mg/m^2, administered over 30 minutes infusion on day 1, followed by cisplatin at a dose of 60 mg/m^2 on day 1; And capecitabine at a dose of 1000 mg/m^2, taken orally twice a day on days 1 to 14, for each cycle. For those with cisplatin intolerance, lobaplatin were replaced at a dose of 30 mg/m^2 on day 1.

Number of Trial Patients:

25 patients will be enrolled

Statistical Analysis Plan

Sample Size Estimation:

The null hypothesis was an ORR of ≤20% for R/M NPC patients failed to at least one prior line of anti-PD1 therapy, and the alternate hypothesis was an ORR ≥ 45% for the treatment of this trial. In the first stage, 10 patients will be accrued. If there are 2 or fewer responders in these 10 patients, enrollment will discontinue. Otherwise, 12 additional patients will be accrued for a total of 22 patients. If there were more than 7 patients with PR or CR, then the treatment regimen was considered a success. With an estimated 10% shedding rate, a total of 25 patients should be finally included.

Analysis of Efficacy:

The primary endpoint of this study is ORR per RECIST v1.1. ORR analysis will be performed based on the FAS, using the Clopper Pearson method to estimate 95% confidence intervals (CIs). Time to event endpoints (DoR, PFS, and OS) will be analyzed using the Kaplan-Meier method. Measured and evaluated values of target lesions, non-target lesions, and new lesions are recorded according to RECIST v.1.1.

Analysis of Safety:

The frequencies and incidences of each AE and treatment-related parameters will be detailed in tabular form. The summary statistical results of AEs will be listed according to their seriousness (SAEs), severity and causality with the study drug, and AEs and AESIs that lead to discontinuation will also be summarized. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V5.0 and will be described using preferred terms (PTs) of the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory abnormalities and toxicity levels will be derived and summarized according to NCI CTCAE V5.0.

1. Background

1.1 Nasopharyngeal carcinoma (NPC)

Nasopharyngeal carcinoma (NPC) is a special type of head and neck tumors due to its distinct geographical, etiological and biological characteristics.1 It has a high prevalence in South China, Southeast Asia, and North Africa, and is closely linked to Epstein-Barr virus (EBV) infections.[1-3] The incidence of distant metastasis of newly diagnosed NPC patients is approximately 6-15%, and about 20% of non-metastatic NPC experience recurrent or metastasis eventually after definitive treatments.[4,5]

1.2 Treatment of recurrent/metastatic NPC

The results from recently studies have established the combination of gemcitabine plus cisplatin and PD-1 inhibitor as the standard first-line regimens for recurrent or metastatic NPC (RM-NPC) patients.[6-8] With objective response rate (ORR) of 69.5% to 87.3% though, the median progression-free survival (mPFS) was 9.2 to 21.4 months.[6-8] Under such conditions, most patients will develop disease progression within 1 to 2 years. Recent studies showed that the prognosis of these patients was poor under later line therapy, with an ORR of 22.68% to 34.3% and mPFS of 4.4 to 7.9 months.[9-11] Therefore, novel treatment options are urgently needed to improve the efficacy and prognosis for RM-NPC who failed to at least one line of systemic chemotherapy and anti-PD-1 therapy.

1.3 Cadonilimab in NPC

Cadonilimab (AK104) is humanized bispecific antibody that targets to PD-1 and CTLA-4.12 Its tetravalent and no Fc binding design contribute to its high binding activity in the tumor microenvironment and improved safety profile.[13] Recent studies have shown encouraging efficacy and manageable toxicity of cadonilimab in several different cancer types.[14-16] Cadonilimab monotherapy has shown an ORR of 30% and disease control rate (DCR) of 70%, with the median disease-free survival time of 3.71 months in patients with RM-NPC at the second line setting.[17] There is no study available to explore the role of cadonilimab in anti-PD-1 resistant RM NPC patients.

1.4 TPC regimen in NPC

Our previous study prospectively proven the superiority of TPC regimen (paclitaxel, cisplatin, and capecitabine) versus cisplatin and fluorouracil (PF) as induction treatment for patients with stage IVA NPC in NPC patients.[18] Besides, after achieved disease control from TPC regimen, capecitabine maintenance therapy significantly improved PFS for patients with newly diagnosed

metastatic NPC with tolerable toxicities.[19] These results suggest the promising application prospect of TPC regimen in RM-NPC patients.

In this phase 2 trial, we firstly assessed the efficacy and safety of cadonilimab plus TPC chemotherapy as the second or later-line treatment in patients with RM-NPC who failed to at least one line of systemic chemotherapy and anti-PD-1 therapy.

2. Objectives

2.1 Primary Objectives

To assess objective response rate (ORR) of cadonilimab in combination with the TPC (NAB-paclitaxel, platin and capecitabine) chemotherapy regimen for the treatment of recurrent/advanced nasopharyngeal carcinoma after failure of at least one line of systemic chemotherapy and anti-PD-1 therapy based on the criteria of RECIST V1.1.

