Toripalimab plus intensity-modulated radiotherapy for recurrent nasopharyngeal carcinoma: an open-label single-arm, phase II trial

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ABSTRACT

Background Toripalimab is a humanized immunoglobulin G_4 monoclonal antibody against programmed death 1. We aimed to investigate the efficacy and safety of toripalimab in combination with intensity-modulated radiotherapy (IMRT) for recurrent nasopharyngeal carcinoma (rNPC).

Methods We conducted a single-arm, phase II trial with patients with rNPC who had biopsy-proven disease and were unsuitable for local surgery. Eligible patients received IMRT in combination with toripalimab administered via intravenous infusion of 240 mg once every 3 weeks for a maximum of seven cycles. The primary endpoint was the objective response rate at 3 months post radiotherapy. The secondary endpoints included safety profiles, progression-free survival (PFS).

Results Between May 2019 and January 2020, a total of 25 patients with rNPC were enrolled (18 men (72.0%) and 7 women (28.0%); median (IQR) age, 49.0 (43.5–52.5) years). With a median (IQR) follow-up duration of 14.6 months (13.1–16.2) months, 19 patients (79.2%) achieved an overall response, and disease control was achieved in 23 (95.8%) patients at 3 months post radiotherapy. The 12-month PFS was 91.8% (95% CI 91.7% to 91.9%). The incidences of acute (grade ≥3) blood triglyceride elevation, creatine kinase elevation, skin reaction, and mucositis were 1 (4.0%), 1 (4.0%), 2 (8.0%), and 1 (4.0%), respectively. The incidences of late severe (grade ≥3) nasopharyngeal wall necrosis, nasal bleeding, and trismus were 28.0%, 12.0%, and 4.0%, respectively.

Conclusions Toripalimab combined with IMRT was tolerable and showed promising antitumor activity in patients with rNPC.

Trial registration number NCT03854838.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) has the highest prevalence in Southeastern Asia, with age-standardized rates ranging from 22.2 to 27.2 per 100,000 among men.[1] The incidences of local recurrence in endemic NPC range from 10% to 20% after previous radical radiotherapy.[2 3] In this subgroup of patients with resectable diseases, surgery is the standard of care and first-line treatment.[4 5] However, reirradiation is routinely performed in patients with unresectable lesions. Despite the utilization of intensity-modulated radiotherapy (IMRT) and combined chemotherapy, the response rate was reported to be approximately 50%–65.4%,[6] and the 3-year overall survival (OS) rate was reported to be only 41.8%–68.7%, with high rates of grade 5 treatment-related toxicities of approximately 33.0%.[7 8] Therefore, there is an urgent need to develop new therapies combined with IMRT in unresectable recurrent NPC (rNPC) that potentially reduce toxicity and improve survival benefit.

Immune checkpoint inhibitors against programmed death 1 (PD-1), exemplified by the humanized monoclonal antibodies pembrolizumab and nivolumab, have been approved for the treatment of patients with relapsed squamous cell carcinoma of the head and neck (HNSCC) after previous platinum-based therapy. Recently, the promising anti-tumor activity and good tolerance of PD-1 therapies including nivolumab, pembrolizumab, toripalimab and camrelizumab were reported in several phase 1/2 trials for recurrent or metastatic NPC; however, the efficacy of PD-1 therapy alone was moderate, with a reported objective response rate of 20%–30%.[9–11] Theoretically, radiotherapy can improve the efficacy of tumor immunotherapy by modulating the peptide repertoire and enhancing major histocompatibility complex (MHC) I expression,[12 13] which reveals the rationale behind combining radiotherapy and PD-1 therapy. Recently, two
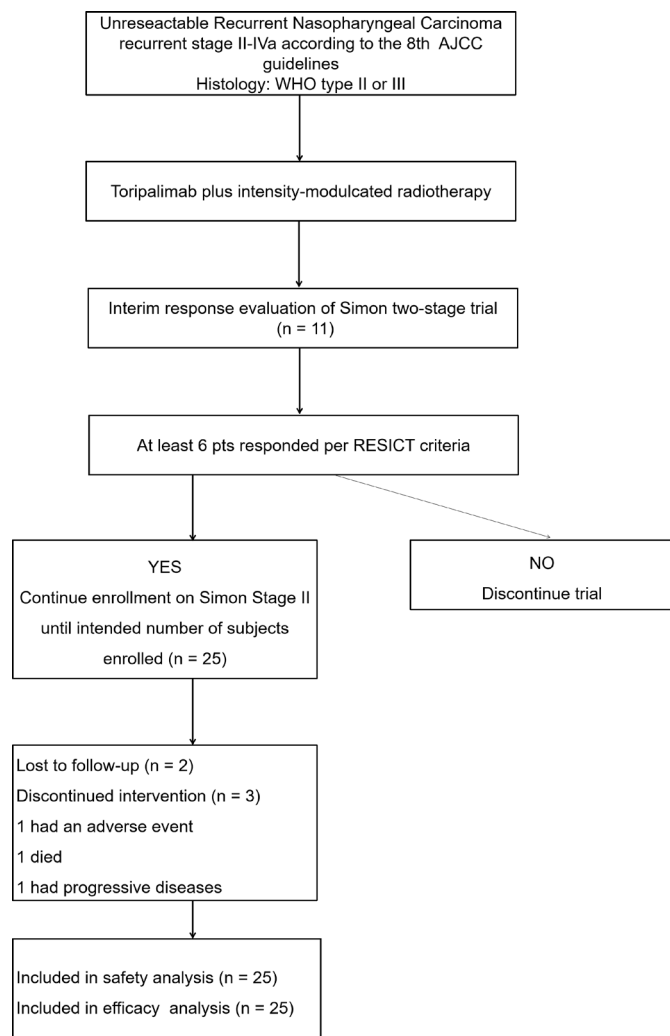
Figure 1 Trial profile. RECIST, Response Evaluation Criteria in Solid Tumors. AJCC, American Joint Committee on Cancer.

