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ORIGINAL RESEARCH

Efficacy and Safety of Re-Challenging PD-1 Inhibitors in Second-Line Treatment in Metastatic Nasopharyngeal Carcinoma Previously Treated with Chemotherapy and PD-1 Inhibitors

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Background: We aim to evaluate the efficacy and safety of anti-PD1 rechallenge in combination with chemotherapy in patients with metastatic nasopharyngeal carcinoma (mNPC) who have progressed on prior anti-PD1 therapy.

Patients and Methods: We enrolled patients with mNPC who received chemotherapy combined with PD-1 immune-checkpoint inhibitors (ICIs) or chemotherapy alone after prior progression of anti-PD1 therapy. The primary endpoint was progress-free survival (PFS), and the secondary endpoints included overall survival (OS), disease control rate (DCR) and objective response rate (ORR).

Results: A total of 96 patients were eligible between January 2015 and December 2020. Thirty-seven (38.5%) were in the PD-1 ICIs re-challenge group, while the remaining 59 patients (61.5%) were in the chemotherapy group. The ORR and DCR of PD-1 ICIs group and chemotherapy group were 37.8% vs 23.7% and 86.5% vs.74.5%, respectively. After a median follow-up period of 21.1 months (IQR 16.1–28.7), the log-rank analysis demonstrated a significantly improved PFS in the PD-1 ICIs re-challenge group compared to the chemotherapy group (8.4 months [95% CI 4.3–14.0] vs 5.0 months [95% CI 2.8–7.2], $P = 0.03$). However, no significant difference in OS was observed between the two groups (28.3 vs 24.1 months, $P = 0.09$). The two groups had similar adverse reactions, but the incidence of grade 3 or 4 thrombocytopenia was significantly higher in the PD-1 ICIs re-challenge group (18.9% vs 3.4%, $P = 0.025$).

Conclusion: mNPC patients who progressed from prior anti-PD1 therapy could benefit from the anti-PD1 rechallenge in combination with chemotherapy. However, further validation is needed.

Keywords: metastatic nasopharyngeal carcinoma, chemotherapy, PD-1 immune checkpoint inhibitors, second-line treatment strategies

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor associated with Epstein–Barr virus (EBV) that is highly metastatic compared to other head and neck tumors.[1] Over 20% of patients who have undergone radical chemoradiotherapy and approximately 6–15% of newly diagnosed patients develop distant metastasis, which is the leading cause of death. Platinum-based combination chemotherapy has been the standard first-line treatment for patients with metastatic nasopharyngeal carcinoma (mNPC).[1,2] Currently, several Phase III, randomized, double-blind controlled trials have shown that adding PD-1 immune-checkpoint inhibitors (ICIs) to standard-of-care therapy confers significant improvements in progression-free survival (PFS) and overall survival (OS), leading that combination therapy was recommended as preferred first-line treatment according to the Chinese Society of Clinical Oncology (CSCO) guidelines.[3–6]

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However, nearly half of mNPC patients experience disease progression within one year after first-line chemotherapy combined with PD-1 ICIs. In the past, single-agent chemotherapy, such as S-1, capecitabine and gemcitabine, was recommended. However, traditional chemotherapy often has low efficacy with ORR of nearly 30–40% and median PFS of nearly 5 months, with serious side effects.[7] In recent years, PD-1 ICIs directed against PD-1 or PD-L1 have transformed treatment options for mNPC patients. Initially, PD-1 ICIs were approved for palliative second-line treatment of mNPC patients. The Keynote-028 study, NCI-9742 study, Polaris-02 study and SHR-1210 study were achieved similar ORR of about 20–30% with less toxicity and median PFS of about 1.9–3.7 months.[8–11] Not only is immune monotherapy treatment effective, but combination therapy also confers a survival benefit. So, there is a need to explore the feasibility of challenging PD-1 ICIs with the second-line setting.[3,5] In non-small cell lung cancer (NSCLC), the Keynote-010 study indicated that continuing pembrolizumab treatment after disease progression led to favorable outcomes, with an objective response rate (ORR) of 42.9% and a disease control rate (DCR) of 78.6% in patients who had received 2 years of pembrolizumab treatment.[12] Another study demonstrated that NSCLC patients who were re-challenged with atezolizumab in the second-line treatment after disease progression had improved 1-year OS rate (71% vs 37%) compared to those who switched to non-immune therapies.[13] In melanoma, a study showed that continuing PD-1 ICIs after disease progression led to better PFS compared to discontinuing PD-1 ICIs, with a 19% ORR.[14] However, due to the lack of large-scale clinical trial data, there is currently no consensus on whether re-challenging with PD-1 ICIs is appropriate after disease progression in mNPC.

