BMC Medicine

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Efficacy and safety of cadonilimab (PD-1/CTLA-4 bispecific) in combination with chemotherapy in anti-PD-1-resistant recurrent or metastatic nasopharyngeal carcinoma: a single-arm, open-label, phase 2 trial

Yaofei Jiang[1,2†], Weixin Bei[1†], Lin Wang[1†], Nian Lu[3†], Cheng Xu[4†], Hu Liang[1], Liangru Ke[3], Yanfang Ye[5], Shuiqing He[1], Shuhui Dong[1], Qin Liu[1], Chuanrun Zhang[1], Xuguang Wang[1], Weixiong Xia[1], Chong Zhao[1], Ying Huang[4*], Yanqun Xiang[1*] and Guoying Liu[6*]

Abstract

Background We aimed to evaluate the efficacy and safety of cadonilimab (anti-PD-1 and CTLA-4 bispecific antibody) plus TPC chemotherapy (NAB-paclitaxel, cisplatin or lobaplatin, and capecitabine) in patients with recurrent or metastatic nasopharyngeal carcinoma (RM-NPC) who failed to PD-1 inhibitor-containing regimens.

Methods In this single-arm, open-label, phase 2 study, RM-NPC patients who failed to at least one line of systemic chemotherapy and anti-PD-1 immunotherapy were enrolled and received cadonilimab plus TPC chemotherapy every 3 weeks for up to 6 cycles, followed by cadonilimab plus capecitabine every 3 weeks for a maximum of 2 years. The primary endpoint was the objective response rate (ORR). The secondary endpoints included progression-free survival (PFS), overall survival (OS), duration of response (DoR), and safety.

Results Twenty-five patients were enrolled (84% male; median age 44 years (range, 24–60)), with a median follow-up of 10.2 months. The ORR was 68%, with 3 complete responses, 14 partial responses, and 6 stable diseases. The median DoR was 9.1 months (95% CI, 3.8–14.5 months). The median PFS was 10.6 months (95% CI, 5.2–16.0 months). The 12-month OS was 75.6%. Treatment was well tolerated. Grade 3 or 4 treatment-related adverse events occurred in 12 (48%) patients. Fourteen patients (56%) experienced potentially immune-related adverse events (irAEs). One patient

†Yaofei Jiang, Weixin Bei, Lin Wang, Nian Lu, and Cheng Xu contributed equally to this work.

*Correspondence:
Ying Huang
huangying@sysucc.org.cn
Yanqun Xiang
xiangyq@sysucc.org.cn
Guoying Liu
liugy0109@163.com
Full list of author information is available at the end of the article

experienced a grade 3 immune-related rash and another patient had grade 3 immune-related lipase increased. No treatment-related death occurred.

Conclusions Cadonilimab in combination with TPC chemotherapy demonstrated promising antitumoral efficacy and manageable toxicities in patients with RM-NPC who failed frontline immunotherapy. Further trials are warranted to confirm and expand these findings.

Trial registration This trial was registered at chictr.org.cn (ChiCTR2200067057).

Keywords Cadonilimab, PD-1/CTLA-4 bispecific, Nasopharyngeal carcinoma, Immunotherapy rechallenge

Background

Nasopharyngeal carcinoma (NPC) is a special type of head and neck tumor 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]. The results from recent 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 an objective response rate (ORR) of 69.5% to 87.3% though, the median progression-free survival (PFS) 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 a median PFS 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 at least one line of systemic chemotherapy and anti-PD-1 immunotherapy.

Cadonilimab (AK104) is a humanized bispecific antibody that targets 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 26.1% and a disease control rate (DCR) of 56.5%, with a median PFS time of 3.71 months in RM-NPC patients who had failed first-line platinum-based chemotherapy and second-line single agent or combined chemotherapy [17]. There is no study available to explore the role of cadonilimab in anti-PD-1 resistant RM-NPC patients.

Our previous study has 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 achieving disease control from the 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 the TPC regimen in RM-NPC patients.

In this phase II trial, we first 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 anti-PD-1-based therapy.

Methods

Study design and participants

This was an open-label, single-arm, phase II study conducted at Sun Yat-Sen University Cancer Center. The study was performed in accordance with the Declaration of Helsinki and the International Standards of Good Clinical Practice. Trial protocol and consent forms were approved by the Institutional Review Board (IRB) of Sun Yat-Sen University Cancer Center (B2022-722). The trial was registered at the Chinese Ethics Committee of Registering Clinical Trials (ChiCRT2200067057). Informed written consent was obtained from all patients prior to enrollment.

Patients with histologically confirmed differentiated or undifferentiated non-keratinizing RM-NPC, that is refractory to at least one-line prior chemotherapy and anti-PD-1 systemic therapy and unfit for radical local treatment, were enrolled. Other main eligibility criteria for this study included age 18–70 years, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, a life expectancy of at least 3 months, at least one measurable lesion assessed with Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST V.1.1), and adequate organ function. The major exclusion criteria included patients who received TPC chemotherapy within 6 months before enrollment, patients who received the last radiotherapy or antineoplastic treatment within 3 weeks before enrollment, patients who experienced active tuberculosis or autoimmune disease, other uncontrolled malignancies, active hepatitis B or hepatitis C virus infection, and patients who were pregnant or breastfeeding. The full eligibility criteria are available

in the study protocol (available in Additional file 1). All patients provided informed consent.