phase 1 studies demonstrated the safety and promising efficacy of pembrolizumab in combination with chemoradiotherapy in locally advanced HNSCC and non-small cell lung cancer.[14 15] However, there are still no reports of radiotherapy combined with PD-1 therapy in NPC.

We therefore conducted a phase 2, Simon two-stage clinical trial investigating the efficacy and safety of toripalimab, a humanized immunoglobulin G_4 monoclonal antibody against PD-1, in combination with IMRT in rNPC.

PATIENTS AND METHODS
Study design
This report presents the analysis of a single-arm, phase 2 trial to assess the preliminary antitumor activity and safety of toripalimab combined with IMRT as the first-line therapy for patients with unresectable locally rNPC. The trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All

participants provided written informed consent. The trial was registered at ClinicalTrials.gov.

Patient selection
The eligibility criteria for this trial included age 18–65 years; histologically confirmed NPC; patients with local recurrence (recurrent II–IVa) after curative radiotherapy who are unsuitable for local surgery; recurrence interval more than 12 months from the end of prior radiotherapy; no previous systemic chemotherapy for recurrent disease; an Eastern Cooperative Oncology Group performance status of 0 or 1; at least one measurable lesion assessed with Response Evaluation Criteria in Solid Tumors V.1.1 (RECIST V.1.1) by the investigators; and adequate organ function. Exclusion criteria included a history of active autoimmune disease; medical conditions requiring the use of immunosuppressive medications; active hepatitis B or C virus infection; uncontrolled hypertension and cardiac disease; previous treatment with anti-PD-1 or anti-programmed death-ligand 1 (PD-L1) antibodies; and patients who were pregnant or breast feeding.

Pretreatment evaluation included a complete medical history and physical examination; hematologic and biochemical analyses; nasopharyngoscopy; and MRI or contrast-enhanced CT if patients had contraindications to MRI of the head and neck. ^{18}F-fluorodeoxyglucose positron emission tomography was utilized to exclude distant metastasis.

Procedures
Toripalimab was administered via intravenous infusion of 240 mg once every 3 weeks for a maximum of seven cycles or until disease progression, death, or dose-limiting toxicities occurred or the patient requested to stop treatment. Off-protocol anticancer drugs were not allowed before the occurrence of protocol-defined disease progression. Dose modifications of toripalimab were not permitted. Details of the interruption and discontinuation of toripalimab are provided in the online supplemental file, Protocol.

Patients received IMRT after the first cycle of toripalimab. IMRT target volumes were delineated according to a previously described institutional treatment protocol. Briefly, the primary NPC tumor (gross tumor volume (GTV)nx) and gross cervical lymph nodes (GTVnd) were delineated. The clinical tumor volume (CTV) was then defined by GTVnx with a 0.5–1.0 cm margin. The prescribed doses were 60 Gy, 60 Gy and 54 Gy in 27 fractions for the planning target volumes derived from GTVnx, GTVnd, and CTV, respectively. Complete details on the radiotherapy planning are provided in the online supplemental appendix.