Primary endpoints will be analyzed based on the FAS. For the analysis of the primary endpoints, IRC-assessed ORR and its 95% confidence interval (Clopper-Pearson method) will be estimated.

2.2 Secondary Objectives

To evaluate progression-free survival (PFS), overall survival (OS), duration of response (DoR), median time to response (mTTR), and safety evaluation (Treatment-related adverse events are assessed according to NCI-CTCAE V5.0; Appendix I) of cadonilimab in combination with the TPC (NAB-paclitaxel, platin and capecitabine) chemotherapy regimen for the treatment of recurrent/advanced nasopharyngeal carcinoma after failure of anti-PD-1 therapy.

2.3 Exploratory Objectives

Tumor tissue biomarkers: including but not limited to PD-L1 expression, tumor mutation burden (TMB), immune-related gene expression, and changes in tumor immune microenvironment.

3. Trial Scheme

Ten patients were enrolled in the first stage. If there are 2 or fewer responders in these 10 patients, enrollment will discontinue. Otherwise, 12 additional patients will be accrued for a total of 22 patients. If there were more than 7 patients with PR or CR, then the treatment regimen was considered a success. With an estimated 10% shedding rate, a total of 25 patients should be finally included.

4. Patients Enrollment

4.1 Eligibility Criteria

1) Pathologically confirmed diagnosis of non-keratinizing carcinoma of the nasopharynx (differentiated or undifferentiated).
2) Confirmed diagnosis of metastatic or recurrent nasopharyngeal carcinoma that is not amenable to radical local treatment.
3) Patients must have progressed to at least one line of systemic chemotherapy and anti-PD-1 therapy.
4) Age ≥ 18 years and ≤ 70 years.
5) ECOG score (Appendix II) of 0-1 and have an expected survival more than 3 months.
6) At least one measurable lesion (according to RECIST 1.1), lesions that have received radiotherapy and have clearly progressed on imaging and are measurable may be considered as target lesions.
7) Adequate organ function: Hemoglobin (HGB) ≥ 85 g/L, white blood cells (WBC) ≥ 3×10E9 /L, platelets (PLT) ≥ 75×10E9 /L. Total bilirubin (TBIL) < 1.5 × upper limit of normal (ULN), alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) < 2.5 times the upper limit of normal (ULN); If the patient has liver metastases, ALT or AST<5 × ULN. Creatinine level ≤1.5 × ULN.
8) Voluntarily participate in this study and sign informed consent.
9) Fertile female subjects and male subjects with fertile sexual partners must agree to apply reliable contraceptive methods (e.g. condoms, contraceptive pills used regularly as prescribed, etc.) for 6 months from screening until 6 months after the last treatment.

4.2 Exclusion Criteria

A. Pathology of keratinizing squamous cell carcinoma (WHO staging type I).
B. A history of monoclonal antibody hypersensitivity.
C. A known history of interstitial pneumonia.
D. A history of serious infection within 4 weeks before enrollment, including but not limited to

complications requiring hospitalization, sepsis or severe pneumonia;

E. Patients treated with aspirin (> 325 mg/day) or dipyridamole, ticlopidine, clopidogrel, and cilostazol within 3 weeks before enrollment, or anticoagulants requiring INR monitoring (e.g., warfarin), or any blood component and cell growth factor support therapy within 1 week before enrollment.
F. Active infections requiring systemic therapy.
G. Patients with active hepatitis B (HBV-DNA ≥ 1000 IU/mL) despite treatment, except for patients with cured hepatitis C.
H. Receive TPC chemotherapy within 6 months before enrollment.
I. Received the last radiotherapy or antineoplastic treatment within 3 weeks before enrollment.
J. Has a known history of active tuberculosis or autoimmune diseases.
K. With HIV infection.
L. Concurrently suffering from other uncontrolled malignancies.
M. Patients presenting with abnormal function of vital organs such as heart, brain or lungs, or the presence of clinically significant hydronephrosis, ascites or pericardial effusion, or being treated with thrombolytic therapy.
N. Women who are pregnant or breastfeeding.
O. Persons with personality or psychiatric disorders, civil capacity or restricted civil capacity.
P. Currently participating in an interventional clinical study or have received other investigational drugs within 4 weeks before enrollment.

4.3 Criteria for withdrawal from protocol treatment

Patients who discontinue the trial treatment for any reason are considered to have withdrawn. Patients may withdraw from the study for the following reasons:

a) The patients or their legal representative withdraw consent.
b) Investigators believe that the termination of the treatment is beneficial to patients.
c) Poor compliance did not meet the requirements of this study.
d) The test results of the subject's β-HCG test indicated that the subject was pregnant. At the same time, pregnancy will also be reported as a serious adverse event reporting procedure.
e) Use of prohibited medications or other medications that the investigator believes will cause a toxic reaction or affect the results of the study.
f) Patients suffering from an intercurrent disease that significantly affects the assessment of clinical status or necessitates discontinuation of the drug, or both.
g) Tumor progression.
h) Appears of a second primary cancer.
i) Discontinue study therapy for more than 30 days.
j) Death

5. Treatment Plan

5.1 Pretreatment Assessment

All patients are under standardized management for NPC, and they need to perform a series of examinations as well as provide relevant information to confirm pathologic diagnosis and clinical stage before admitted into trial.

