Efficacy and safety of sintilimab plus bevacizumab in metastatic nasopharyngeal carcinoma after failure of platinum-based chemotherapy: an open-label phase 2 study

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Summary

Background There are limited treatment options for patients with metastatic nasopharyngeal carcinoma (mNPC) after failure of platinum-based chemotherapy. In this trial, we assessed the efficacy and safety of sintilimab plus bevacizumab in patients with mNPC where platinum-based chemotherapy has been ineffective.

Methods This was a single-centre, open-label, single-arm, phase 2 trial in Guangzhou, China for patients with mNPC progressed after at least one line of systemic therapy. Eligible patients were between 18 and 75 years old, were histologically confirmed differentiated or undifferentiated non-keratinized NPC, were ineffective after platinum-based chemotherapy, and they had at least one measurable metastatic lesion assessed with Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST V.1.1) by investigators and unsuitable for local surgery or radiotherapy. Key exclusion criterion was previous treatment with anti–PD-1/PD-L1 antibodies plus anti-VEGF antibodies and high risk of hemorrhage or nasopharyngeal necrosis. Patients were enrolled and received sintilimab (200 mg) plus bevacizumab (7.5 mg/kg) intravenously every 3 weeks. Intention-to-treat population was included in primary endpoint analyses and safety analyses. The primary endpoint was objective response rate (ORR) assessed by investigators following the guidelines of RECIST V1.1. Key secondary endpoints were progression-free survival (PFS), overall survival (OS), duration of response (DOR), and safety. This trial is registered with ClinicalTrials.gov (NCT04872582).

Findings Between July 29, 2021 and August 16, 2022, 33 patients were enrolled. Median age was 46 years (range, 18–64 years), and 63.6% of patients had previously received two or more lines of chemotherapy for metastatic disease. Median follow-up was 7.6 months (range, 4.1–17.5 months). ORR was 54.5% (95% CI, 36.4–71.9%) with 3 complete responses (9.1%) and 15 partial responses (45.5%). Median PFS was 6.8 months (95% CI, 5.2 months to not

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estimable). Median DOR was 7.2 months (95% CI, 4.4 months to not estimable). Median OS was not reached. The most common potential immune-related adverse event (AE) was Grade 1–2 hypothyroidism (42.4%). Treatment-related grade 3 or 4 AEs occurred in 7 patients (21.2%), including nasal necrosis (3/33), hypertension (1/33), pruritus (1/33), total bilirubin increased (1/33) and anaphylactic shock (1/33). No treatment-related deaths and severe epistaxis occurred.

Interpretation This phase 2 trial showed that sintilimab plus bevacizumab demonstrated promising antitumour activity and manageable toxicities in patients with mNPC after failure of platinum-based chemotherapy. Further trials are warranted, and the detailed mechanisms need to be elucidated.

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Keywords: Sintilimab; Bevacizumab; Metastatic nasopharyngeal carcinoma; Clinical trial

Research in context

Evidence before this study

Treatment options are limited for patients with nasopharyngeal carcinoma (NPC) after progression from the first line of platinum-based chemotherapy. Anti-PD-1 monotherapy achieved modest objective response rate (ORR) in previous phase 1 studies, including KEYNOTE-028 and NCI-9742. Anti-angiogenesis treatment has been shown to improve immunotherapy efficacy in various cancers. Therefore, it is worth exploring the potential enhanced antitumoural efficacy with the combination of PD-1 antibody and vascular endothelial growth factor (VEGF) inhibitors in this deadly malignancy at the second- and greater-line setting. We searched PubMed for studies from the time of the inception of the database to the date of April 6, 2023 using the search terms "nasopharyngeal carcinoma", "bevacizumab" and "sintilimab". There are no clinical trials of sintilimab plus bevacizumab in metastatic NPC (mNPC) reported to date.

Added value of this study

This is the first reported study that evaluated the efficacy of sintilimab (200 mg) plus bevacizumab (7.5 mg/kg) combination therapy (21-day cycle) in mNPC at the second- and greater-line setting. This study provides evidence that sintilimab plus bevacizumab has promising antitumour activity and manageable toxicity profile in previously heavily treated mNPC.

Implications of all the available evidence

The promising antitumour activity and manageable toxicities of this study suggest the combination of sintilimab and bevacizumab as a potential option with manageable safety profile for previously heavily treated patients with mNPC. However, randomised, double-blinded and multi-centre trials are warranted, and the detailed mechanisms of enhanced antitumoural efficacy with additional anti-angiogenesis to immunotherapy need to be elucidated.

Introduction

Nasopharyngeal carcinoma (NPC) is an invasive epithelial malignancy with high prevalence in Southern China, East and Southeast Asia, and North Africa, and is strongly associated with Epstein–Barr virus (EBV) infections.[1] Annually, there are about 129,000 new cases of NPC worldwide and 73,000 deaths attributed to this disease.[2] Approximately, 20% of patients with non-metastatic NPC eventually experience metastatic disease even after definitive treatments, which requires systemic therapy.[3,4] The prognosis in patients with metastatic NPC (mNPC) remains poor that first-line platinum-based chemotherapy achieved median overall survival of 19.0–22.1 months and median progression-free survival (PFS) 5.0–7.0 months.[5–7] There are limited treatment options for patients with NPC after failure of platinum-based chemotherapy. Therefore, effective therapy options are still in great demand.