Procedures

After screening, the eligible subjects received cadonilimab in combination with a TPC regimen (NAB-paclitaxel, cisplatin/lobaplatin, and capecitabine) every 3 weeks for a maximum of 6 cycles as induction treatment, followed by cadonilimab and capecitabine every 3 weeks as maintenance treatment until documented progressive disease (PD), death, intolerable toxicity, withdrawal of consent, or finishing scheduled 24-month treatment. Cadonilimab was intravenously given at a dose of 10 mg/kg on day 1. The TPC regimen included NAB-paclitaxel administered at a dose of 200 mg/m^2 on day 1, 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, cisplatin was replaced with lobaplatin at a dose of 30 mg/m^2 on day 1. Dose modifications of cadonilimab were not permitted. Details about the criteria of discontinuation of cadonilimab and step-wise strategies of dose adjustment of other drugs are provided in the study protocol.

Assessments

After the treatment was initiated, tumor response was evaluated according to the RECIST V.1.1 based on the imaging examination at baseline, every two cycles during the induction phase, every three cycles during the maintenance therapy phase, and 3 months thereafter until PD, withdrawal of informed consents, death, initiation of other anti-tumor therapies, study discontinuation, whichever occurs first. Safety evaluation was evaluated in every cycle throughout the treatment period and 30 days after treatment discontinuation (90 days for immune-related adverse events, irAEs) and was graded according to the National Cancer Institute Common Terminology for Adverse Events Version 5.0 (NCI CTCAE V5.0).

Outcomes

The primary endpoint was ORR, which was defined as the proportion of patients with complete response (CR) or partial response (PR) according to RECIST V.1.1. The secondary endpoints include PFS, defined as the time from treatment initiation to disease progression or death from any cause, whichever occurs first; overall survival (OS), defined as the time from treatment initiation until death; 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 from treatment initiation to response and safety.

Statistical analysis

This study was based on Simon's optimal two-stage design, with a one-sided type I error rate of 5% and a power of 80%. The null hypothesis ORR was 20% and the target ORR was 45%. 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.

Efficacy analysis was performed in the intention-to-treat (ITT) population. Safety analyses were performed in patients who received at least one cycle of study treatment. ORR was calculated using the Clopper Pearson method and estimated 95% confidence intervals (CIs). Time-to-event endpoints (DoR, PFS, and OS) were analyzed using the Kaplan–Meier method. Clinical outcomes, demographic characteristics, and AEs were performed using proportions, frequencies, medians, and interquartile ranges (IQRs). We used R software V 4.3.0 to perform all statistical tests. A p value less than 0.05 was considered statistically significant.

Results

Patients and treatment

Between February 15, 2023, and June 28, 2023, we screened 38 patients, and 25 of them were finally enrolled in this study and received at least one cycle of study treatment (ITT and safety set; Fig. 1). One patient refused to continue the treatment after the first cycle of treatment due to personal reasons. The remaining 24 patients had at least one post-treatment tumor assessment and were evaluable for treatment responses (Fig. 2).

Baseline characteristics of the enrolled patients are summarized in Table 1. The median age was 44 years (range, 24–60 years). All patients received at least one line of prior systemic therapy for advanced disease, with 3 (12%) receiving 2 lines and 6 (24%) receiving ≥ 3 lines. There were 5 (20%) patients who previously received two or more different PD-1 inhibitors. Twelve patients (48%) had > 3000 copies/ml plasma EBV DNA level before treatment. The median interval of the last anti-PD-1 immunotherapy to enrollment was 2.03 months (range, 0.7–16.03 months). Detail information of previous treatment regimens was shown in Additional file 2: Table S1.

Efficacy

Of the 10 patients enrolled in the first stage, 7 patients obtained confirmed responses, which achieved the requestion of the first stage and the trial continued to full