1) Medical history review.
2) Personal data collection.
3) Current medications and treatment.
4) Body examinations, include height, weight and vital signs.
5) Physical examination of head and neck region, include nasopharynx and cervical lymph nodes.
6) Physical examination of the nervous system.
7) Nasal endoscopy and lesion biopsy.
8) Complete blood count and differential, electrolytes, liver and renal function test.
9) Recurrent or metastatic biopsy specimens, blood specimens (when necessary)
10) EBV antibodies and EBV DNA testing.
11) Virological examination (completed within 14 days prior to the first dose): HBsAg (if positive, HBV-DNA is required), HBsAb, HBeAg, HBeAb, HBcAb, HCV-Ab (if positive, HCV-RNA is required), HIV-Ab.
12) Electrocardiogram and Echocardiography.
13) Imaging, including enhanced MRI or enhanced CT of the head and neck (CT is indicated only in patients with contraindication to MRI).
14) Chest CT.
15) ECT bone scan.
16) Abdominal CT/MR.
17) PET/CT is optional and is performed at the discretion of the attending physician.

5.2 Pretreatment Staging Criteria

The disease stage of subjects will be staged according to the 8th edition of the Union for International Cancer Control / American Joint Committee on Cancer (UICC/AJCC) staging system (Appendix III).

5.3 Immunotherapy and chemotherapy

5.3.1 Induction therapy phase

5.3.1.1 Cadonilimab

Cadonilimab was intravenously given at dose of 10 mg/kg, administered as a 120-minutes (± 10 min) infusion on day 1; repeat every 3 weeks.

5.3.1.2 Chemotherapy with TPC regimen

The TPC regimen consisted of NAB-paclitaxel at a dose of 200 mg/m^2, administered over 30 minutes infusion on day 1, followed by cisplatin at a dose of 60 mg/m^2 on day 1; And capecitabine at a dose of 1000 mg/m^2, taken orally twice a day on days 1 to 14; repeat every 3 weeks. For those with cisplatin intolerance, lobaplatin were replaced at a dose of 30 mg/m^2 on day 1.

After the infusion of cadonilimab, NAB-paclitaxel and cisplatin are successively administered intravenously after an interval of at least 30 min. Cadonilimab and TPC chemotherapy were given every 3 weeks for a maximum of 6 cycles.

5.3.2 Maintenance therapy phase

5.3.2.1 Cadonilimab

Cadonilimab was intravenously given at dose of 10 mg/kg, administered as a 120-minutes (± 10 min) infusion on day 1; repeat every 3 weeks.

5.3.2.2 Capecitabine

Capecitabine were given at dose of 1000 mg/m^2, taken orally twice a day on days 1 to 14; repeat every 3 weeks.

Cadonilimab and capecitabine were given every 3 weeks for a maximum of 24 months. The treatment was discontinued when there were signs documented progressive disease (PD), death, intolerable toxicity, treatment duration of 24 months, or withdrawal of consent. The subject will be allowed to continue treatment if judged by the investigator to have been clinically benefited and be able to tolerate cadonilimab at the time of the first PD confirmed by imaging assessment.

5.4 Salvage therapy

Nasopharyngeal surgery, neck dissections, secondary radiotherapy, chemotherapy, or immunotherapy may be given to patients with relapse or metastasis after treatment according to guidelines of National Comprehensive Cancer Network (NCCN).

5.5 Dosage adjustment principle

Dose modification and toxicity management will be performed based on the severity of toxicities according to National Cancer Institute Common Terminology for Adverse Events Version 5.0 (NCI CTCAE V5.0) grading system. Dosage may not be reduced or discontinued if the investigator considers that the adverse reaction is unlikely to develop into a serious or life-threatening events and will not result in delay or interruption of treatment. If one agent is discontinued due to unacceptable toxicity, patients are able to continue the study with the other agent. Dose interruptions are permitted for reasons other than toxicity, such as medical/surgical events or logistical reasons (e.g., unrelated medical events, elective surgery). The acceptable length of interruption will be at the discretion of the investigator. Reasons for dose modification or delay, the supportive measures taken, and the outcome will be documented.

5.5.1 Adjustment for Cadonilimab

In the event of ≤ Grade 2 infusion-related reactions, the infusion rate of cadonilimab may be reduced, or infusion may be interrupted until resolution of the event (up to 4 hours). If a subject experiences a Grade 3 or 4 infusion-related reaction at any time, cadonilimab treatment must be discontinued.