In addition to the close association with chronic EBV infection, NPC is characterised by upregulated expression of programmed death-ligand 1 (PD-L1) and abundant lymphocytic infiltration, which provides a rationale for the development of immunotherapy against NPC.[8] A number of phase 1/2 studies have shown encouraging results for anti-PD-1 monotherapy in recurrent or metastatic NPC in second- and greater-line settings, with an objective response rate (ORR) of 20–34%.[9–14] Given the modest ORR seen with anti-PD-1 monotherapy, there is a great interest in testing novel drugs and various combinations. Subsequent phase 3 studies have demonstrated that the addition of anti-PD-1 antibodies to chemotherapy at the first line setting for

patients with recurrent or metastatic NPC provided superior PFS compared to chemotherapy alone.[15,16] Thus, the combination of anti-PD-1/PD-L1 antibodies with other therapeutic modalities has emerged as new strategies to treat mNPC after failure of platinum-based chemotherapy.

Angiogenesis is another feasible target for NPC treatment. Vascular endothelial growth factor (VEGF) inhibitors have demonstrated anti-angiogenesis effects as well as to attenuate VEGF-mediated immunosuppression.[17] Previous studies have shown that the addition of VEGF inhibitor bevacizumab to standard chemoradiation or chemotherapy delays the progression of subclinical distant disease and improves response rate in patients with NPC.[18,19] Nevertheless, growing evidence revealed that the combination of an immune checkpoint inhibitor with an anti-VEGF antibody exhibits antitumoural effects in many solid tumours with an ORR of 12.5–64.1%.[20–32] The latest research demonstrated that camrelizumab plus apatinib had promising antitumour activity in patients with recurrent/metastatic NPC who progressed on first-line therapy, with an ORR of 65.5% (80% for locoregional recurrence only and 54.5% for metastatic lesions, respectively), with treatment-related adverse events (TRAEs) of grade 3 or higher of 58.6%.[33] It is worth exploring the potential high efficiency and low toxicity of this combination in this deadly malignancy at the second- and greater-line setting.

In this phase 2 study, we aimed to evaluate the efficacy and safety of sintilimab plus bevacizumab for patients with mNPC after failure of platinum-based chemotherapy. This is a proof-of-concept trial with a single-arm, Simon's two-stage design to collect preliminary evidence on the efficacy and safety profile of this combination therapy.

Methods

Study design and participants

This was a single-arm, open-label, phase 2 trial conducted at the Sun Yat-sen University Cancer Center (Guangzhou, China). The trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants were informed about the trial and provided written consent. The protocol, and amendments, are available in the Supplementary Materials. All protocols and amendments were approved by the Ethics Committee of Sun Yat-sen University Cancer Center. The trial was registered at ClinicalTrials.gov (NCT04872582).

The eligibility criteria for this trial included the following: age 18–70 years, histologically confirmed differentiated or undifferentiated non-keratinized NPC, patients with at least one measurable metastatic lesion assessed with Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST V.1.1) by investigators, unsuitable for local surgery or radiotherapy, failure after platinum-based chemotherapy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function. Exclusion criteria included uncontrolled blood pressure, previous treatment with anti–PD-1/PD-L1 antibodies plus anti-VEGF antibodies, active autoimmune disease, active hepatitis B or hepatitis C virus infection, high risk of hemorrhage or nasopharyngeal necrosis, and patients who were pregnant or breast feeding.

Study treatment

Patients received sintilimab 200 mg and bevacizumab 7.5 mg/kg intravenously every 3 weeks for a maximum of 24 months. The treatment was discontinued when there were signs of disease progression, unacceptable levels of toxicity, or withdrawal of consent. Bevacizumab was discontinued when there were signs of nasopharyngeal necrosis. Details regarding interruption and discontinuation of sintilimab are provided in the Supplemental File. Dose modifications of sintilimab were not permitted. Off-protocol anticancer drugs were not allowed before the occurrence of protocol-defined disease progression.

Assessments

The responses were assessed by investigators and radiologists according to RECIST V.1.1 using computed tomography or magnetic resonance imaging at baseline, followed by once every three cycles (9 weeks) for the maximum of 24-month of treatment. Tumour responses had to be confirmed with a repeat scan at least 4 weeks later. Adverse events (AEs) were monitored throughout the treatment period and 30 days after treatment discontinuation (90 days for serious AEs) and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Endpoints

The primary endpoint was ORR, which is defined as the proportion of patients with complete response (CR) or partial response (PR) according to RECIST V.1.1, as assessed by investigators. All responses were confirmed by a secondary radiological assessment. Secondary endpoints were PFS (time from treatment initiation to disease progression according to RECIST version 1.1 or death from any cause), overall survival (OS, time from treatment initiation to death from any cause), duration of response (DOR, time from first evidence of response to disease progression) and safety.