Tumor response after radiotherapy was based on the RECIST criteria V.1.1 and assessed by nasopharyngoscopy and MRI of the primary site. We defined a complete response (CR) as a complete lack of unequivocal soft tissue mass in the local region and cervical lymph nodes

Table 1 Baseline demographics and disease characteristics

Characteristic	Toripalimab plus IMRT N=25
Sex	
Female	7 (28.0%)
Male	18 (72.0%)
Age, years	
Median	49.0
IQR	43.5–52.5
Karnofsky performance status score	
90–100	25 (100.0%)
70–80	0 (0.0%)
Smoking status	
Smokers	2 (8.0%)
Non-smokers	23 (92.0%)
Histology	
Non-keratinizing undifferentiated (type III)	23 (92.0%)
Non-keratinizing differentiated (type II)	2 (8.0%)
EBV DNA copy number	
Median	77.5
IQR	0–382.5
Primary T classification	
T1	3 (12.0%)
T2	6 (24.0%)
T3	9 (36.0%)
T4	7 (28.0%)
Primary N classification	
N0	1 (4.0%)
N1	7 (28.0%)
N2	16 (64.0%)
N3	1 (4.0%)
Primary M classification	
M0	25 (100.0%)
M1	0 (0.0%)
Chemotherapy during primary therapy	
Yes	24 (96.0%)
No	1 (4.0%)
Recurrent T classification	
T2	2 (8.0%)
T3	16 (64.0%)
T4	7 (28.0%)
Recurrent N classification	
N0	16 (64.0%)

Table 1 Continued

Characteristic	Toripalimab plus IMRT N=25
N1	9 (36.0%)
Recurrent M classification	
M0	25 (100.0%)
M1	0 (0.0%)
Recurrent stage	
II	2 (8.0%)
III	16 (64.0%)
IVa	7 (28.0%)
PRANCIS prognostic index	
Low risk	17 (68.0%)
High risk	8 (32.0%)
Disease-free interval, median months (IQR)	37.0 (21.5–73.0)
Previous radiotherapy	
No	0 (0.0%)
Yes	25 (100.0%)

Data are presented as the median or n (%) unless otherwise stated.
EBV, Epstein-Barr virus; IMRT, intensity-modulated radiotherapy; PRANCIS, Predicting Radioresistant Nasopharynx Carcinoma Survival.

that all had a short axis of less than 10 mm according to the RECIST guidelines.[16]

Patients were followed up after the completion of radiotherapy every 3 months until death to evaluate the efficacy and safety of the treatment. We recorded the survival status and subsequent lines of therapies. Adverse events (AEs) were scored according to the Common Terminology Criteria for Adverse Events V.5.0 and the acute and late radiation morbidity scoring criteria of the Radiation Therapy Oncology Group at each follow-up visit. Acute AEs were defined as those occurred during the radiotherapy or within 3 months post radiotherapy, while late AEs were defined as those occurred over 3 months after the end of radiotherapy.

Study endpoints

The primary endpoint of the study was the objective response rate (ORR) at 3 months after radiotherapy, which was defined as the proportion of patients who had a confirmed objective response (defined as complete or partial response according to RECIST V.1.1). The secondary endpoints included safety profiles, progression-free survival (PFS) (defined as the time from enrollment to locoregional or distant metastasis relapse or death from any cause, whichever occurred first), OS (defined as interval from enrollment to death due to any cause) and biomarker analysis. Imaging results to assess the ORR and PFS were centrally reviewed.

Table 2 Response and survival data

	Toripalimab plus IMRT
Overall response at 3 months post radiotherapy*	N=24
Overall response	19 (79.2%; 95% CI 59.5% to 90.8%)
Disease control	23 (95.8%)
Complete response	11 (45.8%)
Partial response	8 (33.3%)
Stable disease	4 (16.7%)
Progressive disease	1 (4.2%)
Best overall response after radiotherapy	N=25
Overall response	23 (92.0%; 95% CI 75.0% to 97.8%)
Disease control	25 (100.0%)
Complete response	18 (72.0%)
Partial response	5 (20.0%)
Stable disease	2 (8.0%)
Progressive disease	0 (0.0%)
Time to response, months	2.65 (1.88–5.27)
Median duration of response, months (IQR)	NR (NR-NR)
Progression-free survival (PFS)	
Failure	5
Median PFS, months (95% CI)	18.67 (12.04 to 25.29)
PFS rate at 12 months (95% CI)	91.8% (91.7% to 91.9%)

*As there was one patient who did not undergo radiology examination for tumor response evaluation at 3 months post radiotherapy, a total of 24 patients were included in the analysis of overall response at 3 months post radiotherapy.
IMRT, intensity-modulated radiotherapy .