Adverse events related to cadonilimab may be immunologically related and may occur shortly after the first dose or several months after the last dose. For suspected immune-related AEs (irAEs), ensure adequate evaluation to confirm etiology or exclude other causes. In general, administration of cadonilimab may be continued for most of Grade 1 irAEs. For Grade 2 irAEs, treatment with cadonilimab will be discontinued until Grade 2 irAEs resolve to ≤ Grade 1. In the event of a Grade 3 irAE, cadonilimab treatment may be discontinued based on individual toxicity. In the event of a Grade 4 irAE, treatment with cadonilimab must be discontinued. Cadonilimab should be permanently discontinued if irAEs can not resolve within 12 weeks, expect for the condition that the use of corticosteroids for irAEs and glucocorticoid dose reduction process, or due to treatment of AEs that are possibly unrelated or unrelated to cadonilimab.

Grade 1 non-irAEs do not require cadonilimab adjustment. Cadonilimab should be hold until Grade 2 AEs resolves to Grade 1 or baseline level. For Grade 3 or higher AEs related to cadonilimab that do not meet treatment discontinuation criteria, cadonilimab dosing may be

interrupted. The missed doses will no longer be administered thereafter. For laboratory abnormalities that are clearly not attributable to cadonilimab or are not deemed to be clinically significant will not require a dose omission. Dose reductions are not permitted.

The dose adjustment of cadonilimab is performed according to the following principles.

Table 1: Dose adjustment of cadonilimab

	Adverse events（CTC V5.0）	Treatment adjustment
Pneumonia	Grade 2	Suspend drug until recover to Grade 0-1
	Grade 3-4 or Recurrent Grade 2	Permanent withdrawal
Diarrhea and colitis	Grade 2-3	Suspend drug until recover to Grade 0-1
	Grade 4	Permanent withdrawal
Hepatitis	Grade 2	Suspend drug until recover to Grade 0-1
	Grade 3-4	Permanent withdrawal
Nephritis	Grade 2-3 elevated creatinine	Suspend drug until recover to Grade 0-1
	Grade 4 elevated creatinine	Permanent withdrawal
Endocrine disease	Grade 2-3	Suspend drug until recover to Grade 0-1
	Grade 4	Permanent withdrawal
Cutaneous AEs	Grade 3	Suspend drug until recover to Grade 0-1
	Grade 4	Permanent withdrawal
Neurological irAEs	Grade 2	Suspend drug until recover to Grade 0-1
	Grade 3-4	Permanent withdrawal
Other irAEs	Grade 3-4 elevated blood amylase or lipase Grade 2-3 pancreatitis Grade 2 myocarditis Grade 2-3 other irAEs for the first time	Suspend drug until recover to Grade 0-1
	Grade 4 pancreatitis or recurrent pancreatitis Grade 3-4 myocarditis Grade 3-4 encephalitis Grade 4 other irAEs for the first time	Permanent withdrawal
Recurrent or persistent AEs	Recurrent Grade 3-4 Grade 2 or 3 AEs did not recurrent to grade 0-1 within 12 weeks of the last treatment	Permanent withdrawal
infusion reaction	Grade 2	Slow down the drip rate or suspend the drug
	Grade 3-4	Permanent withdrawal

5.5.2 Dosage adjustment for NAB-paclitaxel

Hematologic adverse events

The hematological toxicity is assessed according to the NCI CTCAE V5.0 classification standard.

Table 2: Dosage adjustment of NAB-paclitaxel for hematologic toxicity

Toxicity	Grade	Time	NAB-paclitaxel
Anemia	Any	Any	Full dosage
Neutropenia	Grade 3	Any	Full dosage
	Grade 4	First time	160 mg/m^2
		Second time	120 mg/m^2
		Third time	Stop
Neutropenic fever	Grade 3-4	First time	160 mg/m^2
		Second time	120 mg/m^2
		Third time	Stop
Thrombocytopenia	Grade 4	First time	160 mg/m^2
		Second time	120 mg/m^2
		Third time	Stop

Peripheral neuritis and extremities joint myalgia

If a patient develops one of the above symptoms, the following methods are recommended to adjust the dosage of NAB-paclitaxel according to the duration and severity of the symptoms. Symptomatic treatment with non-steroidal anti-inflammatory drugs can be given alleviate extremities joint myalgia.

Table 3: Dosage adjustment of NAB-paclitaxel for non-hematologic toxicity

Adverse events	Grade	Duration of adverse events		
		1-7 days	Over 7 days	Persistent
Pain/paresthesia/sensory disturbances, but does not affect function	1	Full dose	Full dose	160 mg/m^2
Pain/paresthesia/sensory disturbances that affect function but do not affect daily activities	2	Full dose	Full dose	120 mg/m^2
Pain/paresthesia/sensory disturbances, with functional impairment, and interference with daily activities	3	Full dose	120 mg/m^2	Stop
Pain/paresthesia/sensory disturbances resulting in loss of function or life threating	4	Stop	Stop	Stop

5.5.3 Dosage adjustment for cisplatin (lobaplatin)

Hematologic adverse events

The hematological cisplatin is assessed according to the NCI CTC AE V5.0 classification standard.