Currently, to address this crucial gap, we propose a retrospective study focused on patients with mNPC who experienced disease progression after first-line chemotherapy combined with PD-1 ICIs. This study aims to elucidate the clinical benefits, suitable patient profiles, and safety considerations of re-challenging patients with PD-1 ICIs in the second-line setting.

Materials and Methods

Patient Cohort

With institutional review board approval and a waiver of patient consent requirements, we conducted this single-center, retrospective study that used information from the institutional database at Sun Yat-Sen University Cancer Center (SYSUCC) between January 2015 and December 2020. The study included mNPC patients aged 18 to 70 who had progressed after first line platinum-based chemotherapy combined with PD-1 ICIs therapy. All patients had received at least 2 cycles of chemotherapy with or without PD-1 ICIs as the second-line treatment. In first- and second-line, the PD-1 inhibitors used include: Nivolumab, Pembrolizumab, Toripalimab, Camrelizumab, and Tislelizumab.

We obtained baseline clinical and demographic data from patients within 4–6 weeks prior to the initiation of treatment. Furthermore, subgroup analysis was performed by estimating Kaplan–Meier curves according to specific details for first-line treatment. In addition, we categorized subgroups based on the following criteria: efficacy evaluation of prior first-line treatment (CR/PR group, SD/PD group), EBV-DNA clearance during prior first-line treatment (CR group and non-CR group), the duration of immunotherapy during prior first-line treatment (<9 cycles, ≥9 cycles), and the time without chemotherapy during the first-line treatment (with or without PD-1 ICIs treatment) until disease progression (≤3 months, >3 months).

Outcomes

The primary endpoint was progression-free survival (PFS), which was defined as the interval from the first day of second-line to the date of disease progression or death. The second endpoints were disease control rate (DCR), objective response rate (ORR) and overall survival (OS). DCR is defined as the proportion of patients who achieved complete response (CR), partial response (PR), or stable disease (SD); ORR is defined as the proportion of patients with a partial or complete response to treatment; OS was recorded from the first day of second-line treatment to the date of death or last follow-up. Progressive disease with PD-1 ICIs was defined according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). Response assessment by CT or MRI scans was performed every two cycles during treatment and thereafter every three months until the disease progressed or the patient died.

Statistical Analysis

The primary characteristics of patients were summarized using frequencies and proportions for categorical variables, and using median, interquartile range (IQR), and range for continuous variables. Baseline characteristics were compared between the two treatment groups using Wilcoxon rank sum test for continuous variables and Pearson's χ^2-test for categorical variables. Fisher's exact test was used for categorical variables when the expected count per cell was less than 5. We used the Kaplan–Meier approach to estimated survival curves and median survival time. We compared survival differences using the Log rank test. We performed Cox proportional hazards models to calculate the stratified hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Statistical results were calculated using SPSS (version 22.0), and R 4.1.2. All tests were two-sided; A p value of less than 0.05 is considered statistically significant.

Results

Patient Population

A total of 257 patients with mNPC progressed during or after first-line platinum-based chemotherapy combined with PD-1 ICIs therapy. Of these, 96 patients were enrolled, with 38.5% patients (n=37) received chemotherapy plus PD-1 ICIs (PD-1 ICIs re-challenge group) and 61.5% patients (n=59) accepted chemotherapy alone (chemotherapy group) as second-line therapy. The study flow chart is shown in Figure 1. The median age was 46 years (IQR, 37–52). The majority of patients were male (78.1%) and had an ECOG performance status of 0 or 1 (94.8%). As recorded by the first-line treatment, 62 (64.6%) patients were achieved CR/PR and 34 (35.4%) were SD/PD as best response. During first-line treatment, 46 (47.9%) patients could achieve EBV-DNA clearance, while 50 (52.1%) patients have not completely cleared EBV-DNA. The groups were well balanced for most characteristics (Table 1). Compared with PD-1 ICIs re-challenge group, there were significantly more patients with liver metastases in chemotherapy group (47.5% vs 21.6%, P =0.02).