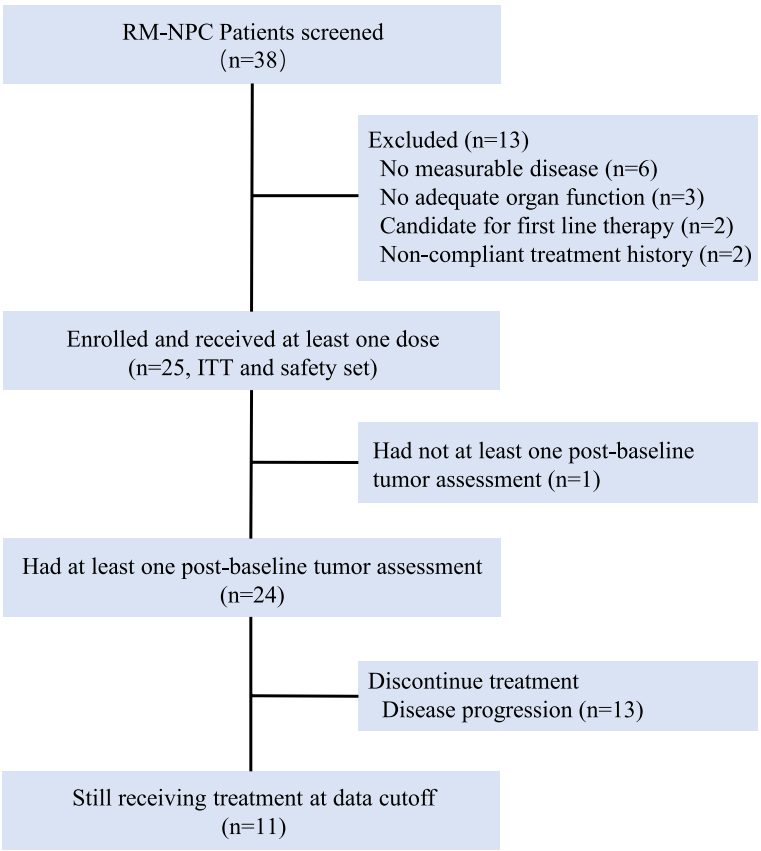

Fig. 1 Trial profiles

accrual. In the ITT set ($n=25$), 17 patients reached a confirmed objective response (ORR 68%, 95% CI, 48–88%), with 3 CR (12%), and 14 PR (56%) (Table 2, Fig. 2, Additional file 3: Fig. S1). Six patients maintained stable disease (SD), one patient with PD (Additional file 2: Note S1), and one patient was not evaluated. Interestingly, 20 patients (20/24, 83.33%) had EBV DNA levels decrease by ≥ 50% from baseline to the first post-treatment assessment, and 17 patients (17/24, 70.83%) decreased by ≥ 90%. Patients with a plasma EBV DNA level decrease of ≥ 50% from baseline to the first post-treatment assessment had significantly higher ORR than those with a plasma EBV DNA level decrease of < 50% (17/20 vs. 4/4, $p<0.001$). Furthermore, the EBV DNA level decrease, the interval of the last administration of immunotherapy to the enrollment, and previous immunotherapy efficacy showed a numerical correlation with ordered response variables (PD, SD, PR to CR) decided by Cochran-Armitage trend test, although there was not a significant difference ($p>0.05$) (Additional file 3: Fig. S2).

To the date cutoff (March 25, 2024), the median follow-up was 10.2 months (range, 4.3–13.5 months). The mTTR was 1.7 months (range, 1.2–4.9 months). The median DoR was 9.1 months (95% CI, 3.8–14.5 months; Fig. 3A). The median PFS was 10.6 months (95% CI, 5.2–16.0 months; Fig. 3B). The median OS has not reached, and 12-month OS was 75.6% (Fig. 3C). Intriguingly, we observed that patients with EBV DNA level decrease ≥ 50% from baseline to the first post-treatment assessment had a significantly longer PFS ($p=0.006$) and OS ($p=0.008$, Additional file 3: Fig. S3) than those with a plasma EBV DNA level decreased by < 50%. However, no significant difference was observed between EBV DNA level at baseline and survival (PFS and OS). Up to the date cutoff, fourteen patients (14/25, 52%) discontinued the study treatment, with thirteen developing disease progression, and one declined further therapy after the first cycle of the study treatment (Figs. 1 and 2, Additional file 2: Table S2).

Safety

In the safety set, twenty-four patients (24/25, 96%) experienced at least one treatment-related adverse event (TRAE) of any grade. TRAEs with an incidence greater than 50% included hypoesthesia ($n=19$, 76%), anemia ($n=18$, 72%), decreased appetite ($n=18$, 72%), fatigue