Exploratory studies

Currently, there are no noninvasive diagnostic techniques available for identification of ideal candidates for PD-1 inhibitor combined anti-VEGF therapy. Previous *in vivo* studies have used blood oxygen level-dependent

magnetic resonance imaging (BOLD-MRI), which is sensitive to iron deposition and deoxyhemoglobin concentration in the microenvironment thereby serves as an indirect reflection of oxygen metabolism, to predict intra-tumoural hypoxia, metastatic potential and treatment response during chemotherapy.[34–36]

BOLD-MRI was obtained before treatment. Inclusion criteria were: (1) patients with pathologically confirmed NPC, (2) suspected or confirmed NPC hepatic metastases and (3) at least one metastasis >1 cm in diameter. The exclusion criteria were: (1) inadequate or non-evaluable quantitative BOLD-MRI sequences, (2) refuse to have MRI examination and (3) refuse to sign the informed consent form of BOLD-MRI. All MRI images were performed on a 3.0 T MR machine (uMR790; United Imaging Healthcare Co., Ltd) with an abdomen coil. After data acquisition, all images were transferred to an independent workstation for analysis with manufacturer-supplied Functool software. This program creates a set of color-coded parametric images of R2* (s−1) from a voxel basis to an exponential function, which defines the expected signal decay as a function of TE and solving for the unknown value of R2*. On the map, red indicates the highest R2* levels and reflects a high concentration of deoxyhemoglobin, while blue indicates the lowest R2* levels and reflects a low concentration of deoxyhemoglobin. On the color-coded R2* maps, the R2* values in the tumour were calculated using manual placement of a region of interest (ROI) by an experienced radiologist (Z.C.). The R2* value of each region of interest was recorded and an average R2* value was obtained for each lesion. For each metastatic lesion evaluated, the following were recorded: lesion size (the maximum diameter measured on axial T1-weighted images), and R2* value. Therapeutic response was determined on a lesion-by-lesion basis by evaluating changes in tumour size after therapy.[37] A metastatic lesion was classified as responding if it had a 30% or more reduction in the maximum transverse diameter; otherwise, it was considered nonresponding.

Statistical analysis

A Simon's minimax two-stage design was employed with a one-sided type I error rate of 5% and power of 80%. The null hypothesis was an ORR of ≤20%, and the alternate hypothesis was an ORR ≥40%. Consequently, 18 patients were enrolled in the first stage. If more than 4 responders were observed, then the treatment would be considered worthy of further investigation, and 15 more patients would be enrolled in the second stage for a total sample size of 33 patients. If there were more than 10 patients with PR or CR, then the treatment regimen was considered a success.

Safety analyses were performed in all patients who had received at least one dose of the study treatment (safety population). ORR and 95% CIs were calculated using the Clopper-Pearson method. The DOR, PFS, and OS were analysed using the Kaplan–Meier method. Summary statistics were provided for clinical and demographic characteristics and AEs. In post-hoc analyses, Cochran-Armitage trend test was used to assess the relationship between the response and EBV DNA status. We assessed the association between ORR and exploratory subgroups using the $\chi 2$ test or Fisher's exact test and estimated the PFS in exploratory subgroups with the Kaplan–Meier method, and we compared them using log-rank tests. Cox proportional hazards regression models were used to calculate the HRs and corresponding 95% CIs. The proportional hazard assumption was confirmed based on the Schoenfeld residuals. We performed all statistical tests using R software, version 4.1.0 (R Group for Statistical Computing).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 29, 2021 and August 16, 2022, we screened 48 patients, of whom 33 eligible patients were enrolled and received the study treatment. In recruitment stage, two patients were excluded because of previous diagnosis of immune-related pneumonia, nine without one measurable metastatic lesion, two without first-line chemotherapy and two with high risk of hemorrhage. Of the patients with high risk of hemorrhage, one patient was diagnosed with NPC along with lung metastasis and pulmonary arteriovenous invasion. Another patient was diagnosed with metastatic NPC with nasopharyngeal recurrence and necrosis invading the internal carotid artery. Therefore, both of them had high risk of hemorrhage if exposed to bevacizumab. Baseline characteristics of the population are summarised in Table 1. The median age was 46 (range, 18–64) years. All patients received at least one line of prior platinum-based systemic therapy, with 21 (63.6%) receiving ≥2 lines. All 33 patients (33/33, 100%) had at least one on-treatment tumour radiological assessment and were included in the efficacy-evaluable population (Fig. 1). As for the data cutoff (January 4, 2023), the median follow-up was 7.6 months (range, 4.1–17.5 months). A total of twenty patients (20/33, 60.6%) discontinued treatment because of different reasons including disease progression (18/33, 54.5%), AEs (1/33, 3.0%), and withdrawal of consent (1/33, 3.0%).