Antitumor Activity

In the second-line treatment, the PD-1 ICIs re-challenge group exhibited a slightly higher ORR compared to the chemotherapy group, with no statistically significant difference (37.8% vs 23.7%, P = 0.17). Concerning the DCR, the

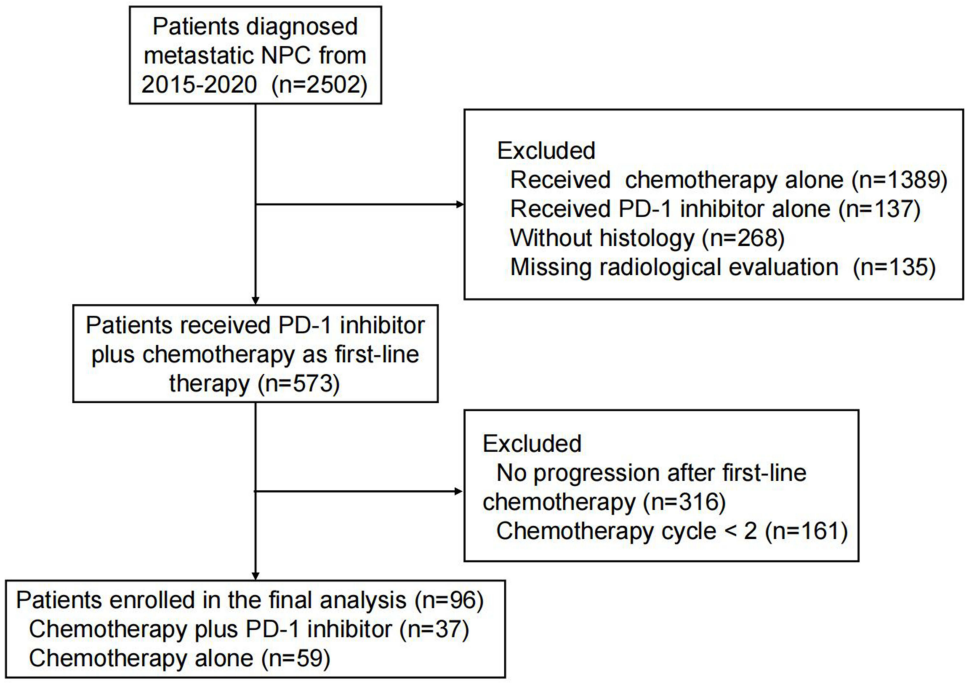

Figure 1 Patient selection diagram.

Table 1 Baseline Patient Demographic and Clinical Characteristics

	ALL (n=96)	PD-1 ICIs Re-Challenge Group (n=37)	Chemotherapy Group (n=59)	*P*
Age	46.0 [37.8–52.0]	47.0 [38.0–53.0]	46.0 [37.5–51.5]	0.268
Gender				0.188
Male	75 (78.1%)	32 (86.5%)	43 (72.9%)	
Female	21 (21.9%)	5 (13.5%)	16 (27.1%)	
Smoking status				0.673
No	69 (71.9%)	28 (75.7%)	41 (69.5%)	
Yes	27 (28.1%)	9 (24.3%)	18 (30.5%)	
Drinking status				0.745
No	85 (88.5%)	32 (86.5%)	53 (89.8%)	
Yes	11 (11.5%)	5 (13.5%)	6 (10.2%)	
History				0.563
No	79 (82.3%)	32 (86.5%)	47 (79.7%)	
Yes	17 (17.7%)	5 (13.5%)	12 (20.3%)	
ECOG				0.153
2	5 (5.21%)	0 (0.00%)	5 (8.47%)	
0–1	91 (94.8%)	37 (100%)	54 (91.5%)	
Oligometastasis				1.000
No	63 (65.6%)	24 (64.9%)	39 (66.1%)	
Yes	33 (34.4%)	13 (35.1%)	20 (33.9%)	
Primary Metastases				0.671
No	66 (68.8%)	24 (64.9%)	42 (71.2%)	
Yes	30 (31.2%)	13 (35.1%)	17 (28.8%)	
Number of involved sites				0.273
One	49 (51.0%)	22 (59.5%)	27 (45.8%)	
Multiple	47 (49.0%)	15 (40.5%)	32 (54.2%)	
Bone metastasis				1.000
No	53 (55.2%)	20 (54.1%)	33 (55.9%)	
Yes	43 (44.8%)	17 (45.9%)	26 (44.1%)	
Liver metastasis				0.020
No	60 (62.5%)	29 (78.4%)	31 (52.5%)	
Yes	36 (37.5%)	8 (21.6%)	28 (47.5%)	
Lung metastasis				0.771
No	54 (56.2%)	22 (59.5%)	32 (54.2%)	
Yes	42 (43.8%)	15 (40.5%)	27 (45.8%)	
Lymph metastasis				0.871
No	60 (62.5%)	24 (64.9%)	36 (61.0%)	
Yes	36 (37.5%)	13 (35.1%)	23 (39.0%)	
EBV DNA level (copies/mL)				0.645
≤ 4000	40 (41.7%)	17 (45.9%)	23 (39.0%)	
>4000	56 (58.3%)	20 (54.1%)	36 (61.0%)	
1st line response				1.000
SD/PD	34 (35.4%)	13 (35.1%)	21 (35.6%)	
CR/PR	62 (64.6%)	24 (64.9%)	38 (64.4%)	
1st line EBV-DNA clearance				0.923
CR	46 (47.9%)	17 (45.9%)	29 (49.2%)	
Non-CR	50 (52.1%)	20 (54.1%)	30 (50.8%)	
1st line ICIs cycle				0.232
≤ 3 months	45 (46.9%)	14 (37.8%)	31 (52.5%)	
>3 months	51 (53.1%)	23 (62.2%)	28 (47.5%)	