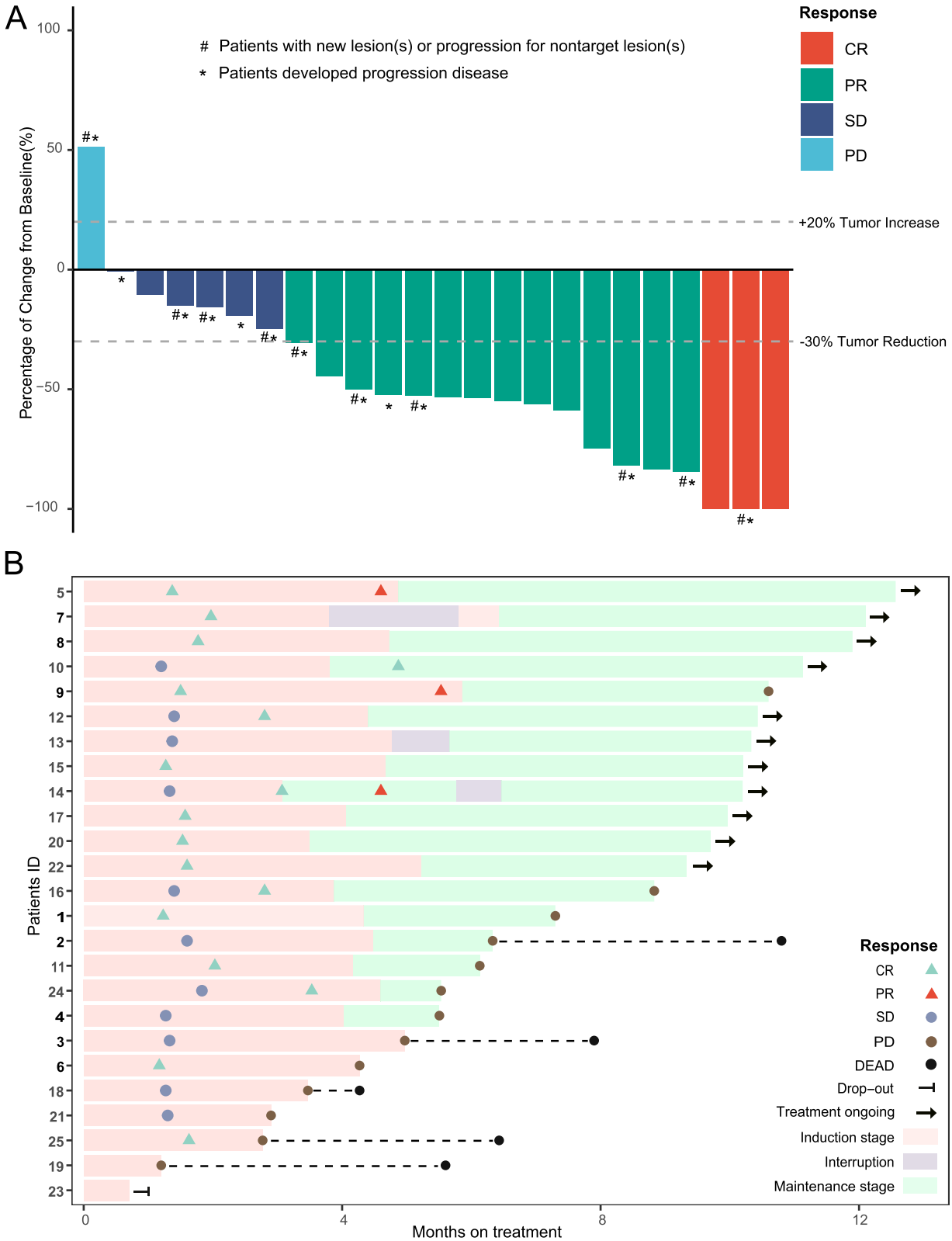

Fig. 2 Antitumor activity. **A** Best percentage change from baseline in target lesion ($n = 24$). **B** Swimmer plot ($n = 25$). Abbreviation: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

Table 1 Characteristics of the patients at baseline

Characteristic	Value (*N* = 25)
Age, years, median (range)	44 (24–60)
Gender, no. (%)	
Female	4 (16)
Male	21 (84)
ECOG[a] performance-status score, no. (%)	
0	19 (76)
1	6 (24)
Initial stage[b], no. (%)	
II–III	9 (36)
IVa	10 (40)
IVb	6 (24)
Location of recurrences/metastases, no. (%)	
Local recurrence	2 (8)
Regional lymph nodes	3 (12)
Liver	12 (48)
Lung	10 (40)
Distant lymph nodes	13 (52)
Bone and soft tissue	15 (60)
EBV DNA copy number, no. (%)	
≤ 3000 copies/mL	13 (52)
> 3000 copies/mL	12 (48)
Time from initial cancer diagnosis to study enrollment, months, median (range)	25.43 (6.2–105.43)
Prior radiotherapy, no. (%)	
Yes	22 (88)
None	3 (12)
Prior therapy lines for advanced disease, no. (%)	
1	16 (64)
2	3 (12)
≥ 3	6 (24)
ICI-free interval, months, median (range)	2.03 (0.7–16.03)
No. of types of prior ICI, no. (%)	
1	20 (80)
2	4 (16)
3	1 (4)
Previous treatment for advanced disease	
PD-1 inhibitor, no. (%)	25 (100)
Toripalimab	13 (52)
Camrelizumab	8 (32)
Sintilimab	5 (20)
Palivizumab	2 (8)
Tislelizumab	1 (4)
Other therapy, no. (%)	25 (100)
Cisplatin	24 (96)
Gemcitabine	22 (88)
Paclitaxel	10 (40)
Capecitabine	5 (20)
Nimotuzumab	4 (16)
Carboplatin	2 (8)
Tegafur	2 (8)
Apatinib	1 (4)
Cetuximab	1 (4)
Anlotinib	1 (4)
Bevacizumab	1 (4)

The initial stage of all enrolled patients was referred to the TNM staging system of the American Joint Committee on Cancer, 8th edition

Abbreviations: *EBV* Epstein-Barr virus, *ICI* Immune checkpoint inhibitor

[a] Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability

[b] The initial stage of all enrolled patients was referred to the TNM staging system of the American Joint Committee on Cancer, 8th edition