Table 4: Dosage adjustment of cisplatin (lobaplatin) for hematologic toxicity

Toxicity	Grade	Time	cisplatin	lobaplatin
Anemia	Any	Any	Full dosage	Full dosage
Neutropenia	Grade 3	Any	Full dosage	Full dosage
	Grade 4	First time	50 mg/m2	24 mg/m2
		Second time	40 mg/m2	18 mg/m2
		Third time	Stop	Stop
Neutropenic fever	Grade 3-4	First time	50 mg/m2	24 mg/m2
		Second time	40 mg/m2	18 mg/m2
		Third time	Stop	Stop
Thrombocytopenia	Grade 4	First time	50 mg/m2	24 mg/m2
		Second time	40 mg/m2	18 mg/m2
		Third time	Stop	Stop

Other non-hematological toxicity

If other toxicity reaction less than grade 3 occur, symptomatic treatment should be given whenever possible. If grade 3 or 4 toxicity occurs, treatment should be suspended, and when toxicity reverts to grade 1 or below, cisplatin should be administered at 80% of the initial dosage for the next course of treatment

5.5.4 Dosage adjustment for capecitabine

Adverse reactions should be closely monitored during treatment and the dose should be adjusted as needed to enable patients to tolerate the treatment. Once the dose of the drug has been reduced, it should not be increased later. Dose adjustment is not recommended when grade 1 adverse events occur. Capecitabine treatment should be suspended if grade 2 or 3 adverse reactions occur. Treatment can be restarted with the original dose of capecitabine or at the dose adjusted in Table 1 once the adverse reaction has disappeared or the severity has reduced to grade 1. If grade 4 adverse reactions occur, treatment should be suspended until the adverse reactions disappear or the severity is reduced to grade 1, and then treatment should be restarted at 50% of the original dose. Missing capecitabine doses due to toxic reactions should be no longer.

Table 5: Dosage adjustment of capecitabine

NCI assessed advent events	During treatment	Dose of the next cycle (% original dose)
Grade 1	Full dose	Full dose

Grade 2		
First time	Suspended until returned to grade 0~1	100%
Second time	Suspended until returned to grade 0~1	75%
Third time	Suspended until returned to grade 0~1	50%
Grade 3		
First time	Suspended until returned to grade 0~1	75%
Second time	Suspended until returned to grade 0~1	50%
Third time	Permanent termination	
Grade 4		
First time	Permanent termination or suspended until returned to grade 0~1 if researcher believe it is in the patient's interest to continue treatment	50%
Note: patients with hand-foot syndrome would be recommended treated with topical emollient, topical corticosteroid cream, or creams containing urea		

6. Observation and Assessment During Treatment

Investigators would review all inclusion and exclusion criteria for patients to ensure that the patients meet the requirements. After that, each patient must sign the informed consent document before enrollment. The following items need to be assessed during the treatment period.

- Eastern Cooperative Oncology Group (ECOG) performance status, weight, and height.
- Vital signs measurement prior to each treatment cycle, including blood pressure, heart rate, temperature, respiratory rate
- A full physical examination prior to each treatment cycle, including the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems.
- Cardiac function tests using echocardiograms if clinical indicated.
- Acute and late toxicity assessment (including immune-related toxicity), including hematological toxicity, gastrointestinal reactions, hepatotoxicity, nephrotoxicity, mucositis, neurotoxicity, ototoxicity, etc
- Laboratory tests: routine blood tests and blood biochemistry are required for each cycle, other tests are routinely suggested but not mandated for each cycle, including coagulation function

(prothrombin time, activated partial thromboplatin time [APTT], international normalized ratio [INR], thrombin time [TT], fipinogen [FIB], fibrinogen degradation products [FDP], DDimer, antithrombin III [AT III]); Urine routine (blood, glucose, ketones, protein, specific gravity, microscopic exam); Stool routine test; Thyroid function test (total triiodothyronine [T3], free triiodothyronine [free T3], total thyroxine [T4], free thyroxine [free T4], thyroid stimulating hormone); EBV-DNA loading.

- Computed tomography (CT) or magnetic resonance imaging (MRI) of chest, abdomen, and pelvis were used to evaluate the image information before the first treatment and subsequent tumor assessments. Bone scans or CT/MRI scan and nasopharynx and neck CT/MRI will also be performed if clinically indicated. Response evaluation is conducted every two cycles during induction therapy phase, every three cycles during maintenance therapy phase, and three months thereafter by the investigators with radiologists using RECIST V1.1. Per RECIST v1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. At the investigator's discretion, CT scans or MRI should be repeated at any time if progressive disease is suspected.

7. Exploratory analysis and translational study

7.1 Exploratory analysis

Pathologic evaluation of tissue specimens from recurrent or metastatic site biopsy collected before enrollment and when the subject achieves first disease response or PD if conditions permit, and fresh tumor tissues will be obtained for relevant biomarker analysis.