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ICIs, immune-checkpoint inhibitors.

PD-1 ICIs re-challenge group demonstrated a DCR of 86.5%, while the chemotherapy group had a DCR of 74.5%, with no statistically significant variance (P = 0.20, as depicted in Supplement Table 1).

Survival Outcomes

The median follow-up time was 21.1 months (IQR 16.1–28.7). For the entire cohort, the median PFS was 5.22 months (95% CI:1.33–17.14) and median OS was 10.23 months (95% CI:1.50–32.09). The median time to progression after first-line treatment was significantly different between PD-1 ICIs re-challenge group [8.43 (95% CI 4.3–14.0) months] and chemotherapy alone group [5.0 (95% CI 2.8–7.2) months; P =0.027]; the median OS in the PD-1 ICIs re-challenge group and chemotherapy group was 28.3 (95% CI 23.1–61.5) months and 24.1 months (95% CI 9.6–38.5, P =0.09, Figure 2). Treatment specifics for the PD-1 ICIs re-challenge group and the chemotherapy group are illustrated in Supplement Figure 1.

Univariable Cox proportional hazard analysis identified the 1st line EBV-DNA clearance, red blood cell count (RBC), hemoglobin (Hb) and mean corpuscular hemoglobin concentration (MCHC) as pretreatment prognostic markers of OS. The time without chemotherapy in first-line, hematocrit (Hct), eosinophil, monocyte percentages and alkaline phosphatase (ALP) correlated with PFS in univariable analysis. Univariable analysis was shown in Supplement Table 2. Multivariate analysis revealed 1st line response as an independent predictive factor for better PFS, as well as 1st line time without chemotherapy, Hct, ALP and 1st line ICI cycle. Multivariate analysis on OS showed that 1st line EBV-DNA clearance was associated with better OS. The results of multivariate analysis are listed in Table 2.

Subgroup Analysis Based on First-Line Treatment

In order to gain a deeper understanding of the patient population that would benefit from re-challenging with PD-1 ICIs, we conducted comprehensive subgroup analyses. Patients achieving objective response during first-line treatment showed significantly improved PFS when re-challenged with PD-1 ICIs compared to those receiving chemotherapy alone (P < 0.05). However, no significant difference in OS was observed between the two groups (P = 0.44). For patients achieving SD/PD during first-line treatment, there were no significant differences in PFS and OS between the two groups (P = 0.68 and P = 0.07, respectively, Figure 3 and Supplement Figure 2).

Patients who achieved EBV-DNA clearance (EBV-DNA=0 copies/mL) during first-line treatment exhibited significantly prolonged PFS when re-challenged with PD-1 ICIs compared to chemotherapy alone (P < 0.05). However, no