Table 2 Antitumor activity

Response evaluation	Value (*N* = 25)
Objective response rate, no. (%)	17 (68)
95% CI	0.48–0.88
Disease control rate, no. (%)	23 (92)
95% CI	0.81–1.03
Best overall response, no. (%)	
Complete response	3 (12)
Partial response	14 (56)
Stable disease	6 (24)
Progressive disease	1 (4)
Unevaluable	1 (4)

(*n* = 18, 72%), leukopenia (*n* = 17, 68%), nausea (*n* = 16, 64%), and increased thyroid-stimulating hormone (*n* = 13, 52%, Table 3). Grade 3 or 4 TRAEs occurred in 12 patients (48%), the most common of which (the incidence of preferred term ≥ 2%) were anemia (*n* = 6, 24%), neutropenia (*n* = 6, 24%), thrombocytopenia (*n* = 4, 16%), hypoesthesia (*n* = 2, 8%), fatigue (*n* = 2, 8%), leukopenia (*n* = 2, 8%), rash (*n* = 2, 8%), and febrile neutropenia (*n* = 2, 8%). Fourteen patients (14/25, 56%) reported potentially irAEs. The most common irAEs (the incidence of preferred term ≥ 10%) include grade 1–2 TSH elevation (*n* = 10, 40%), hypothyroidism (*n* = 8, 32%), musculoskeletal (*n* = 8, 32%), pruritus (*n* = 7, 28%), mucositis (*n* = 6, 24%), and rash (*n* = 4, 16%). Only two patients experienced grade 3 irAEs, one with rash and another with lipase increased. Both of them were managed with supportive measurements and signs/symptoms subsided without sequelae.

During the induction phase, twenty-one patients completed at least four cycles of TPC chemotherapy (Additional file 2: Table S2). Of the other four patients, three progressed and one dropped out. Twelve patients (48%) finished all six cycles of the TPC treatment. Dose