Efficacy

Among the first 18 patients enrolled, confirmed responses were noted in 12 patients. The ORR threshold for the first stage of Simon's two-stage was reached, and the trial continued to full accrual. Of the total population enrolled (n = 33), 18 patients (ORR 54.5%, 95% CI,

Characteristics	Patients (n = 33)
Age, years	46 (18–64)
Sex	
Female	4 (12.1%)
Male	29 (87.9%)
Initial stage[a]	
II-III	9 (27.3%)
IVa	10 (30.3%)
IVb	13 (39.3%)
NA	1 (3.0%)
Initial tumor category	
1–2	6 (18.2%)
3–4	26 (78.8%)
NA	1 (3.0%)
Initial node category	
0–1	6 (18.2%)
2–3	26 (78.8%)
NA	1 (3.0%)
Initial metastasis category	
0	20 (60.6%)
1	13 (39.4%)
Location of recurrences/metastases	
Local recurrence	2 (6.1%)
Regional lymph nodes	3 (9.1%)
Liver	15 (45.5%)
Lung	20 (60.1%)
Distant lymph nodes	9 (27.3%)
Bone and soft tissue	2 (6.1%)
Target lesion size, mm	42 (13–207)
Time from initial cancer diagnosis to study enrollment, months	25.5 (8.4–102.7)
Previous platinum	33 (100%)
Previous gemcitabine	16 (48.5%)
Previous paclitaxel	28 (84.8%)
Previous PD-1	6 (18.2%)
Previous radiotherapy	27 (81.8%)
No. of previous systemic therapies	
1	12 (36.4%)
2	12 (36.4%)
3	9 (27.3%)
Karnofsky performance status score	
70	1 (3.0%)
80	4 (12.1%)
90	27 (81.8%)
100	1 (3.0%)
EBV DNA copy number at baseline, copy/mL	1140 (0–712,000)
≤3000 copies/mL	20 (60.6%)
>3000 copies/mL	13 (39.4%)

Abbreviations: EBV, Epstein–Barr virus; PD-1, programmed death-1. Median (range); n (%). [a]Staging was according to the 8th edition of the American Joint Committee on Cancer staging system.

Table 1: **Baseline demographics and disease characteristics.**

36.4–71.9%) achieved a confirmed objective response, with 3 CRs (9.1%) and 15 PRs (45.5%; Table 2) (Fig. 2A and B). There were 2 patients with stable disease (SD). The disease control rate (DCR, the proportion of patients who achieved CR, PR or SD) was 81.8% (95% CI, 64.5–93.0%; Table 2). The median DOR was 7.20 months (95% CI, 4.43 months to not estimable; Figs. 2C and 3A). The median PFS was 6.77 months (95% CI, 5.20 months to not estimable; Fig. 3B). No deaths occurred, and the median OS was not reached. Interestingly, patients with ≥50% decrease in EBV DNA level from baseline to the first post-treatment assessment had significantly better ORR than those with <50% decrease in EBV DNA level (ORR 75.0% vs 41.7%, P = 0.037). There was a correlation between baseline EBV DNA status (cut-off values of 3000, 2000, 1000 copies/mL) with ordered response variables (PD, SD, PR to CR) decided by Cochran-Armitage trend test (P = 3.71e-18, 1.09e-18 and 7.87e-13, respectively) (Supplemental Fig. S2). In addition, we observed longer median PFS of 9.03 months (95% CI, 5.4 months to not estimable) in patients with EBV-DNA load ≤3000 copies/mL than those with EBV-DNA load >3000 copies/mL (3.67 months, 95% CI, 2.07 months to not estimable; HR 3.06, 95% CI, 1.20–7.82, P = 0.019) (Figs. 2C and 3C). Multivariate Cox analyses suggested that Age ≥45 years (HR, 5.02, 95% CI, 1.15–21.8; P = 0.032) and EBV-DNA load >3000 copies/mL at baseline (HR, 12.12, 95% CI, 2.10–70.06; P = 0.005) were independent poor prognostic factors for PFS (Supplement Fig. S3).

Safety

Twenty-six patients in the safety population (26/33, 78.8%) experienced at least one treatment-related AE (Table 3). Treatment-related grade 3 or 4 AEs occurred in 7 patients (7/33, 21.2%), including one patient with grade 3 hypertension (3.0%), three with grade 3 nasal necrosis (9.1%), one with grade 3 pruritus (3.0%), one with grade 3 total bilirubin increased (3.0%) and one with grade 4 anaphylactic shock (3.0%). Severe treatment-related AE was observed in one patient (3.0%; Data Supplement), who experienced grade 4 anaphylactic shock, led to permanent discontinuation of sintilimab. No treatment-related deaths and severe epistaxis occurred. All of the enrolled patients (33/33, 100%) received at least one complete cycle of sintilimab plus bevacizumab. Ten patients (10/33, 30.3%) required one or more dose interruption for bevacizumab; they all continued the study with sintilimab monotherapy. The proportion of patients at each bevacizumab adjustment and the reasons for bevacizumab discontinuation are summarised in the Data Supplement. Seventeen patients (17/33, 51.5%) had potentially immune-related AEs associated with sintilimab. The most common potentially immune-related AE was hypothyroidism (42.4%; Table 3). One patient with grade 3 immune-related pruritus had complete resolution with corticosteroids and refused to continue sintilimab treatment.