Exploratory studies

Tumor biopsy samples were obtained from patients before treatment initiation. PD-L1 expression was detected by immunohistochemistry (IHC) using the antibody 22C3 pharmDx assay (Dako, Agilent Technologies, Santa Clara, California). PD-L1 expression was evaluated on tumor cells and on tumor-infiltrating immune cells by certified pathologists. PD-L1-positive status was defined as the presence of membrane staining of any intensity in 1% or more tumor cells or the presence of PD-L1 staining of any intensity in tumor-infiltrating immune cells covering 1% or more of the tumor area occupied by tumor cells, associated intratumoral cells, and contiguous peritumoral stroma.[17]

All tumor samples for sequencing were histologically confirmed as NPC and obtained at enrollment at Sun Yat-sen University Cancer Center (Guangzhou, China). Eighteen qualified primary nasopharyngeal lesions were obtained for subsequent whole-exome sequencing (WES), among which 7 primary lesions were formalin-fixed and parrffin-embedded (FFPE) samples and 11 were fresh frozen tissues. WES was performed using the Sure-Select Human All Exon V.6 Kit (Agilent) on tumor biopsies and matched peripheral blood mononuclear cell samples. Genomic alterations including single nucleotide variants, short and long insertions/deletions (indels), copy number variants, and gene fusions were assessed. The tumor mutation burden (TMB), frameshift indels, neoantigen burden, copy number burden—the weighted Genome Integrity Index (wGII) score and microsatellite instability score were determined.

Statistical planning and analysis

A Simon two-stage optimal design with a one-sided type I error rate of 5% and power of 80% was utilized. The null hypothesis was an ORR at 3 months post radiotherapy of ≤50%, and the alternate hypothesis was an ORR ≥75%. Consequently, 11 subjects were enrolled in the first stage. If six or fewer responded at the initial stage, the trial would be terminated, and the study would be concluded. If more than 6 patients achieved a partial or CR, then the treatment would be considered worthy of further investigation, and 14 more subjects would be enrolled in the second stage for a total sample size of 25 subjects. If there were more than 16 subjects with partial or CR, then the treatment regimen was considered a success.

All enrolled patients were included in the efficacy and safety analyses. For all patients, the median follow-up time was calculated using the reverse Kaplan-Meier method. The ORR and 95% CIs were calculated using the Clopper-Pearson method. The duration of response, PFS, and OS were analyzed using the Kaplan-Meier method. Summary statistics were provided for clinical and demographic characteristics and for AEs.

In post-hoc analyses, the associations between PD-L1 expression, genome/clinical characteristics and CR and PFS were assessed. For the comparison between patients with CR or not, χ^2 test or Fisher's exact test and Wilcoxon rank-sum test were used. Univariate analysis of the effects of these parameters on PFS was conducted by the Cox proportional hazards model to calculate the HRs and 95% CIs. We performed all statistical tests using Stata V.14.2 software (StataCorp). The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (www.researchdata.org.cn), with the approval RDD number RDDA2021851016.

