BMC Medicine

RESEARCH

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Nimotuzumab combined with docetaxel and cisplatin as first-line treatment for patients with recurrent or metastatic nasopharyngeal carcinoma: a multicenter, phase 2 trial

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Abstract

Background To evaluate the efficacy and safety of nimotuzumab combined with docetaxel and cisplatin (TPN) as the first-line therapy in patients with recurrent or metastatic nasopharyngeal carcinoma (RM-NPC).

Methods In this multicenter, open-label, phase 2 trial (ClinicalTrials.gov identifier: NCT03708822), patients with RM-NPC received intravenous nimotuzumab (200 mg on days 1, 8, and 15), docetaxel (75 mg/m^2 on day 1), and cisplatin (75 mg/m^2 on day 1) every 3 weeks for 6 cycles. The primary endpoint was the objective response rate (ORR), and the secondary endpoints included the disease control rate (DCR), duration of response (DOR), time to response (TTR), progression-free survival (PFS), overall survival (OS), and safety.

Results Between October 15, 2018, and July 20, 2022, 52 patients were enrolled. The ORR and DCR in the intention-to-treat population were 65.4% and 90.4%, respectively. With a median follow-up of 38.1 months, the median PFS and OS were 7.4 and 40.4 months, respectively. The majority of adverse events were grades 1–2. Grade 3/4 adverse events were neutropenia (42.3%), leukopenia (32.7%), febrile neutropenia (11.5%), nausea (7.7%), fatigue (5.8%), infection (5.8%), thrombocytopenia (1.9%), and anorexia (1.9%). There was no treatment-related death. Low baseline plasma Epstein-Barr virus (EBV) DNA level and the clearance of plasma EBV DNA after 2 cycles of treatment were associated with longer PFS. Additionally, patients who received ≥ 2400 mg of nimotuzumab and ≥ 4 cycles of docetaxel plus cisplatin had superior ORR and survival.

Conclusions First-line therapy with the TPN regimen showed promising efficacy with a well-tolerated safety profile in RM-NPC patients.

Trial registration ClinicalTrials.gov: NCT03708822.

Keywords Nimotuzumab, Docetaxel, Cisplatin, First-line therapy, Recurrent or metastatic nasopharyngeal carcinoma

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Background

Nasopharyngeal carcinoma (NPC) is a relatively uncommon carcinoma in most regions worldwide but prevails in East and Southeast Asia [1, 2]. Non-keratinizing NPC constitutes the majority of cases in endemic areas and is associated with Epstein-Barr virus (EBV) infection [1]. Approximately 5–11% of patients are initially diagnosed with metastatic disease, while an additional 15–30% of patients treated with chemo-radiotherapy encounter distant recurrence [3, 4]. Palliative systemic treatments are the primary therapeutic approach for recurrent or metastatic NPC (RM-NPC).

Addition of immune checkpoint inhibitor (ICI) to chemotherapy as the first-line therapy has resulted in dramatic improvement in treatment response as well as survival outcomes in RM-NPC patients [5, 6]. The combination of gemcitabine plus cisplatin (GP) with ICI is now recommended as the preferred first-line regimen for RM-NPC. However, not all patients are suitable candidates for ICI therapy. The objective response rate (ORR) for platinum-based doublet chemotherapeutic regimens was 42 to 66% with median overall survival (OS) of only 12.4–29.1 months [5, 7, 8]. Accordingly, the exploration novel treatment regimens not based on ICI are needed.

Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein belonging to the human epidermal growth factor receptor (HER) family involved in the regulation of various cellular functions, including apoptosis, angiogenesis, cell proliferation, migration, and invasion [9]. Elevated EGFR expression has been demonstrated in distant metastatic NPC tissues [10]. EGFR overexpression has also been recognized as an independent prognostic indicator for disease-free survival and OS in patients with NPC [11]. These results provide rationality for targeting EGFR therapy in NPC.

Monoclonal antibodies against EGFR have shown promising efficacy in patients with NPC. Nimotuzumab, a humanized EGFR-targeting monoclonal antibody (mAb), inhibits proliferation and promotes apoptosis of tumor cells [12]. Compared with other EGFR-targeting mAb (e.g., cetuximab), nimotuzumab has longer half-life and larger area under the curve (AUC) at the same dose levels [13]. Two retrospective analyses reported clinical benefits of nimotuzumab plus chemotherapy versus chemotherapy alone as first-line treatment in RM-NPC patients [14, 15]. A phase 2 trial reported 71.4% ORR and 7.0-month median PFS in RM-NPC patients receiving nimotuzumab combined with cisplatin and 5-fluorouracil as the first-line therapy [16]. A retrospective analysis of 12 RM-NPC patients receiving cetuximab plus paclitaxel and carboplatin as first-line treatment reported 58.3% ORR and 4.1-month median PFS [17]. A phase 2 trial in 43 RM-NPC patients undergoing first-line treatment with cetuximab plus docetaxel and cisplatin followed by concurrent chemoradiotherapy with cetuximab and cisplatin, and capecitabine maintenance reported 79.1% ORR [18]. Furthermore, in a preliminary retrospective analysis of 40 RM-NPC patients from this research group, nimotuzumab combined with docetaxel and cisplatin (TPN) regimen was associated with 72.5% ORR (unpublished data). These findings suggested that the combination of anti-EGFR mAb and docetaxel with cisplatin may be an effective therapeutic strategy for RM-NPC.

Therefore, this multicenter, open-label, phase 2 trial was conducted to evaluate the efficacy and safety of TPN regimen as first-line treatment for RM-NPC.