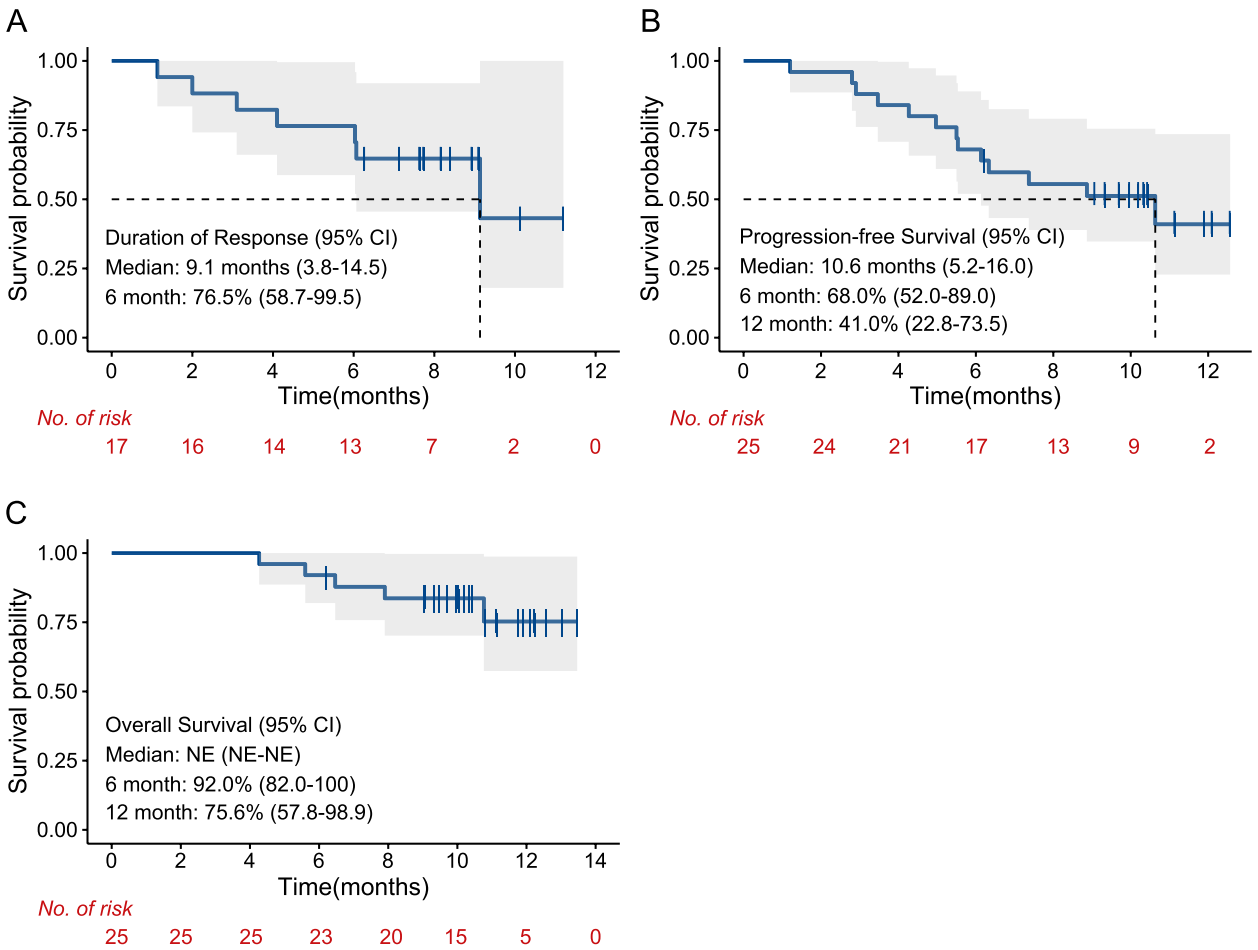

Fig. 3 Kaplan–Meier plots of survival outcomes. **A** Duration of response (DoR) was assessed in responders ($n=17$). **B** and **C** Progression-free survival (PFS) and overall survival (OS) in the intention-to-treat population ($n=25$). NR, not reached; NE, not evaluable

reduction occurred in 11 (44%) patients, with the reasons of gastrointestinal reaction ($n=5$), hand-foot syndrome ($n=3$), and hematologic AEs ($n=3$). One patient required interruption of the treatment because of a fall-induce femoral fracture (Additional file 2: Table S2). Nineteen patients received the maintenance treatment, in which two patients (8%) required capecitabine dose reduction and cadonilimab interruption, respectively (Additional file 2: Table S2). Fourteen patients are still on the study treatment at the date cutoff.

Discussion

This is the first trial to prospectively evaluate the efficacy and safety of additional bispecific antibody (anti PD-1/CTLA-4) cadonilimab to TPC chemotherapy in patients with RM-NPC who progressed to at least one line of systemic chemotherapy and anti-PD-1 immunotherapy. In this study, cadonilimab plus TPC chemotherapy exhibited promising anti-tumoral activity, evidenced by favorable ORR, PFS, DoR, and manageable toxicities.

Patients who developed immunotherapy resistance have poor prognosis and limited treatment options. Immunotherapy rechallenge has not been much successful in various cancer types [20–23]. Rechallenge strategies include combination mode (such as anti-PD-1 plus anti-CTLA-4 or antiangiogenic therapy) and replacement mode (such as changing ICI types) [24–26]. Our retrospective study demonstrated that immunotherapy plus target therapy with or without chemotherapy showed a relatively better survival than chemotherapy only in RM-NPC patients who failed prior anti-PD-1 immunotherapy, with an ORR of 31.25% and 22.68%, respectively [9]. So far, several clinical trials reported the outcome of immunotherapy rechallenge in patients with RM-NPC which were resistant to anti-PD-1 immunotherapy. Results of the trials showed an ORR of 33.3% with anti-PD-1 camrelizubam plus famitinib and 34.3% with camrelizumab plus apatinib respectively [10, 11]. These data demonstrate that immunotherapy rechallenge indeed exhibits a certain but not yet satisfactory anti-tumoral

Table 3 Treatment-related adverse events

Event	*N* = 25		
Any TRAE, No. (%)	**Grade 1–2**	**Grade 3**	**Grade 4**
Hypoesthesia	17 (68)	2 (8)	0
Decreased appetite	17 (68)	1 (4)	0
Fatigue	16 (64)	2 (8)	0
Nausea	15 (60)	1 (4)	0
Leukopenia	15 (60)	0	2 (8)
Blood thyroid-stimulating hormone increased	13 (52)	0	0
Anemia	12 (48)	6 (24)	0
Creatine phosphokinase elevation	12 (48)	0	0
Musculoskeletal pain	12 (48)	0	0
Hypomagnesemia	10 (40)	1 (4)	0
Hyperuricemia	10 (40)	0	0
Constipation	10 (40)	0	0
Pruritus	10 (40)	0	0
Dizziness	9 (36)	0	0
Insomnia	9 (36)	0	0
Vomiting	9 (36)	0	0
Abdominal pain	9 (36)	0	0
Mucositis	8 (32)	0	0
Hypothyroidism	8 (32)	0	0
Hypoalbuminemia	7 (28)	0	0
Hypokalemia	6 (24)	1 (4)	0
Cough	6 (24)	0	0
Thrombocytopenia	5 (20)	2 (8)	2 (8)
Hypocalcemia	5 (20)	1 (4)	0
Hand-foot syndrome	5 (20)	0	0
Headache	5 (20)	0	0
Hiccups	5 (20)	0	0
Diarrhea	5 (20)	0	0
Serum creatinine elevation	5 (20)	0	0
Rash	4 (16)	2 (8)	0
Neutropenia	3 (12)	2 (8)	4 (12)
Weight loss	3 (12)	0	0
Hyponatraemia	2 (8)	0	0
Fever	2 (8)	0	0
Lipase increased	1 (4)	1 (4)	0
Febrile neutropenia	0	2 (8)	0
Total bilirubin elevation	1 (4)	0	0
Amylase increased	1 (4)	0	0
Hypertension	1 (4)	0	0
Colonitis	1 (4)	0	0
ALT elevation	1 (4)	0	0
AST elevation	0	1 (4)	0
Potential irAEs, No. (%)			
TSH elevation	10 (40)	0	0
Hypothyroidism	8 (32)	0	0
Musculoskeletal pain	8 (32)	0	0
Pruritus	7 (28)	0	0
Mucositis oral	6 (24)	0	0
Rash	3 (12)	1 (4)	0
Lipase increased	1 (4)	1 (4)	0
Hypertension	1 (4)	0	0
Colonitis	1 (4)	0	0
Amylase increased	1 (4)	0	0