EBV DNA clearance rate.

7.2 Translational study

1) Signed informed consent is required prior to each biological sample collection.
2) Clinical specimens for the above cases whose informed consent have been signed will be collected by designated professionals, and all specimens collected will be used for subject-related scientific research only.
3) After collection, tumor tissue specimens will be collected by the principal investigator and stored in a refrigerator at -80 °C or transferred to a designated laboratory for processing and analysis.

8. Safety Evaluation

All observations relevant to the safety of the drug under study will be documented in the case report form (CRF) and the final summary report. Safety indicators are as follows: adverse events, laboratory changes (hematology, blood biochemistry), changes in vital signs (blood pressure, heart rate, respiratory rate, body temperature), and changes in electrocardiogram and chest CT.
During the treatment period, the safety of cadonilimab will be assessed by the investigator. AEs will be graded as per NCI CTCAE V5.0, and judged for their relationships with the study drug. Depending on the severity and causality of the AE, the investigator will take a series of measures and concomitant therapies to ensure the safety of the subjects.

Safety evaluation was evaluated in every cycle throughout the treatment period and 30 days after treatment discontinuation (90 days for immune-related AEs) and were graded according to the NCI CTCAE V5.0. A SAE is any life-threatening medical adverse event that occurs at a variety of drug doses:

- Causing death or endangering life. It should be noted that the term "lifethreatening" in the definition of "severe" means that at the time of the event, the patient is at risk of death. It's not a hypothetical event.
- Causing permanent or severe disability/dysfunction.
- Teratogenicity/birth defects.
- Resulting in prolonged hospital stays.
- Lead to secondary tumors.
- Other unpredictable drug related AEs

In the event of a serious adverse event, whether or not related to the study drug, the investigator shall immediately notify the Clinical Investigation Center (GCP) of the Serious Adverse Event table within 1 business day (in any case). The form must be dated and signed by the person filling it out.

All adverse events, whether or not they are thought to be drug-related, should be documented in the case report, including diagnosis, start/end time, interventions taken, discontinuation of treatment, remedies, outcomes, and other possible causes. The investigator should determine the association of all adverse events with treatment and the severity of the event. The severity of acute adverse events should be graded according to CTCAE V5.0. The most severe severity should be recorded in the CRF.

9. Follow Up

Regardless of the cause of the study's treatment interruption, patients should be reviewed approximately one month after the last treatment cycle and all emerging adverse events recorded. The patient will be evaluated for the following items during the visit:

- Physical examination includes weight, vital signs, evaluation of physical condition, general condition and toxicity;

- All abnormal laboratory test values that occurred when the patient dropped out of the study.
- Tumor evaluation

Tumor imaging should be performed whenever there is clinical suspicion of disease progression. A survival follow-up visit will be performed every 3 months after the last dose to obtain information on survival and subsequent tumor treatment after discontinuation until 36 months after study entry or subject death, withdrawal of consent, or end of study, whichever occurs first.

10. Safety Measures and Quality Control

Researchers is responsible for obtaining informed consent signed by each subject or his or her agent; carefully fill out the case report form; complete records of laboratory examinations, clinical records, and original medical records of the subjects.

A. Provide systematic learning program for every member in the research group.
B. Make monitoring plan of adverse effects and emergency plan.
C. Research plan is made by all participating centers and approved by Ethics Committee.
D. Develop all kinds of standard operation procedures related to this study.
E. Establish standardized evaluation system to unify diagnostic criteria, curative effect judging criteria, etc.
F. Establish professional statistical plan.
G. Research staffs are trained before the study.
H. Ensure that every participating center conducts the study at the same pace.
I. Arrange quality controller, make quality control plan and check regularly.
J. Set up coordination committee, curative effect judging group and follow-up team.
K. Made records in a true, timely, complete and standardized manner.
L. Sort out the corresponding project files, which will be archived and saved after being quality control checked.
M. The management of the clinical research unit shall check the feasibility of the research carried out.

11. Data Collection and Data Management

11.1 Case Report Form (CRF)

The CRF is completed by the investigator and must be completed by each enrolled patient. After the completed CRF is reviewed by the clinical supervisor, the first copy is transferred to the data administrator for data entry and management.

11.2 Data Entry and Modification

All information about the enrolled patients after registration will be sent to Sun Yat-sen University Cancer Center for management. We have stewards taking charge of data entry and management. Data administrators use EpiData 3.1 software to compile data entry program and carry out data entry and management. In order to ensure the accuracy of the data, two data administrators should independently conduct double input and proofreading. If there are any questions in the CRF, the data administrator will send questioned data to the investigator for verification. The investigator should answer and return the questions as soon as possible. The data administrator can modify, confirm and enter the data according to the answers of the investigator.

11.3 Data Locking

After confirming that the established database is accurate, the main researchers, data administrators, and statisticians will lock the data. The locked data file will not be modified.