Methods

Study design and patients

Patients (18–70 years of age) with newly diagnosed, untreated stage IVB NPC according to the eighth edition of the American Joint Committee on Cancer/Union for International Cancer Control staging system, or with recurrent NPC beyond 6 months after radical chemoradiotherapy and unsuitable for local therapy were eligible. Other requirements for enrolment included (1) ECOG PS of 0–2; (2) at least one measurable disease according to the RECIST v1.1 [19]; (3) estimated life expectancy exceeding 3 months; (4) adequate bone marrow function (absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and hemoglobin ≥ 90 g/L), renal function (creatinine $\leq$ the upper limit of normal [ULN] and creatinine clearance ≥ 60 mL/min), and hepatic function (total bilirubin $\leq$ ULN, alanine aminotransferase [ALT] and aspartate aminotransferase [AST] ≤ 2.5 times ULN, and alkaline phosphatase ≤ 5 times ULN).

Patients were excluded if they were eligible for local therapy; were allergic to any drugs in the TPN regimen; were pregnant or lactating; had other malignant neoplasms; had participated in other clinical trials within 3 months; had serious infections, comorbidities, or vital organ dysfunction. More details on the inclusion and exclusion criteria are shown in the protocol (Additional file 1: Study protocol).

This trial was approved by the institutional ethics committees of the institution, and conducted per the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. All participants provided written informed consent.

Procedures

All eligible patients received intravenous nimotuzumab (200 mg on days 1, 8, and 15) plus docetaxel (75 mg/m^2 on day 1) and cisplatin (75 mg/m^2 on day 1) every 3 weeks for a maximum of 6 cycles, or until disease progression, or death, or intolerable toxicity, or treatment

delay of more than 14 days, whichever occurred earlier. Given the highly emetic nature of cisplatin, a three-drug antiemetic strategy, including neurokinin 1 receptor blockers, 5-hydroxytryptamine-3 receptor blockers, and dexamethasone, was recommended. Diuretics and adequate hydration were used to mitigate cisplatin-induced nephrotoxicity.

The EBV DNA level was detected using a real-time quantitative polymerase chain reaction method [20]. EGFR expression was assessed using immunohistochemical staining of formalin-fixed paraffin-embedded (FFPE) tumor specimens at baseline, and classified into four levels: negative, weak (+, light brown staining only under high magnification), intermediate (+ +, between weak membrane staining and strong membrane staining), and strong (+ + +, dark brown staining under low magnification).

Tumor response was assessed according to RECIST v1.1. Computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) scans were performed every 2 cycles during the TPN treatment. Nasopharyngoscopy and biopsy were optional.

Treatment-related adverse events (TRAEs) were evaluated based on patient report, physical examinations, and laboratory testing at the trial visits. All TRAEs were graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE 4.0). Serious adverse events (SAEs) were defined as those leading to death, life-threatening events, hospitalization or prolonged hospitalization, permanent disability, secondary tumor, congenital malformations, or birth defect.

Follow-up visit was conducted 1 month after completing TPN treatment, once every 3 months during the first 3 years, once every 6 months in the fourth and fifth years, and annually thereafter.

Outcomes

The primary endpoint was ORR, defined as the proportion of patients who achieved partial response (PR) and complete response (CR) according to RECIST v1.1. Secondary endpoints were DCR (the proportion of patients who achieved CR, PR, or stable disease [SD]), duration of response (DOR, time interval from the first day of documented response to PD or death from any cause), time to response (TTR, time interval from the enrolled date to the first CR or PR), PFS (time interval from the enrolled date to the documented PD or death from any cause or censored at the last follow-up), OS (time interval from the enrolled date to death from any cause or last follow-up), and TRAEs. Exploratory endpoints were the relationship between clinical characteristics and response, PFS, and OS.

Statistical analysis

The sample size requirement was estimated based on the Simon two-stage design [21]. The ORR (45%) of cetuximab combined with docetaxel and cisplatin was used as the reference for the null hypothesis testing [22]. We assumed that the targeted ORR of the TPN regimen was 65% with 80% power at a significance level of 0.05. In the initial stage, if a response was observed in at least 7 out of the 15 evaluable patients, the trial would proceed to the second stage; otherwise, the trial would be stopped. The estimated total sample size for the study was 48 patients with a dropout rate of 10%.

Statistical analysis was performed using SPSS version 25.0 and GraphPad Prism 8 software. The two-sided 95% confidence interval (CI) for a response was calculated using the Clopper-Pearson exact method. For exploratory analysis, Pearson's chi-square test or Fisher's exact test was used to compare responses and other categorical variables among different subgroups. Survival curves were plotted using the Kaplan–Meier method for survival outcomes. The univariate comparison of the difference was performed by log-rank test. Multivariate Cox proportional hazards regression analysis was performed to identify factors that were independently associated with the PFS and OS. A two-sided P value of <0.05 was considered statistically significant.

Results

Demographics and baseline characteristics of the participants

A total of 56 patients with RM-NPC were screened between October 15, 2018, and July 20, 2022; 52 were enrolled (Fig. 1). The median age was 44 years (range 25–63 years) (Table 1). Twenty-nine (55.8%) patients had primary metastatic disease, and 44.2% of the patients were recurrent after radical concurrent chemoradiotherapy.

Treatment

The median number of treatment cycles of TPN regimen was 6 (IQR 4–6). Most patients (36/52, 69.2%) received 6 cycles of docetaxel/cisplatin, with 8 patients (15.4%) receiving 1–2 cycles and 8 patients (15.4%) receiving 4–5 cycles. The median exposure to nimotuzumab was 3600 mg (IQR 2400–3600 mg).