Abbreviations: *TRAEs* Treatment-related adverse events, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *irAEs* Immune-related adverse events, *TSH* Thyroid stimulating hormone

efficacy. More effectively new medications and combination therapy strategies should be explored for this patient population who developed immunotherapy resistance.

Cadonilimab (AK104) is a symmetric tetravalent bispecific antibody that can target both PD-1 and CTLA-4 [13]. It was reported that the preferential retention of cadonilimab may improve drug retention and bring better antitumor efficacy and safety [13]. Cadonilimab has been shown promising antitumor efficacy either used as monotherapy or combination therapy. Cadonilimab monotherapy can reach an ORR of 26.1% in RM-NPC patients [17] and 13.4% to 32.3% in other advanced solid tumors [14, 15], respectively. Whereas the combination of cadonilimab and lenvatinib in advanced hepatocellular carcinoma at the first-line setting showed an ORR of 36% and median PFS of 9 months in COMPASSION-08 study [16]. Besides, the safety profile of cadonilimab was proved to be relatively better than the combination of anti-PD-1 and anti-CTLA-4 therapy, with the incidence of grade ≥ 3 TRAEs being 6.7 to 28% versus 18–37% [14, 15, 17, 27–30]. With our previous studies elaborated the anti-tumor activity of TPC regimen, here, we performed this study to rechallenge using cadonilimab in combination with TPC in patients with RM-NPC who failed to frontline anti-PD-1 immunotherapy.

In this trial, we observed satisfactory ORR of 68% (3 CR (12%) and14 PR (56%)) in patients with RM-NPC who progressed to at least one line of systemic chemotherapy and anti-PD-1 immunotherapy, which was doubled numerically compared to previous reports (ORR: 31.3–34.3%) [9–11]. The median DoR of this study was 9.1 months, which was much higher than previously reported numbers (2.9–4.2 months) [10, 11]. The median PFS was 10.6 months, which was also much longer than the previously reported median PFS of 4.5–7.2 months [10, 11]. These results strongly suggest that the additional cadonilimab to TPC chemotherapy showed robust and durable antitumoral efficacy in patients with

immunotherapy-resistant RM-NPC. A recent study reported that patients may regain sensitivity to immunotherapy after prolonged suspension of ICIs [10]. In this study, we also found that the patients with longer intervals from the last administration of immunotherapy to enrollment had a numerically higher ORR.

Measurement of plasma EBV-DNA level at baseline and dynamic changes was proved to be a useful biomarker for outcomes and monitoring disease progression [31–33]. In this study, the combination therapy achieved 83.33% of patients with a ≥ 50% decrease and 70.83% of patients with a ≥ 90% decrease in plasma EBV DNA level. Noteworthily, we found that patients with plasma EBV DNA level decrease of ≥ 50% from baseline to the first post-treatment assessment had a significantly higher ORR, longer PFS, and OS than those with plasma EBV DNA level decrease of < 50%. These results were consistent with data from the CAPTAIN study [33], which hint at the value of plasma EBV DNA changes as a reliable clinical efficacy predictor for immunotherapy rechallenge for patients with RM-NPC who progressed to anti-PD-1 immunotherapy. Since almost all NPCs in endemic areas are associated with EBV infection [34], whether the clinical outcomes of immunotherapy rechallenge with cadonilimab plus TPC chemotherapy could be extrapolated to the non-endemic regions still needs further investigation.

The safety profiles of cadonilimab plus TPC chemotherapy in RM-NPC were consistent with previous reports derived from the same patient population or patients with other cancers [10, 11, 14–17]. With chemotherapy addition in our study, however, TRAEs were still comparable to that of the other common regimens with grade ≥ 3 TRAE of 58.6–94% in RM-NPC [6, 7, 11]. In this study, grade ≥ 3 TRAE were reported in 12 patients (48%) which was similar to that reported in a retrospective study that patients with RM-NPC who progressed to anti-PD-1 immunotherapy received camrelizumab plus famitinib (44.4%) [10]. The main grade ≥ 3 TRAEs were anemia, hypoesthesia, fatigue, thrombocytopenia, rash, and neutropenia, which was also consistent with the previously reported safety profile [17, 19]. The irAEs in this study were similar to previously reported cadonilimab-related AEs, including hypothyroidism, musculoskeletal, pruritus, and rash [14, 15, 26]. These results suggest that the combination of cadonilimab and TPC chemotherapy did not result in any unexpected grade 3 or 4 TRAEs or irAEs in this trial, and the combination regimen is well tolerated.