RESULTS

Patients and treatment

Between May 2019 and January 2020, a total of 25 patients with rNPC were enrolled in the study. All 25 patients' lesions were recurrent in the irradiation field. All 25 patients were included in the efficacy and safety analysis (figure 1).
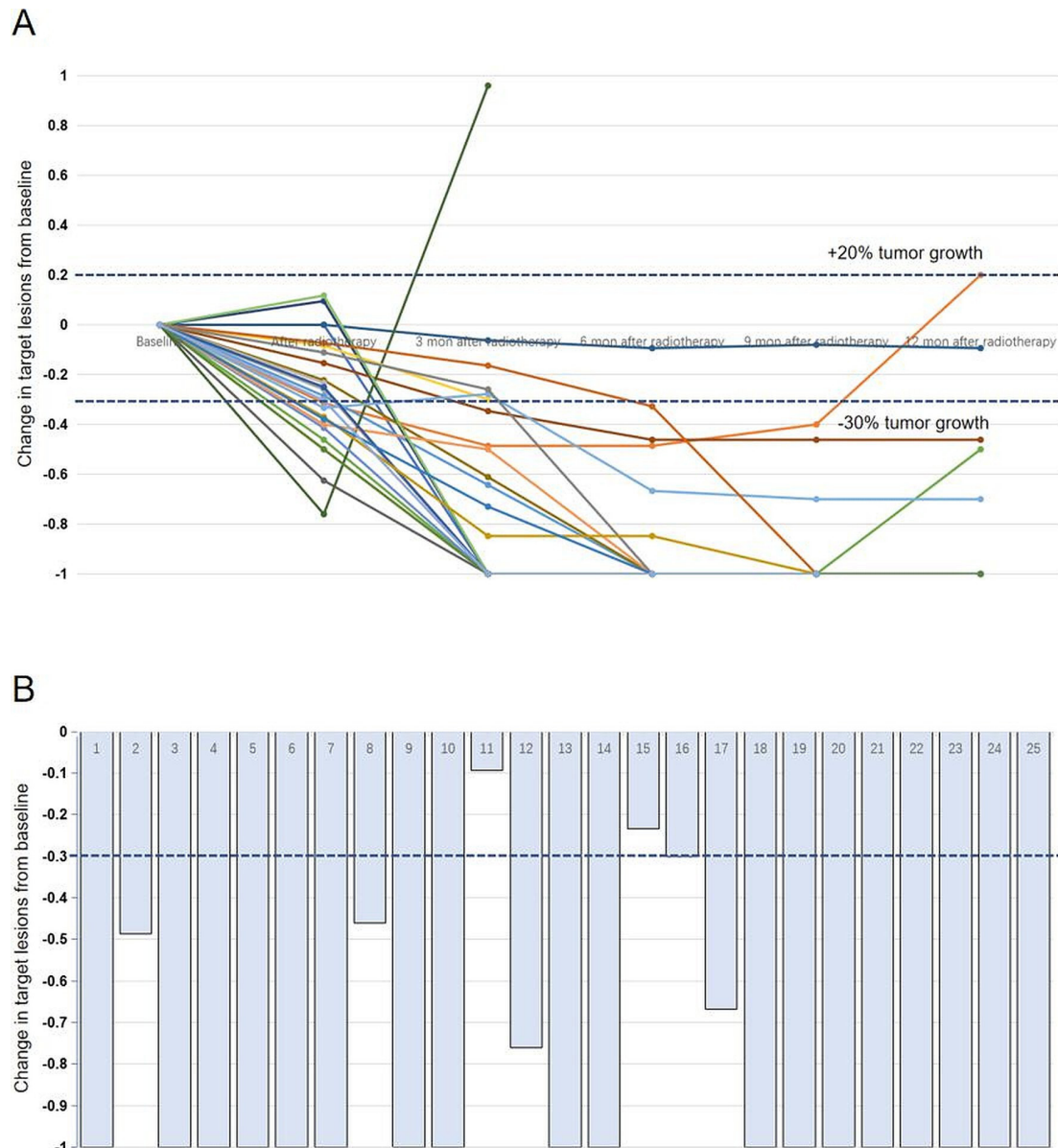
Figure 2 Antitumor activity. (A) Change in individual tumor burden during the first 12 months after the completion of radiotherapy from baseline assessed by Investigators per RECIST V.1.1 (N=25); (B) maximal change in tumor size from baseline assessed by investigators per RECIST V.1.1 (N=25). The length of the bar represents the maximal decrease or minimal increase in target lesions. RECIST, Response Evaluation Criteria in Solid Tumors.

The baseline demographics and disease characteristics are listed in table 1. The median age was 49.0 (IQR 43.5–52.5) years. Twenty-three of 25 (92.0%) patients were stage rT3–T4, and 25 of 25 (100.0%) patients were stage rN0-N1. Seventeen of 25 (68.0%) patients were defined as low risk, while 8 of 25 (32.0%) patients were defined as high risk according to Predicting Radioresistant Nasopharynx Carcinoma Survival (PRANCIS) prognostic model.[2] Twenty-four of the 25 patients (96.0%) were treated with platinum-based chemotherapy during their primary therapy. Twenty-two of the 25 patients (88.0%) completed all seven cycles of toripalimab; one patient received only five cycles because of death from hemorrhage. Two patients received six cycles (one patient developed disease progression, and one patient discontinued

treatment due to AEs). No modifications of the dose of toripalimab were observed. Toripalimab administration was delayed in one patient due to the COVID-19 pandemic. All 25 patients (100.0%) completed the protocol-defined IMRT. The median dose of IMRT was 60.21 Gy (IQR, 60–60.21 Gy), and the median duration of IMRT was 36 days (IQR, 35–38 days) (online supplemental table 1).