12. Statistical Analysis

12.1 Endpoint Definitions

12.1.1 Primary End Point

The primary endpoint was ORR, which was defined as the objective tumor response as per the RECIST 1.1 and is obtained by dividing the number of patients whose is CR or PR by the number of patients.

12.1.2 Secondary End Points

Progression-free survival (PFS), defined as the time from treatment initiation to disease progression according to RECIST V1.1 or death from any cause, whichever occurs first. Cases in which disease progression has not yet occurred will be censored using their last tumor evaluation date;

Overall survival (OS), defined as the time from treatment initiation until death. Cases that are still alive will be censored using their last follow-up date.

Duration of response (DoR), defined as the time from the first evidence of response to disease progression or death;

Median time to response (mTTR), defined as the median time to response;
Safety evaluation, treatment-related adverse events are assessed according to CTCAE V5.0.

12.2 Sample Size and Power Calculations

A Simon's optimal two-stage design was employed with a one-sided type I error rate of 5% and power of 80%. The reported data indicated that the ORR of pembrolizumab in R/M NPC patients who received at least one prior line of platinum-based chemotherapy in NCI-9742 was 20.8%.[20] Our data suggested that ORR was 22.68% in R/M NPC patients failed to at least one prior line of anti-PD1 therapy and received chemotherapy as following treatment.[9] The null hypothesis was an ORR of $\leqslant$ 20% for R/M NPC patients failed to at least one prior line of anti-PD1 therapy, and the alternate hypothesis was an ORR $\geq$ 45% for the treatment of this trial. In the first stage, 10 patients will be accrued. If there are 2 or fewer responders in these 10 patients, enrollment will discontinue. Otherwise, 12 additional patients will be accrued for a total of 22 patients. If there were more than 7 patients with PR or CR, then the treatment regimen was considered a success. With an estimated 10% shedding rate, a total of 25 patients should be finally included.

12.3 Analytical Approach

Patients who received at least one dose of the study regimen were included in the protocol analysis set (intention-to-treatment (ITT) and safety set). The primary endpoint of this study is ORR per RECIST v1.1. ORR analysis will be performed based on the FAS, using the Clopper Pearson method to estimate 95% confidence intervals (CIs). Time to event endpoints (DoR, PFS, and OS) will be analyzed using the Kaplan-Meier method. Measured and evaluated values of target lesions, non-target lesions, and new lesions are recorded according to RECIST v.1.1. The frequencies and incidences of each AE and treatment-related parameters will be detailed in tabular form. The summary statistical results of AEs will be listed according to their seriousness (SAEs), severity and causality with the study drug, and AEs and AESIs that lead to discontinuation will also be summarized. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V.5.0 and will be described using preferred terms (PTs) of the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory abnormalities and toxicity levels will be derived and summarized according to NCI CTCAE V5.0. Chi-square test was used for measuring data. The statistical software was SPSS 23.0.

13. Ethical Considerations

This study must be approved by an appropriate institutional ethic committee.

An informed consent must be obtained from individual patients. Copy of the Consent Form, contact number of investigator and ethics committee will be available to patient on request.

All serious and unexpected adverse events or death related to the drugs or radiotherapy must be reported to the study coordinator immediately. Serious adverse events (SAE) to be reported include all deaths during or within 30 days of protocol treatment regardless of cause, grade 5 toxicity, life-threatening grade 4 toxicity, and/or unexpected toxicity. The Study Coordinator of respective center should complete form and fax this within 24 hours to the Principal Investigator (Dr. Yan-Qun Xiang, Tel: 020-87343359, Fax: 020-87343392), the center of clinical trials, the institutional ethic committe and Sun Yat-sen University Cancer Center. Together with the Principal Investigator, appropriate and prompt action will be taken if warranted. Reactions and deaths beyond 30 days from protocol treatment that are judged definite unrelated to treatment should not be reported.

14. Administration of Experimental Drugs

Cadonilizumab was provided free of charge by Kangfang BioPharmaceuticals Co., Ltd. The management, distribution, and recovery of clinical drugs in this trial shall be the responsibility of designated researcher. The researcher must ensure that all trial drugs are used only for subjects participating in the clinical trial, that their doses and usage are in accordance with the trial scheme, and that the remaining drugs are returned to the manufacturer. Experimental drugs should not be transferred to any non-clinical trial participant.

15. Principle center and investigator

Principle center: Sun Yat-Sen University Cancer Center
Principle Investigator: Yan-Qun Xiang
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Telephone: 020-87343379
Fax: 020-87343379

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Appendix I: Acute Induction Chemotherapy and Chemoradiotherapy Toxicity Graded by Common Terminology Criteria for Adverse Events (CTCAE 5.0).