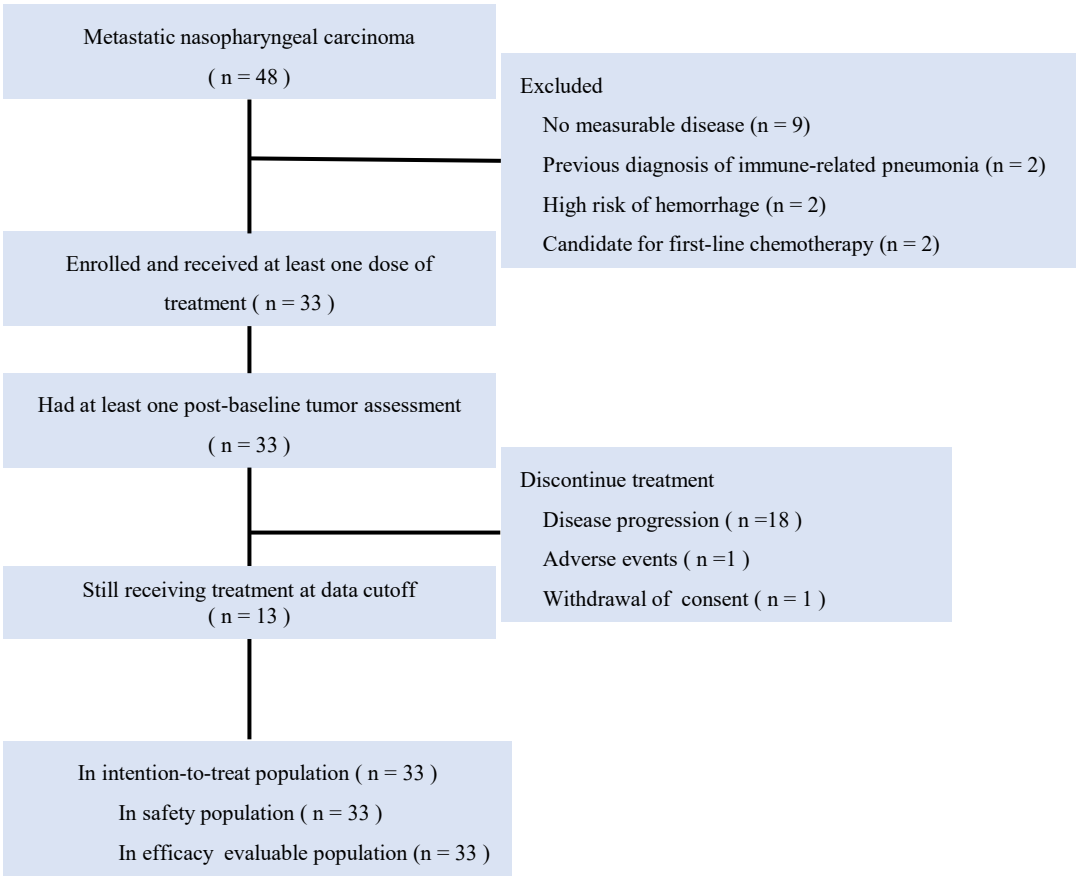

Fig. 1: Trial profile. Abbreviation: n, number of patients.

Exploratory studies

Seven patients (6 male, 1 female, mean age = 48 years, range 26–64 years) with 12 hepatic metastases >1 cm in diameter underwent baseline MR imaging using a standardised imaging protocol, including a BOLD-MRI sequence, which allows the R2* maps to be calculated. The pseudo-color maps (R2* values) are shown in Supplemental Fig. S1a and b. The mean tumour R2* values of patients in no response group (77.5) were significantly greater than in those in response group (34.1) (P = 0.005) (Supplemental Fig. S1C).

Antitumor Activity	% (95% CI, No. of patients)
ORR[a]	54.5 (36.4–71.9, 18)
Liver metastasis (n = 15)	60.0 (32.3–83.7, 9)
DCR[b]	81.8 (64.5–93.0, 27)
Best overall response	
CR	9.1 (3)
PR	45.5 (15)
SD	27.3 (9)
PD	18.2 (6)

Abbreviations: CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease. [a]ORR = (CR + PR)/total × 100%. [b]DCR = (CR + PR + SD)/total × 100%.

Table 2: **Antitumor activity assessed by RECIST version 1.1 (n = 33).**

Discussion

To the best of our knowledge, this is the first reported study that evaluated the efficacy of sintilimab plus bevacizumab combination therapy in mNPC after failure of platinum-based chemotherapy. Our results revealed that sintilimab plus bevacizumab showed promising anti-tumour activity, evidenced with a favorable overall response rate, durable response, and a manageable toxicity profile in previously heavily treated mNPC.

Patients with mNPC have poor prognosis and limited treatment options after platinum-based chemotherapy. There were two international multicentre trials that demonstrated the suboptimal efficacy of anti-PD-1 antibody monotherapy in patients with advanced NPC. One trial showed an ORR of 25.9% and CR rate of 0 among 27 patients with PD-L1 positive NPC treated with pembrolizumab in KEYNOTE-028 study,[9] while the