Twenty-seven (51.9%) patients received second-line treatment after failure of TPN therapy, mostly ICI-containing regimens (25 out of the 27 patients) (Additional file 2: Table S1). These included ICI plus anlotinib ($n=11$), ICI plus gemcitabine and tegafur/gimeracil/oteracil

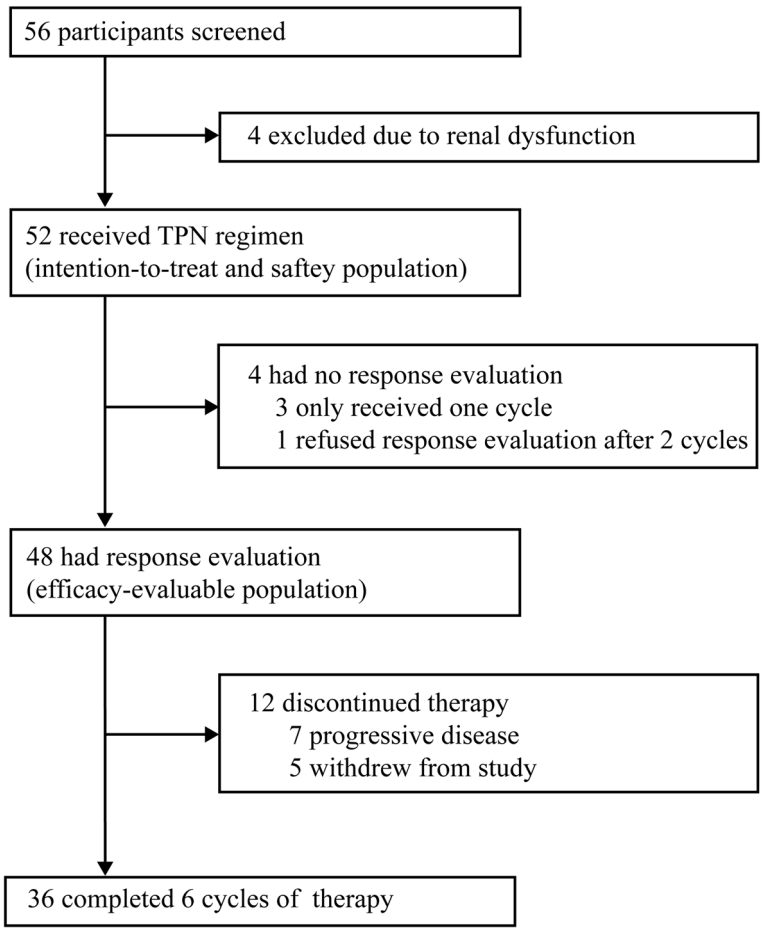

Fig. 1 Trial profile

potassium (S-1) ($n=10$), ICI plus gemcitabine and platinum ($n=2$), ICI plus gemcitabine and capecitabine ($n=1$), and ICI plus transforming growth factor-β (TGF-β) inhibitor ($n=1$).

Treatment response

In the initial stage, 9 of 15 (60.0%) patients had PR, allowing continued enrollment onto the second stage. In the intention-to-treat (ITT) population, the ORR was 65.4% (34/52; 95% CI 50.9–78.0) (Table 2). In the 48 patients with at least one post-treatment assessment, the ORR was 70.8% (34/48; 95% CI 55.9–83.0) (Table 2, Fig. 2).

Post hoc exploratory analyses showed higher ORR in the patients who were female (versus male), who received ≥2400 mg nimotuzumab (versus <2400 mg), and who received ≥4 cycles of docetaxel/cisplatin (versus 3 or less) (Additional file 3: Fig. S1). The ORR was 75.0% in patients with intermediate/strong EGFR expression versus 66.7% in those with negative/weak EGFR expression ($P=0.426$) (Additional file 3: Fig. S2).

The median DOR was 6.1 months (95% CI 5.5–6.7) in the overall cohort (Fig. 3A), 5.8 months in patients with liver metastases versus 7.1 months in those without liver metastases ($P=0.091$). The median TTR was 1.4 months (95% CI 1.4–1.5).

Survival outcomes

At the cutoff date (July 25, 2023), 36 patients experienced PFS events, and 24 deaths were reported. With a median follow-up of 38.1 months (IQR 23.6–47.1), the median PFS and OS were 7.4 months (95% CI 6.5–8.4) and 40.4 months (95% CI 24.7—not reached), respectively (Figs. 3B and 4A). The 1- and 2-year PFS rate was 28.8% (95% CI 17.9–46.2) and 17.3% (95% CI 8.6–34.6), respectively. The 1-year, 2-year, and 3-year OS rate was 83.6% (95% CI 73.9–94.7), 67.9% (95% CI 55.6–82.9), and 50.4% (95% CI 40.7–71.8), respectively.