Efficacy

In the first 11 patients enrolled, confirmed responses were noted in 10 patients. The ORR threshold for the first stage of Simon's two-stage was reached, and the trial continued to full accrual. The data cut-off date for the analysis was February 2021. Two patients were lost to follow-up,
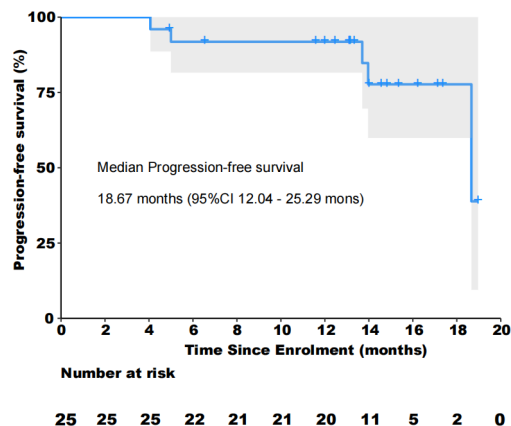
Figure 3 Kaplan-Meier curves of the progression-free survival. Progression-free survival was assessed in the whole population (n=25).

1 patient died, and 22 patients were alive. The median follow-up time for PFS was 14.6 months (IQR 13.1–16.2) months. Nineteen of the 24 patients (79.2%) achieved an overall response, and disease control was achieved in 23 (95.8%) patients at 3 months post radiotherapy (table 2, online supplemental figure 1). Among the 23 patients with a confirmed objective response within 12 months post radiotherapy, the median time to response was 2.65 months (IQR 1.88–5.27), and the median duration of response was not reached (not reached to not reached) (table 2). The treatment response remained ongoing in 17 of 25 patients (68.0%) at the cut-off point. Overall, all 25 patients (100.0%) with at least one post-baseline tumor assessment had a decrease in the size of their target lesions from baseline. The median change from baseline was −100.0% (IQR −71.3% to −100.0%) (figure 2). Five patients had documented disease progression including three local progressions, one regional relapse, and one death. The median PFS was 18.67 months (95% CI 12.04 to 25.29 months), and the 12-month PFS was 91.8% (95% CI 91.7% to 91.9%) (figure 3). The median follow-up time for OS was 15.7 months (IQR 13.9–18.0) months, the median OS was not reached, and the 12-month OS was 96.0% (95% CI 88.4% to 100.0%)

Adverse events

All 25 patients were included in the safety analysis (table 3). The most common AEs were G1-2 fatigue in 22 (88.0%) patients, G1-2 nausea in 19 (76.0%) patients, G1-2 serum creatinine elevation in 13 (52.0%) patients, G1-2 weight loss in 11 (44.0%) patients, G1-2 blood triglyceride elevation in 11 (44.0%) patients, G1-2 hypothyroidism in 8 (32.0%) patients, G1-2 pruritus in 8 (32.0%) patients, G1-2 blood cholesterol elevation in 6 (24.0%) patients, G1-2 creatine kinase elevation in 4 (16.0%) patients, G1-2 leukopenia in 4 (16.0%) patients and G1-2 myositis in 4 (16.0%) patients. G3 serum triglyceride elevation was observed in 1 (4.0%) patient, G4 creatine kinase elevation was observed in 1 (4.0%) patient, G3 skin reaction was observed in 2 (8.0%) patients, and G3 mucositis was observed in 1 (4.0%) patient. Regarding late AEs, the

most common AEs were G1-2 hearing loss in 18 (72.0%) patients, G1-2 dry mouth in 18 (72.0%) patients, G1-2 cranial neuropathy in 9 (36.0%) patients, and G1-2 neck tissue damage in 7 (28.0%) patients. Additionally, we recorded 7 (28.0%) cases of ≥G3 nasopharyngeal wall necrosis, 3 (12.0%) cases of ≥G3 nasal bleeding, and 1 (4.0%) case of G3 trismus. One patient died due to G5 nasal bleeding attributed to artery blowout.

Exploratory studies

Nineteen tumor biopsy samples were obtained for IHC staining of PD-L1. Four PD-L1-negative samples (21.1%) and 15 PD-L1-positive samples (78.9%) were identified. PD-L1-positive status was associated with higher CR rates (86.7% vs 50.0%), and PD-L1-positive patients had a better PFS (HR=0.43); however, these differences were not statistically significant (online supplemental tables 3 and 4).