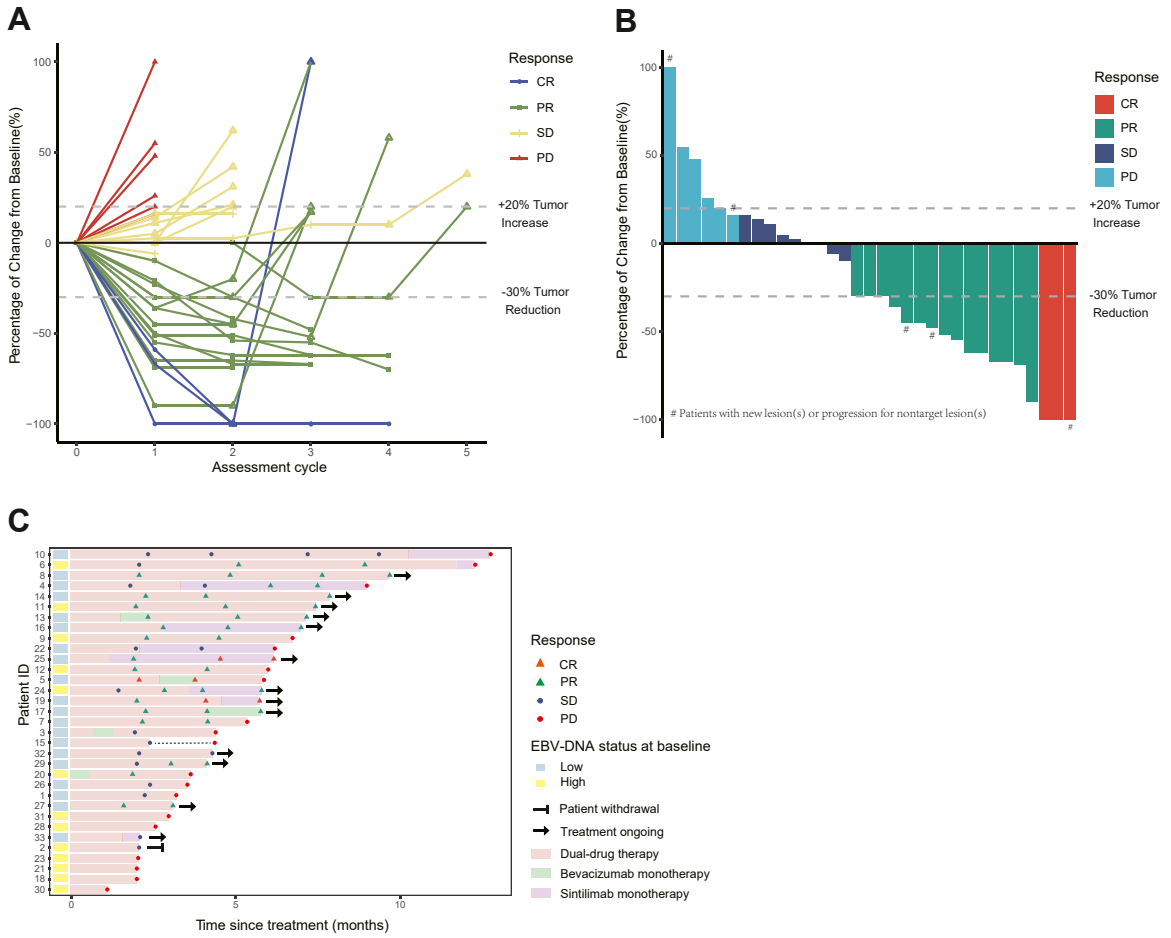

Fig. 2: Antitumour activity. The patients in the efficacy evaluable population are included (n = 33). (A) Change in individual tumour burden after at least three doses of treatment from baseline assessed by Investigators per RECIST V.1.1 (n = 33). (B) Best percentage change from baseline in target lesion; (C) Duration of responses. The length of each bar represents the duration treatment of each patient. Abbreviation: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

other trial showed an ORR of 20.5% and CR rate of 2.3% in 44 patients with pretreated recurrent or metastatic NPC treated with nivolumab in the NCI-9742 study.[10] In the meantime, camrelizumab demonstrated an ORR of 34% (CR rate, 2.2%) at the second-line setting[11] and 28.2% (CR rate, 1.3%) at the third or above-line setting in Chinese patients with recurrent or metastatic NPC.[14] In addition, another anti-PD-1 therapy, toripalimab, showed an ORR of 23.9% and CR rate of 2.2% at the third or above-line setting among 92 Chinese patients with recurrent or metastatic NPC in the POLARIS-02 study.[13] Collectively, these findings support the suboptimal antitumour efficacy of anti-PD-1 antibody monotherapy in chemotherapy-refractory patients with advanced NPC with an ORR of 20–34% and CR rate of 0–2.6%.[9–14] Meanwhile, previous retrospective studies reported an ORR of 6–20% without CR for anti-VEGF/VEGFR monotherapy for patients with recurrent or metastatic NPC.[38–41] Previous research demonstrated that camrelizumab plus apatinib showed an ORR of 54.5% in patients with mNPC.[33] In this trial, we reported the combination of sintilimab plus bevacizumab therapy achieved an ORR of 54.5% and CR rate of 9.1% in patients with mNPC. These findings strongly support that there is a synergistic effect of anti-PD-1 in combination with anti-VEGF in chemotherapy-refractory patients with mNPC.