In the 27 patients who received the next-line treatment, 18 (66.7%) progressive disease (PD) events were reported. The median PFS_2 was 8.9 months (95% CI 5.7–12.1) (Additional file 3: Fig. S3 A). The PFS_2 in the

Table 1 Baseline demographics and disease characteristics of participants ($n = 52$)

Characteristic	Patients
Age, years	
Median	44
Range	25–63
Gender, *n* (%)	
Male	41 (78.8)
Female	11 (21.2)
ECOG performance score, *n* (%)	
0	49 (94.2)
1	3 (5.8)
Smoking status, *n* (%)	
Yes	13 (25.0)
No	39 (75.0)
Disease status, *n* (%)	
Primary metastatic	29 (55.8)
Recurrent	23 (44.2)
Histology, *n* (%)	
Non-keratinizing undifferentiated	51 (98.1)
Poorly differentiated	1 (1.9)
Lung metastases, *n* (%)	
Yes	15 (28.8)
No	37 (71.2)
Liver metastases, *n* (%)	
Yes	23 (44.2)
No	29 (55.8)
Bone metastases, *n* (%)	
Yes	23 (44.2)
No	29 (55.8)
Expression of EGFR, *n* (%)	
Negative	2 (3.8)
Weak staining	37 (71.2)
Intermediate staining	1 (1.9)
Strong staining	7 (13.5)
Unknown	5 (9.6)
Baseline EBV DNA level, copies/mL	
Median	8965
Interquartile range	1965-57,625
≥ 10,000	25 (48.1)
< 10,000	27 (51.9)

Data are shown as number (%) unless otherwise specified

Abbreviations: *ECOG* Eastern Cooperative Oncology Group, *EBV* Epstein-Barr virus, *EGFR* Epidermal growth factor receptor

Table 2 Antitumor activity

Response evaluation	Intention-to-treat population (*n*=52)	Efficacy-evaluable population (*n*=48)
Objective response rate, *n* (%)	34 (65.4)	34 (70.8)
95% CI	50.9–78.0	55.9–83.0
Disease control rate, *n* (%)	47 (90.4)	47 (97.9)
95% CI	79.0–96.8	88.9–99.9
Best overall response, *n* (%, 95% CI)		
Complete response	2 (3.9, 0.5–13.2)	2 (4.2, 0.5–14.3)
Partial response	32 (61.5, 47.0–74.7)	32 (66.7, 51.6–79.6)
Stable disease	13 (25.0, 14.0–38.9)	13 (27.1, 15.3–41.8)
Progressive disease	1 (1.9, 0.1–10.3)	1 (2.1, 0.1–11.1)
Not evaluable	4 (7.7, 2.1–18.5)	-

Data are shown as number (%) or number (%, 95% CI). Responses were assessed in accordance with RECIST version 1.1

11 patients who received ICI plus anlotinib as the next-line therapy was significantly longer than that in the 14 patients who received ICI plus other regimens (median PFS_2: not reached versus 7.4 months; hazard ratio [HR] 0.3, 95% CI 0.1–1.0, $P = 0.032$) (Additional file 3: Fig. S3B). In the 11 patients who received ICI plus anlotinib, the 1-year PFS_2 rate was 68.2%, and the 1- year and 2-year OS rate was 100.0 and 81.8%, respectively (Additional file 3: Fig. S3 C, 3D).

In the subgroup analyses, the median PFS was significantly longer in patients without liver metastases (8.3 versus 6.5 months in those with liver metastases, HR 0.5, 95% CI 0.2–0.9, $P = 0.028$), and in patients who received ≥ 2400 mg nimotuzumab (7.5 versus 4.4 months in those who received < 2400 mg, HR 0.3, 95% CI 0.1–0.8, $P = 0.011$) (Fig. 3C, D). The median PFS was 7.5 and 7.2 months in patients who received ≥ 4 and < 4 cycles of docetaxel plus cisplatin ($P = 0.072$). The median PFS did not differ in patients with different gender ($P = 0.418$), age ($P = 0.759$), Eastern Cooperative Oncology Group performance status (ECOG PS) ($P = 0.235$), smoking status ($P = 0.845$), disease status ($P = 0.976$), EGFR expression ($P = 0.936$), lung metastases ($P = 0.843$), and bone metastases ($P = 0.470$).

The median OS was significantly longer in patients aged < 50 years (52.8 versus 24.7 months in those aged ≥ 50 years; HR 0.4; 95% CI 0.2–1.0; $P = 0.035$), in patients who received ≥ 2400 mg nimotuzumab (42.3 versus 17.9 months, HR 0.4, 95% CI 0.2–1.0, $P = 0.045$) and in patients who received ≥ 4 cycles of docetaxel plus cisplatin (42.3 versus 17.9 months, HR 0.3, 95% CI 0.1–0.8, $P = 0.010$) (Fig. 4B–D). The median OS did not differ in patients with different gender ($P = 0.628$), ECOG PS ($P = 0.372$), smoking status ($P = 0.816$), disease status ($P = 0.721$), EGFR expression ($P = 0.604$), lung metastases ($P = 0.497$), liver metastases ($P = 0.428$), and bone metastases ($P = 0.184$).