WES results were obtained from 18 patients with rNPC. TMB was determined by analyzing somatic mutations within the coding region of the human genome. TMB was generally low in this study, with a median TMB of 0.72 (IQR 0.28–1.44) mutations per million base pairs. Patients with a non-CR tended to have a higher copy number burden (wGII score) (median, 0.30 vs 0.12, p=0.056) and TMB (median, 1.25 vs 0.73, p=0.574) than patients with a CR, while patients with a higher wGII score (HR 2.78, 95% CI 1.04 to 6.88, p=0.037) and TMB (HR 2.91, 95% CI 0.18 to 46.68, p=0.451) tended to have reduced PFS (online supplemental figures 2 and 3).

WES identified 4508 genetic alterations, including 370 missense, 30 non-sense, 49 splice site, 52 frameshift mutations, 2131 amplification and 1876 deletions. According to our previous study, the nuclear factor kappa-B (NF-κB), PI3K-AKT, JAK-STAT, and cell cycle pathways were enriched in somatic mutations in rNPC,[18] and the DNA mismatch repair pathway was associated with radiotherapy sensitivity.[19 20] However, no correlation between somatic mutations or these associated pathway alterations and clinical response or improved PFS was found (online supplemental figure 3).

Additional clinical characteristics analyzed for correlation with clinical efficacy included age, sex, Epstein-Barr virus (EBV) DNA copy number, rT stage, rN stage, GTV, GTV Dmin (minimum dose), GTV Dmax (maximum dose), GTV D95 (dose covering 95% volume) and GTV D50 (median dose). Among the subgroups, early T stages (T2/3) and smaller GTV were associated with a higher CR rate but without a statistically significant difference, while patients with larger GTV had reduced PFS compared with other patients (HR per cc increase 1.04, 95% CI 1.01 to 1.07, p=0.021). However, pretreatment EBV DNA copy number was not significantly associated with PFS outcome, while both rT and rN stages were also not significant prognostic factors of PFS in these patients. (online supplemental tables 3 and 4, online supplemental figure 4).

Table 3 Adverse events and grade

Event	Toripalimab plus IMRT N=25				
	All grades	Grade 1–2	Grade 3	Grade 4	Grade 5
Acute toxicity	Number of patients with event (%)				
Thrombocytopenia	1 (4.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	2 (8.0)	2 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leukopenia	4 (16.0)	4 (16.0)	0 (0.0)	0 (0.0)	0 (0.0)
ALT elevation	5 (20.0)	5 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST elevation	3 (12.0)	3 (12.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total bilirubin elevation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Direct bilirubin elevation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood cholesterol elevation	6 (24.0)	6 (24.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood triglyceride elevation	12 (48.0)	11 (44.0)	1 (4.0)	0 (0.0)	0 (0.0)
Hyperglycemia	9 (36.0)	9 (36.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serum creatinine elevation	13 (52.0)	13 (52.0)	0 (0.0)	0 (0.0)	0 (0.0)
Creatine kinase elevation	5 (20.0)	4 (16.0)	0 (0.0)	1 (4.0)	0 (0.0)
Hypertension	3 (12.0)	3 (12.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypothyroidism	8 (32.0)	8 (32.0)	0 (0.0)	0 (0.0)	0 (0.0
Hyperthyroidism	1 (4.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	19 (76.0)	19 (76.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	2 (8.0)	2 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	1 (4.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	8 (32.0)	8 (32.0)	0 (0.0)	0 (0.0)	0 (0.0)
Capillary hyperplasia	1 (4.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fever	1 (4.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight loss	11 (44.0)	11 (44.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	22 (88.0)	22 (88.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myositis or myalgia	4 (16.0)	4 (16.0)	0 (0.0)	0 (0.0)	0 (0.0)
Joint pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infusion reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin reaction	10 (40.0)	8 (32.0)	2 (8.0)	0 (0.0)	0 (0.0)
Mucositis	23 (92.0)	22 (88.0)	1 (4.0)	0 (0.0)	0 (0.0)
Dry mouth	24 (96.0)	24 (96.0)	0 (0.0)	0 (0.0)	0 (0.0)
Late toxicity					
Nasopharyngeal wall necrosis	11 (44.0)	4 (16.0)	3 (12.0)	4 (16.0)	0 (0.0)
Massive nasal bleeding	3 (12.0)	0 (0.0)	0 (0.0)	2 (8.0)	1 (4.0)
Eye damage	9 (36.0)	9 (36.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deafness	18 (72.0)	18 (72.0)	0 (0.0)	0 (0.0)	0 (0.0)
Trismus	10 (40.0)	9 (36.0)	1 (4.0)	0 (0.0)	0 (0.0)
Dry mouth	18 (72.0)	18 (72.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin reaction	4 (16.0)	4 (16.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neck tissue damage	7 (28.0)	7 (28.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cranial neuropathy	9 (36.0)	9 (36.0)	0 (0.0)	0 (0.0)	0 (0.0)