Measurement of plasma EBV-DNA level before treatment and the dynamic change have been established as a robust predictive biomarker in NPC.[42] Of note, we observed that patients with low EBV-DNA load at baseline exhibited a statistically significant PFS advantage compared to patients with high EBV-DNA level in the present study. Furthermore, significant decrease in EBV DNA level from baseline to the first post-treatment assessment was also associated with a

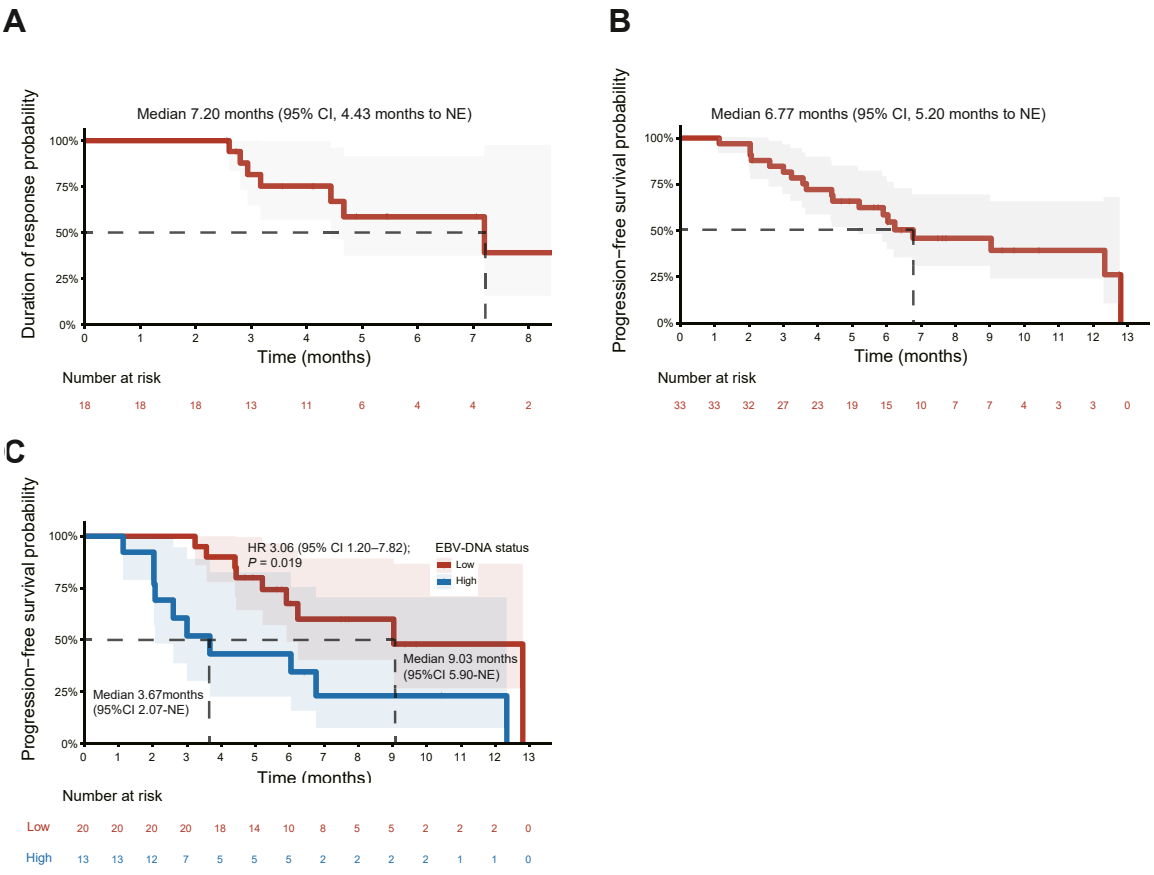

Fig. 3: Kaplan–Meier curves of duration of response and progression-free survival. (A) Duration of response was assessed in responders (n = 33), and (B) progression-free survival (n = 33) and (C) progression-free survival by EBV-DNA load. Abbreviation: CI, confidence interval; NE, not estimable; HR, hazard ratio; EBV, Epstein–Barr virus.

better ORR. Our findings were consistent with data presented in the PLOARIS-02 and CAPTAIN study, indicating the potential predictive value of EBV value at baseline and changes following treatment with immunotherapy.[13,14] Since almost all endemic NPCs are associated with EBV infection, whether the clinical outcomes of sintilimab could be extrapolated to the non-endemic regions still needs further investigation.

The safety profile of sintilimab plus bevacizumab was consistent with that previously reported from other anti-PD-1/PD-L1 antibodies and VEGF pathway inhibitors. Most toxicities reported in our study, which were mainly associated with sintilimab, were manageable with dose reductions, dose interruptions, and supportive care. Hypothyroidism, the most common immune-related AE, occurred in 42.4% of the patients, which was in line with that reported for other PD-1 inhibitors.[11,32] Regarding severe acute toxicities with sintilimab, one patient (3.0%) experienced allergic shock, who had sintilimab discontinued and he continued the bevacizumab monotherapy in the study given partial response. Besides, we noted that gastrointestinal perforation is a known adverse effect of anti-angiogenic therapies.[43] But we did not note any gastrointestinal perforation in our study, and the frequency of gastrointestinal toxicities in our cohort (3.0%) was much lower than that in previous reports,[26,29] which may be due to the difference in primary tumour types. Nasopharyngeal necrosis was the most frequent AE attributed to bevacizumab in our study, with an incidence of 21.2% (7/33). All of these patients with nasopharyngeal necrosis (7/7) previously received radiation therapy and no patients suffered Grade 3–4 epistaxis, which occurred less often in our trial compared with other historical data in patients with NPC (36%–64%),[33,38,41] indicating attention ought to be paid to nasopharyngeal necrosis for patients after radiotherapy when using this treatment.