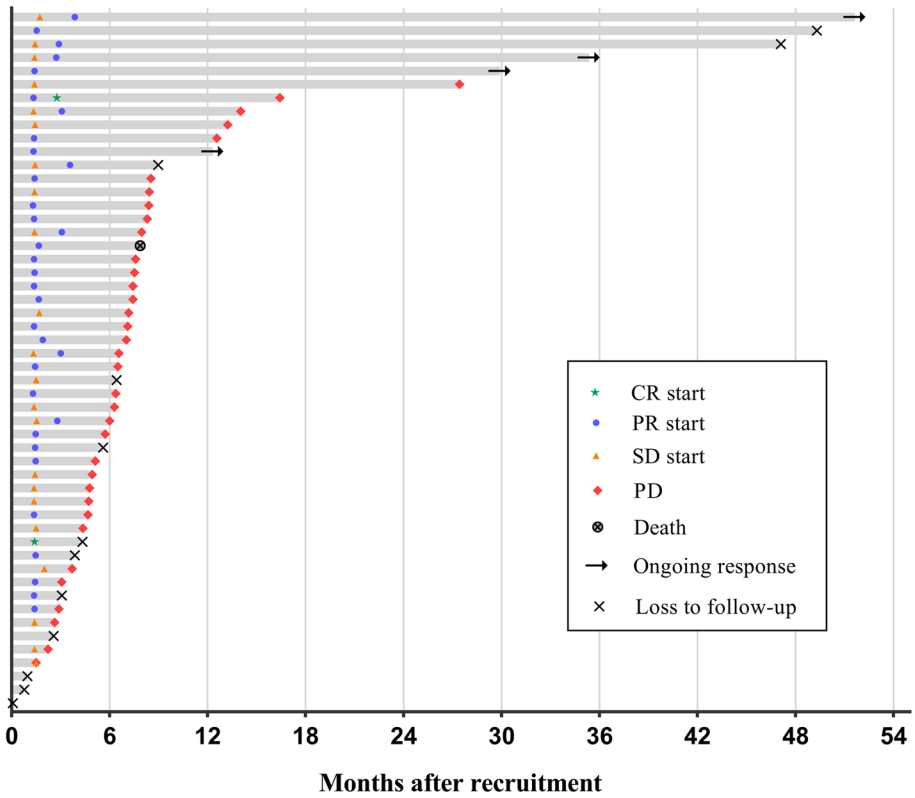

Fig. 2 Swimmer plot of the intention-to-treat population. Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

Clinical significance of plasma EBV DNA level

Patients were divided into a high-EBV DNA group ($n=$ 25) and a low-EBV DNA group ($n=$ 27) using a cut-off value of 10,000 copies/mL [23, 24]. Compared with the high-EBV DNA group, the low-EBV DNA group had longer median PFS (7.9 versus 7.0 months; HR 0.5; 95% CI 0.2–0.9; $P=$ 0.030) (Fig. 3E). However, the two groups did not differ in either ORR (70.4% versus 60.0%; $P=$ 0.432) or median OS (40.4 versus 36.3 months; $P=$ 0.740).

EBV DNA level was available in 39 patients upon completion of two treatment cycles. Patients whose EBV DNA declined to 0 copies/mL after 2 cycles of treatment ($n=$ 15) had a better median PFS (14.0 versus 7.0 months; HR 0.4; 95% CI 0.2–0.9; $P=$ 0.023) than patients whose EBV DNA did not ($n=$ 24) (Fig. 3F). The ORR was 86.7% (13/15) in the patients whose EBV DNA declined to 0 copies/mL versus 62.5% (15/24) in patients with detectable EBV DNA after 2 cycles of treatment ($P=$ 0.206). OS did not differ between the two groups (not reached versus 52.8 months; $P=$ 0.641).

Furthermore, in multivariate Cox proportional hazards regression analysis, longer PFS was associated with $\geq$2400 mg nimotuzumab (HR 0.2; 95% CI 0.1–0.6; $P=$ 0.003) and low-EBV DNA level (HR 0.4; 95% CI 0.2–0.8; $P=$ 0.010) after adjustment. Longer OS was associated with $\geq$4 cycles of docetaxel plus cisplatin (HR 0.3; 95% CI 0.1–0.8; $P=$ 0.014) after adjustment.

Treatment-related adverse events

Among the 52 patients, 50 (96.2%) had any grade TRAEs, and the majority of TRAEs were grades 1–2. TRAEs with $\geq$20% rate included anemia, leukopenia, neutropenia, hypertriglyceridemia, hypercholesterolemia, nausea, limb numbness, hyperglycemia, fatigue, thrombocytopenia, rash, and creatinine elevated (Table 3). Grade $\geq$3 TRAEs included neutropenia, leukopenia, febrile neutropenia, nausea, fatigue, infection, thrombocytopenia, and anorexia (Table 3). All TRAEs were reversible with standard supportive care or dose interruptions.

Twelve patients required dose interruptions of nimotuzumab owing to febrile neutropenia ($n=$ 4), infection ($n=$ 3), fatigue ($n=$ 2), COVID-19 ($n=$ 2), and dyspnea ($n=$ 1). SAEs were reported in 3 patients due to infection. No treatment-related deaths were reported.