Several limitations exist in this study. Firstly, although there is a notable numerical improvement in the antitumoral efficacy of the study regimen compared with previous exploration in the same population, this was a single-arm study without a control group. Also, at present, we could not predict the benefits proportion brought by cadonilimab and TPC chemotherapy for the efficacy of the combination strategy in this study, and thus these promising results need to be validated in a large-scale, randomized controlled, prospective trial. Secondly, the sample size was relatively small which may reduce the certainty of the reported efficacy and limit the exploration of predictive factors. Third, we did not attempt to explore the underlying molecular mechanisms, which is also valuable to understand exceptional clinical outcomes in this study. Lastly, since all enrolled patients are from the NPC endemic region, whether the clinical outcomes of the present treatment regimen would be suitable for non-endemic regions still needs further exploration.

Conclusions

This study's findings suggest that cadonilimab in combination with TPC chemotherapy exhibited promising antitumoral efficacy and manageable toxicities in patients with RM-NPC who failed to frontline anti-PD-1 immunotherapy. This regimen provides a potentially effective treatment option for RM-NPC patients in the era of immunotherapy. Further randomized controlled clinical trial is warranted to validate the clinical benefit of this combination regimen.

Abbreviations

RM-NPC	Recurrent or metastatic nasopharyngeal carcinoma
ORR	Objective response rate
PFS	Progression-free survival
OS	Overall survival
DoR	Duration of response
irAEs	Immune-related adverse events
EBV	Epstein-Barr virus
DCR	Disease control rate
IRB	Institutional Review Board
ECOG	Eastern Cooperative Oncology Group
RECIST V.1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
PD	Progressive disease
NCI CTCAE V5.0	National Cancer Institute Common Terminology for Adverse Events Version 5.0
CR	Complete response
PR	Partial response
mTTR	Median time to response
ITT	Intention-to-treat
CIs	Confidence intervals
IQRs	Interquartile ranges
SD	Stable disease
TRAE	Treatment-related adverse events

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03985-4.

Additional file 1: Trial protocol

Additional file 2: Note S1 History of the patient who received PD at first time of post-baseline tumor assessment. Table S1 Summary of previous treatment regimens in the first, second, third and fourth lines. Table S2 Compliance to the study regimen.

Additional file 3: Fig. S1 Typical imaging of complete response of metastatic lesions. Fig. S2 Cochran-Armitage trend test to assess the relationship between the response and, A plasma EBV DNA level at baseline by cut-off of 3000 copies/mL; B decrease of plasma EBV DNA level from baseline to the first post-treatment assessment by cut-off of 50%; C internal duration from latest immunotherapy by cut-off of median time of patients; and D best previous immunotherapy efficacy. Fig. S3 Kaplan-Meier plots of progression-free survival (PFS) and overall survival (OS). A and B, PFS and OS stratified by the plasma EBV DNA level at baseline (cut-off of 3000 copies/mL); C and D, PFS and OS stratified by the decrease of plasma EBV DNA level from baseline to the first post-treatment assessment (cut-off of 50%).

Acknowledgements
The authors appreciate all the patients and their families, and the study nurses and coordinators for their dedication to this study.

Authors' contributions
YX, and GL contributed to the conception and design of the work. YJ, WB, LW, NL, CX, HL, LK, YY, SH, SD, QL, CZ, XW, WX, CZ, YH, YX, and GL contributed to the acquisition of the data. YJ, WB, LW, NL, and CX contributed to the data analysis. YJ, WB, LW, NL, CX, YH, YX, and GL contributed to interpretation of the data. YJ, WB, YX, and GL drafted the manuscript. All authors were involved in patient and data management, conceived and (locally) supervised the study, interpreted the data, and revised the manuscript. All authors read and approved the final manuscript.

Funding
This study was supported by the National Natural Science Foundation of China (No. 62220106006, and No. 82203755), the Guangdong Basic and Applied Basic Research Foundation (No. 2021B1515120013). The funders of the study did not contribute to the study design, data collection, data analysis, data interpretation, or writing of the report.
Data sharing statement.
De-identified participant data will be made available to qualified researchers upon request, starting 24 months after the completion of the study, including follow-up. Researchers interested in accessing the data should submit a methodologically sound research proposal to the corresponding author, Guoying Liu, via email at liugy0109@163.com. To obtain access, a data access agreement must be signed.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Study procedures were approved by the institutional review boards of the Sun Yat-Sen University Cancer Center (B2022-722), and all patients provided written informed consent.

Consent for publication
All patients had provided informed consent for the participants in the study and publication of any associated data.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Nasopharyngeal Carcinoma, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University Cancer Center, Guangzhou, China. [2]Department of Oncology, The First Affiliated Hospital of Nanchang University, NanChang, China. [3]Department of Radiology, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University Cancer Center, Guangzhou, China. [4]Department of Radiotherapy, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University Cancer Center, Guangzhou, China. [5]Clinical Research Design Division, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China. [6]Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Medical Research Center, Department of Oncology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China.

Received: 15 August 2024 Accepted: 4 March 2025
Published online: 11 March 2025

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