All data are presented as No. (%).
ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; IMRT, intensity-modulated radiotherapy .

DISCUSSION

To our knowledge, this study is the first report to evaluate the combination therapy of an anti-PD-1 antibody and IMRT in patients with NPC. Our results revealed that toripalimab plus IMRT showed promising antitumor activity against unresectable locally rNPC, with a favorable response rate, PFS outcome and manageable toxicity profile.

The ORR at 3 months post reirradiation was reported to be only 50% for rNPC,[21–24] as radiation dose coverage to tumor volumes is often suboptimal due to the close proximity to critical organs at risk.[25] Although the number of studies on combined chemoradiotherapy in rNPC has increased in recent years, such as radiotherapy combined with induction and/or concurrent chemotherapy, the role of combination therapy has also remained undefined, with ORR rates of approximately 60% and 3-year OS rates of 40%–50%, while acute side effects have increased significantly, with severe hematological and non-hematological rates of 11.7%–42.4% and 23.5%–33.3%, respectively.[8 25–27]

The main problem of second-course radiotherapy for rNPC is the unsatisfactory local control rate and severe radiation-related injury. Immunotherapy, such as the use of PD-1 inhibitors, has mild side effects and continuous efficacy. Radiotherapy not only has direct killing effects on tumor cells but also overcomes an immunosuppressive tumor microenvironment and promotes antigen presentation.[12 28] Therefore, radiotherapy combined with PD-1 might be theoretically effective and have lower toxicity. The primary purpose of this trial is to improve the local control rate, especially at the routine assessment point of 3 months after the completion of radiotherapy. Therefore, we prescribed the use of seven cycles of PD-1 therapy, which ended exactly 3 months after the completion of radiotherapy. The ORR findings herein meet the prespecified endpoint for this phase 2 trial. Nineteen (79.2%) patients achieved an overall response at 3 months post radiotherapy, which is better than the historical data of 50%–65.4%[6 25] which all utilized IMRT with standard fractionated scheme of 60 Gy, 27–30 fractions, five fractions per week as the second-course radiation therapy for rNPC with similar rT stages of 92%–100% of rT3–rT4. This suggests that the efficacy of radiotherapy combined with PD-1 monoclonal antibody treatment is promising.

In our study, toripalimab combined with IMRT was well tolerated, with all patients completing IMRT and 88% of patients completing seven cycles of toripalimab. Regarding severe acute toxicities, only 4.0%–8.0% patients were observed G3-4 blood triglyceride elevation, creatine kinase elevation, skin reaction or mucositis, respectively, showing that combined PD-1 therapy did not significantly increase the side effects of radiotherapy and systemic side effects. Regarding late AEs, we recorded 11 (44.0%) cases of nasopharyngeal wall necrosis, which is similar to the historical data[29 30] (31.5%–40.6%). However, only 3 (12.0%) patients had G3-4 nasal bleeding because embolization of the affected internal carotid artery was performed for patients with G3-4 nasopharyngeal necrosis, preventing the occurrence of massive nasal bleeding.

Interestingly, copy number burden (wGII score) was observed to be a potential biomarker for PD-1 plus radiotherapy in rNPC, which was consistent with the findings of previous reports on head and neck cancer, prostate cancer, and other cancers demonstrating that copy number burden is a prognostic factor associated with recurrence and death.[31–33] Finally, we observed that patients with lower GTV had a statistically significant PFS advantage compared with other patients, which also demonstrated that GTV impacted locoregional control in rNPC.[34 35]

We acknowledge that this study has some limitations. First, this was a single-arm study with no control group for comparison, and thus, selection bias could not be ruled out. Second, the small sample size reduces the certainty of the observed effectiveness.

Our data showed that toripalimab combined with IMRT had promising antitumor activity and manageable toxicity in patients with rNPC. Larger randomized controlled trials are warranted to validate our findings.

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