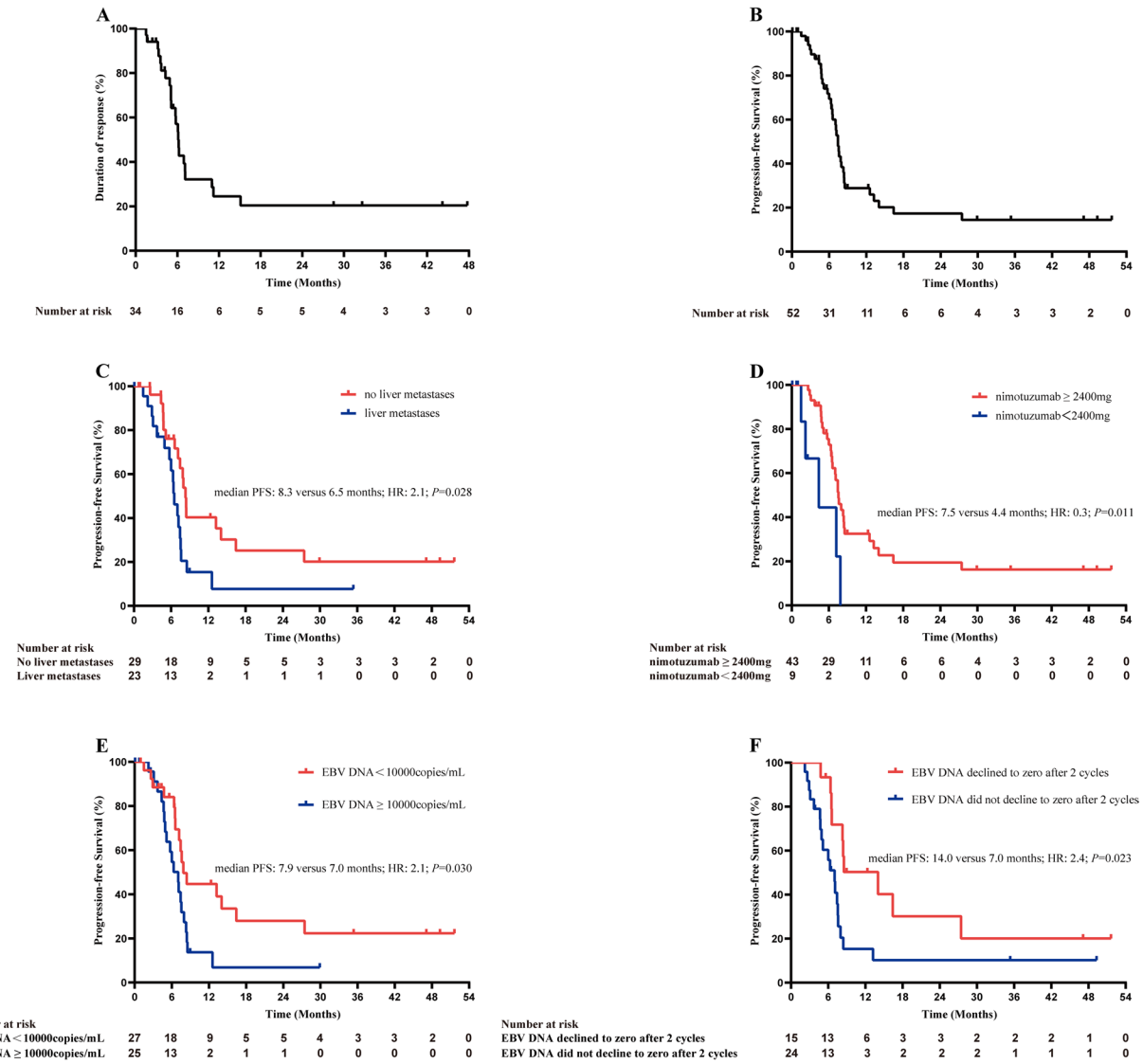

Fig. 3 Kaplan-Meier survival curves. **A** Duration of response of 34 responding patients. **B** PFS of 52 patients. **C** PFS of patients with versus those without liver metastases. **D** PFS of patients who received ≥2400 mg nimotuzumab versus those who received<2400 mg nimotuzumab. **E** PFS of patients at initial diagnosis with EBV DNA ≥10,000 copies/mL versus those with EBV DNA <10,000 copies/mL. **F** PFS of patients whose EBV DNA declined to zero after 2 cycles versus those whose EBV DNA did not. Abbreviations: DOR, duration of response; EBV, Epstein-Barr virus; HR, hazard ratio; PFS, progression-free survival

Discussion

To the best of our knowledge, this is the first study to report the efficacy and safety of the TPN regimen as a first-line treatment in RM-NPC. Our primary endpoint was achieved, with an ORR of 65.4% in the ITT population, and the adverse event profile was manageable, underscoring the substantial efficacy and well-tolerated safety profile of the TPN regimen in treating RM-NPC in the first-line setting.

GP regimen has been recommended as the first-line chemotherapy for RM-NPC based on evidence from a phase 3 trial, with an ORR of 64.0% and median PFS of 7 months [8]. In the current study, the ORR was 65.4% with median PFS of 7.4 months and median OS of 40.4 months. In contrast, the median OS in patients treated with GP regimen in previous trials was 14.6–22.1 months [4, 25, 26]. Such an apparent difference could be largely attributed to the high proportion of patients receiving ICI-containing regimen as next-line therapy in this trial. The extent of true differences between the two chemotherapeutic regimens needs further investigation. Furthermore, GP combined with ICI has been established