Previous studies demonstrated that liver metastasis was a poor prognostic factor in patients with mNPC

	No. (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Any	20 (61)	14 (42)	6 (18)	1 (3)
Hypertension	1 (3)	0	1 (3)	0
Gingival pain	1 (3)	1 (3)	0	0
Nasal necrosis	4 (12)	0	3 (9)	0
Epistaxis	8 (24)	0	0	0
Otitis media	0	1 (3)	0	0
Hoarseness	2 (6)	0	0	0
Mucositis	7 (21)	2 (6)	0	0
Headache	2 (6)	5 (15)	0	0
Fatigue	1 (3)	0	0	0
Pruritus	1 (3)	1 (3)	1 (3)	0
Rash	1 (3)	2 (6)	0	0
Pneumonitis	0	1 (3)	0	0
Constipation	1 (3)	0	0	0
Proteinuria	1 (3)	0	0	0
Hypothyroidism	6 (18)	8 (24)	0	0
Anaemia	2 (6)	1 (3)	0	0
Neutropenia	0	1 (3)	0	0
Total bilirubin increased	0	0	1 (3)	0
Conjugated bilirubin increased	0	1 (3)	0	0
Alkaline phosphatase increased	1 (3)	3 (9)	0	0
Alanine aminotransferase increased	2 (6)	0	0	0
Aspartate aminotransferase increased	3 (9)	1 (3)	0	0
Anaphylactic shock	0	0	0	1 (3)

Abbreviations: n, number of patients.

Table 3: **Treatment-related adverse events in total treated patients (n = 33).**

with oligo or multiple metastases.[6,44,45] However, patients with liver metastatic NPC produced an ORR of 60% (9/15, 95% CI 32.3–83.7) using sintilimab plus bevacizumab in this trial, indicating promising application of our combination therapy in patients with liver mNPC. Therefore, a prospective random controlled trial is ongoing, aimed at verifying the efficacy and safety of sintilimab and bevacizumab and chemotherapy in patients with liver metastatic NPC. Meanwhile, there is an urgent need to the identification of patients with liver metastatic NPC benefit from the combined PD-1 and VEGF inhibitors with noninvasive technique. Previous studies have been conducted to determine if R2* values in BOLD-MRI, a medical imaging indicator of oxygen metabolism and intra-tumoural hypoxia, could predict survival during chemotherapy.[35,36] However, there is no hypoxia imaging methods to be used to evaluate if patients respond to immunotherapy and anti-VEGF therapy. In this trial, for patients with liver metastasis, no response group have higher mean R2* values, suggesting that BOLD-MRI could be a useful method for evaluating treatment response of combined PD-1 and VEGF inhibitors. However, prospective studies are needed to define the optimal duration of the regimens and identify the individuals who might benefit more from this therapy.

We acknowledge that this study has some limitations. First, although there is a notable improvement of the combined regimen compared with previous anti-PD-1 antibody monotherapy, this was a single-arm study with no control group for comparison. Second, the small sample size of the study reduces the certainty of the observed effectiveness. Third, limited numbers and sites of radiomics analysis may introduce bias, and further validation are needed.

In conclusion, our data showed that sintilimab plus bevacizumab has promising antitumour activity and manageable toxicity in mNPC after failure of platinum-based chemotherapy. Larger randomised controlled trials are warranted to further validate our findings.

Contributors

Drs. Lu, Jiang, Xia, Huang, and C.-M. Xie contributed equally to this study. Drs CQ Xie, Liang, and Xiang were joint senior authors.

CQ Xie, Liang, ang Xiang conceived and designed this study. Lu, Jiang, Xia, Huang, C.-M. Xie, Xu, Ye, G.-Y. Liu, Bei, Ke, Li, Zhang, Wang, Q. Liu, X. Chen, Z.-X. Chen, CQ Xie, Liang, and Xiang participated in acquisition, analysis, or interpretation of data. The manuscript was drafted by Lu, Jiang, Xia, Huang, and C.-M. Xie and was reviewed or revised by all authors. The final version was approved to be submitted by all authors. CQ Xie, Liang, and Xiang supervised the study. Drs. CQ. Xie, Liang and Xiang had full access to all the data in the study and had final responsibility for the decision to submit for publication. Drs. CQ. Xie, Liang and Xiang accessed and verified the underlying data.

Data sharing statement

Qualified researchers should submit requests for access to the patient level data to the corresponding author, including a proposal outlining their reasons for requiring the data. The sponsor will grant access to individual deidentified participant data if proposals are approved, provided that the requester signs a data-access agreement. The sponsor will also consider requests for access to the statistical analysis plan. These data will be available 2 years after the completion of the study. Deidentified individual patient-level data will be made available on the Research Data Deposit platform.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102136.

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