The CTCAE V5.0 manual can be found at the following URL:
https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

Appendix II: ECOG Performance Status and Scores

Score	ECOG Performance status*
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead
* Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655. Note: ECOG denotes Eastern Cooperative Oncology Group	

Appendix III: The 8th editions of the AJCC Staging System of Nasopharyngeal Carcinoma

Tumor stage	
Tx	Primary tumour cannot be assessed
T0	No tumour identified, but there is EBV-positive cervical node(s) involvement
T1	Nasopharynx, oropharynx, or nasal cavity without parapharyngeal extension
T2	Parapharyngeal extension, adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T3	Bony structures (skull base, cervical vertebra) and/or paranasal sinuses
T4	Intracranial extension, cranial nerve, hypopharynx, orbit, extensive soft tissue involvement (beyond the lateral surface of the lateral pterygoid muscle, parotid gland)
Node stage	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral cervical, unilateral, or bilateral retropharyngeal lymph nodes, above the caudal border of cricoid cartilage; ≤ 6 cm
N2	Bilateral metastasis in lymph node(s), ≤ 6 cm in greatest dimension, above the caudal border of cricoid cartilage
N3	> 6 cm and/or below caudal border of cricoid cartilage (regardless of laterality)
Metastasis	
M0	No distant metastasis
M1	Distant metastasis
TNM stage	
I	T1 N0 M0
II	T2 N0–1 M0, T0–1 N1 M0
III	T3 N0–2 M0, T0–2 N2 M0
IVa	T4 or N3 M0
IVb	Any T, any N, M1

Summary of changes in protocol

Part (page)	Summary	Changes	Reason
Title (29)	We amend title.	An open-label, phase II study of cadonilimab (anti-PD-1 and CTLA-4 bispecific antibody) in combination with chemotherapy in anti-PD-1 resistant recurrent or metastatic nasopharyngeal carcinoma	Given the poor tolerance of patients to chemotherapy, especially cisplatin, after multiline therapy, lobaplatin was used instead in patients who met the new enrollment criteria and had a clear history of prior cisplatin intolerance. Therefore, we did not specifiy a platinum drug as cisplatin in title. This was approved by the Ethics Committee of Sun Yat-sen University Cancer Center.
Protocol Synopsis (32)	We amend the target subject population	Recurrent or metastatic nasopharyngeal carcinoma patients who unfit for radiotherapy and surgery and progress from at least one line of systemic chemotherapy and anti-PD-1 therapy.	Given the ORR was up to 70% in the first stage (totally 10 patients enrolled), the selection of the population extends from those who progress from first line of chemotherapy and anti-PD-1 therapy to those who progress from at least one line of systemic chemotherapy and anti-PD-1 therapy. (Details can be seen in the changes of eligibility criteria below). This was approved by the Ethics Committee of Sun Yat-sen University Cancer Center.
Objectives (35)	We added exploratory objectives.	3.2 Exploratory Objectives Tumor tissue biomarkers: including but not limited to PD-L1 expression, tumor mutation burden (TMB), immune-related gene expression, and changes in tumor immune microenvironment.	We would further explore the underlying mechanism of the efficacy of this regimen in the future. It was approved by the Ethics Committee of Sun Yat-sen University Cancer Center.
Eligibility Criteria (36)	We added the enrollment of patients who have failed to immunotherapy	3) Patients must have progressed to at least one line of systemic chemotherapy and anti-PD-1 therapy.	The eligibility criteria was amended with following consideration: (1) the ORR was up to 70% in the first stage (totally 10 patients enrolled);

	at second or later line.		(2) Increasing patients who have failed to immunotherapy at second or later line wants to used this study regimen. This was approved by the Ethics Committee of Sun Yat-sen University Cancer Center.
Exclusion Criteria (37)	We supplement a list of exclusion criteria.	H. Receive TPC chemotherapy within 6 months before enrollment.	The exclusion criteria was added with following consideration: (1) reuse of the same regimen of TPC chemotherapy within 6 months before enrollment may discount the therapeutic effect and therefore potentially harm the interests of patients; (2) No enrolled patients before we change protocol received TPC chemotherapy within the 6 months before enrollment. This was approved by the Ethics Committee of Sun Yat-sen University Cancer Center.
Chemotherapy with TPC regimen (39)	We supplement the treatment of patients with clean evidence of prior cisplatin intolerance.	For those with cisplatin intolerance, lobaplatin were replaced at a dose of 30 mg/m^2 on day 1.	Given the poor tolerance of patients to chemotherapy, especially cisplatin, after multiline therapy, lobaplatin was used instead in patients who met the new enrollment criteria and had a clear history of prior cisplatin intolerance. This was approved by the Ethics Committee of Sun Yat-sen University Cancer Center.
Exploratory analysis (45)	We added detailed information of exploratory objectives.	Pathologic evaluation of tissue specimens from recurrent or metastatic site biopsy collected before enrollment and when the subject achieves first disease response or PD if conditions permit, and fresh tumor tissues will be obtained for relevant biomarker analysis.	We would further explore the underlying mechanism of the efficacy of this regimen in the future. It was approved by the Ethics Committee of Sun Yat-sen University Cancer Center.