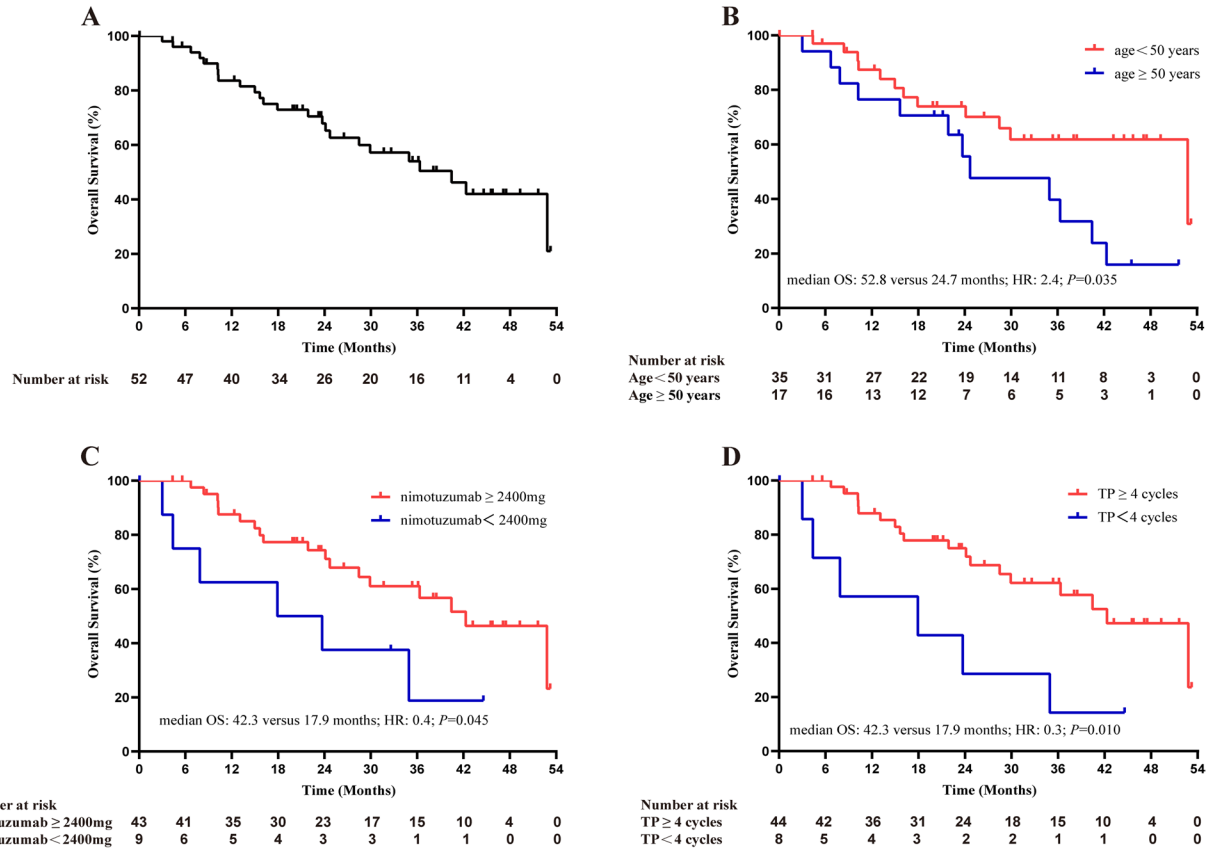

Fig. 4 Kaplan-Meier curves for the OS. **A** OS of 52 patients. **B** OS of patients aged ≥50 years versus those aged <50 years. **C** OS of patients who received ≥2400 mg nimotuzumab versus those who received <2400 mg nimotuzumab. **D** OS of patients who received ≥4 cycles of docetaxel plus cisplatin versus those who received <4 cycles of docetaxel plus cisplatin. Abbreviations: HR, hazard ratio; OS, overall survival; TP, docetaxel plus cisplatin

as the first-line regimen based on three phase 3 trials [6, 27, 28], but options in patients with contraindications to ICI, such as severe auto-immune diseases, history of organ transplantation, and known intolerance to ICI are limited. The TPN regimen may represent an alternative first-line therapy in this subpopulation.

Docetaxel plus cisplatin regimen is also recommended as one of the first-line regimens for RM-NPC by the National Comprehensive Cancer Network (NCCN) Guidelines. Based on the results in this trial (ORR 65.4%; median PFS 7.4 months) as opposed to that reported by a previous phase 2 trial of docetaxel/cisplatin alone in 19 patients with RM-NPC (ORR 52.6%; median PFS 5.6 months) [7], we speculate that adding nimotuzumab to docetaxel/cisplatin may be beneficial. Cross-trial comparison in different eras, however, is subject to potential biases.

Twenty-five patients in this trial received ICI-contained regimens as the next-line treatment, with a median PFS_2 of 8.9 months, which is superior to that in RM patients who received ICI monotherapy [24, 29, 30] or ICI plus bevacizumab [31]. Intriguingly, the 1-year PFS_2 rate was 68.2% in patients who received ICI plus anlotinib, which was numerically longer than that reported for RM-NPC who received ICI plus anti-angiogenic treatments [32–34]. Clearly, ICI is an essential component in the treatment of RM-NPC, whether given in first-line or in second-line. However, the optimal sequence of ICI use requires further investigation.

The TPN regimen was well-tolerated in this trial. The rate of hematological toxicities and elevation of AST or ALT was similar to that reported with the GP regimen [8]. Notably, the rate of TRAEs was comparable to that reported for docetaxel and cisplatin chemotherapy alone in a previous study [7]. Consistent with prior studies of nimotuzumab [15, 16], there were no grade 3/4 skin lesions in this trial. In contrast, cetuximab plus docetaxel/cisplatin was associated with grade 3/4 skin lesions in 16% of the patients [22]. Our finding provides the evidence supporting the superior cutaneous safety profile of nimotuzumab, consistent with the result reported by Takeda et al. [35].

Table 3 Treat-related adverse events ($n = 52$)

TRAEs	All grades	Grade 1–2	Grade 3 or more
Neutropenia	29 (55.8%)	7 (13.5%)	22 (42.3%)
Leukopenia	30 (57.7%)	13 (25.0%)	17 (32.7%)
Febrile neutropenia	6 (11.5%)	0	6 (11.5%)
Thrombocytopenia	11 (21.2%)	10 (19.2%)	1 (1.9%)
Anemia	41 (78.8%)	41 (78.8%)	0
Nausea	19 (36.5%)	15 (28.8%)	4 (7.7%)
Fatigue	13 (25.0%)	10 (19.2%)	3 (5.8%)
Infection	4 (7.7%)	1 (1.9%)	3 (5.8%)
Anorexia	6 (11.5%)	5 (9.6%)	1 (1.9%)
Oral ulcers	3 (5.8%)	2 (3.8%)	1 (1.9%)
Hypertriglyceridemia	20 (38.5%)	20 (38.5%)	0
Hypercholesterolemia	20 (38.5%)	20 (38.5%)	0
Hyperglycemia	14 (26.9%)	14 (26.9%)	0
Limb numbness	14 (26.9%)	14 (26.9%)	0
Creatinine elevated	11 (21.2%)	11 (21.2%)	0
Rash	11 (21.2%)	11 (21.2%)	0
ALT elevated	10 (19.2%)	10 (19.2%)	0
Diarrhea	8 (15.4%)	8 (15.4%)	0
Hypertension	6 (11.5%)	6 (11.5%)	0
AST elevated	6 (11.5%)	6 (11.5%)	0
Edema	4 (7.7%)	4 (7.7%)	0
Alopecia	3 (5.8%)	3 (5.8%)	0
Otitis	2 (3.8%)	2 (3.8%)	0
Hyperkalemia	2 (3.8%)	2 (3.8%)	0
Pigmentation	1 (1.9%)	1 (1.9%)	0
Dyspnea	1 (1.9%)	1 (1.9%)	0

Data are shown as number (%)

Abbreviations: *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *TRAEs* Treat-related adverse events

NPC is closely associated with EBV infection in the process of tumorigenesis and development [1, 36]. Plasma EBV DNA plays a vital role in screening for early asymptomatic NPC, facilitating clinical decision-making, monitoring treatment response, predicting tumor relapse, and evaluating prognosis in patients with NPC [37–39]. Consistent with previous studies [40], low EBV DNA level at baseline (< 10,000 copies/mL) was associated with longer PFS (HR 0.5; $P = 0.030$), as well as a statistically non-significantly higher ORR (70.4% versus 60.0%, $P = 0.432$), which is similar to finding in previous studies [24, 33].

The dynamic change in the EBV titer is closely linked to the response to systemic therapy [24, 40]. Consistent with a previous study [41], the median PFS was longer in patients whose EBV DNA declined to zero after two treatment cycles in this trial. Also consistent with the previous study [16], higher ORR and longer PFS were associated with ≥ 2400 mg nimotuzumab and ≥ 4 cycles of docetaxel plus cisplatin. However, no significant correlations were found between EGFR expression with either ORR or survival outcomes.

This trial had several limitations. First, there was no built-in control group of docetaxel/cisplatin alone. The potential benefits of adding nimotuzumab, thus requires further investigation. Second, treatment response and survival outcomes seemed to differ between patients with different EBV DNA level at the baseline as well as after two treatment cycles, but EBV DNA was not available after treatment cycles in all patients. Finally, the clinical values of the EGFR expression status were not elucidated because of the high proportion of weak staining. Hence, the relationship between EGFR expression and the efficacy of nimotuzumab warrants further exploration.

Conclusions

First-line therapy with the TPN regimen showed promising efficacy with a well-tolerated safety profile in RM-NPC patients.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
CI	Confidence interval
CR	Complete response
CT	Computed tomography
DCR	Disease control rate
DOR	Duration of response
EBV	Epstein-Barr virus
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	Epidermal growth factor receptor
FFPE	Formalin-fixed paraffin embedded
GP	Gemcitabine plus cisplatin
HER	Human epidermal growth factor receptor
HR	Hazard ratio
ICI	Immune checkpoint inhibitor
IQR	Interquartile range
ITT	Intention-to-treat
mAb	Monoclonal antibody
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI-CTCAE 4.0	National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0
NE	Not evaluable
NPC	Nasopharyngeal carcinoma
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PR	Partial response
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RM	Recurrent or metastatic
S-1	Tegafur/gimeracil/oteracil potassium
SAEs	Serious adverse events
SD	Stable disease
TGF-β	Transforming growth factor-β
TP	Docetaxel plus cisplatin
TPN	Nimotuzumab combined with docetaxel and cisplatin
TRAEs	Treatment-related adverse events
TTR	Time to response
ULN	Upper limit of normal

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04103-0.

Additional file 1: Study protocol.

Additional file 2: Table S1. Regimens of the second-line treatment (*n*=27).

Additional file 3: Figures S1-S3. Fig. S1- [Stacked bar plots showing the treatment response in different subgroups of the intention-to-treat population]. Fig. S2- [Forest plot showing subgroup analyses of ORR in the intention-to-treat population]. Fig. S3- [Kaplan-Meier survival curves. (A) PFS_2 of patients received the second-line treatment. (B) PFS_2 of patients who received ICI plus anlotinib versus those who received ICI plus other regimens. (C) PFS_2 of patients who received ICI plus anlotinib as the second-line treatment. (D) OS of patients who received TPN followed by ICI plus anlotinib].

Acknowledgements
The authors gratefully thank the patients and their families for participating in this study. Nimotuzumab was provided by Biotech pharmaceutical co., Ltd. The authors thank Home for researchers editorial team (www.home-for-researchers.com) for their help with language editing service, and Dr. Kehong Zhang from the Ivy Medical Editing for editing the manuscript during the revision.

Authors' contributions
Study conceptualization and design: QQC, YX, TYH, QHZ; Study execution: QQC, YX, PPL, LXL, NS, ZHL, XCW, XPT; Data curation: QHZ, YCZ, LRL, YXL; Formal analysis, Methodology, Visualization, Validation: QHZ, YC, YLL, YF; Roles/Writing-original draft: QHZ, YC, YLL, HW; Investigation, Resources writing-review & editing: All authors; Supervision: QQC, YX. Funding acquisition: QQC. All authors read and approved the final manuscript.

Funding
This work was supported by grants from National Natural Science Foundation of China (No. 81672686 to Prof. Qingqing Cai).

Data availability
All data used or analyzed in the study are available from the lead contact upon reasonable request.

Declarations

Ethics approval and consent to participate
This trial was approved by the Ethics Committee of Sun Yat-Sen University Cancer Center (B2018-097). All participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 7 May 2024 Accepted: 25 April 2025
Published online: 06 May 2025

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