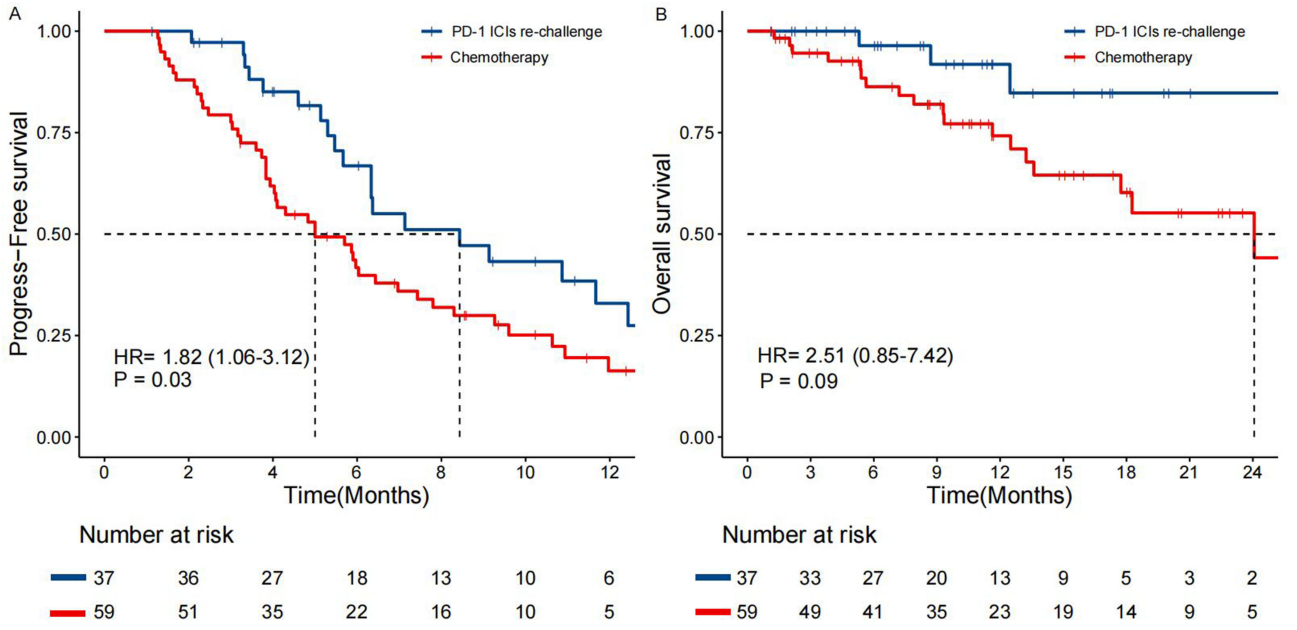

Figure 2 Progression-free survival (**A**) and overall survival (**B**) of patients. Kaplan–Meier curves are stratified by treatment group. The log rank test was used to compare survival between the groups.

Table 2 Multivariable Analysis for PFS and OS

	PFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
Liver metastasis	0.79 (0.44, 1.44)	0.44	0.87(0.29, 2.54)	0.79
Number of involved sites	1.15 (0.61, 2.17)	0.68	0.78(0.21, 2.87)	0.71
Oligometasis	0.79 (0.42, 1.49)	0.47	0.49 (0.12, 2.00)	0.32
Primary metastases	0.80 (0.41, 1.55)	0.50	0.48 (0.11, 1.98)	0.31
EBV DNA level	1.37 (0.74, 2.53)	0.32	0.63 (0.18, 2.20)	0.47
1st line EBV-DNA clearance	1.36 (0.73, 2.55)	0.33	5.02 (1.37, 18.30)	P<0.05
1st line response	2.01 (1.03, 3.90)	P<0.05	0.84 (0.21, 3.29)	0.80
1st line ICI cycle	2.30 (1.11, 4.78)	P<0.05	1.68 (0.40, 7.18)	0.48
1st line time without chemotherapy	1.00 (1.00, 1.00)	P<0.01	1.00 (1.00, 1.00)	0.33
RBC	0.43 (0.16, 1.14)	0.09	0.27 (0.04, 1.98)	0.20
MCHC	2.35 (0.91, 6.07)	0.08	2.68 (0.41, 17.48)	0.30
Mono%	1.59 (0.87, 2.89)	0.13	2.99 (0.99, 9.04)	0.05
HCT	3.74 (1.68, 8.34)	P<0.01	2.20 (0.47, 10.35)	0.32
HGB	1.59 (0.54, 4.71)	0.40	0.62 (0.08, 4.68)	0.64
ALP	2.90 (1.23, 6.82)	P<0.05	3.97 (0.78, 20.31)	0.10

Abbreviations: PFS, progression-free survival; OS, overall survival; RBC, red blood cell; MCHC, mean corpuscular hemoglobin concentration; MONO%, monocyte percentages; HCT, hematocrit; HGB, hemoglobin; ALP, alkaline phosphatase.

substantial improvement in OS was observed (P = 0.19). For patients who did not achieve EBV-DNA clearance during first-line treatment, there were no significant survival benefits in terms of both PFS and OS between the two groups (P = 0.38 and P = 0.18, respectively, Figure 3 and Supplement Figure 2).

Among patients who received fewer than 9 cycles of PD-1 ICIs during first-line treatment, re-challenging with PD-1 ICIs in the second-line setting led to a significantly extended PFS compared to chemotherapy alone ($P < 0.05$). For patients who received 9 or more cycles of PD-1 ICIs during first-line treatment, no significant differences were observed in PFS and OS between the PD-1 ICIs re-challenge group and the chemotherapy-alone group (P = 0.31 and P = 0.19, respectively, Figure 3 and Supplement Figure 2).

When the chemotherapy-free interval during first-line treatment was >3 months, the PD-1 ICIs re-challenge group demonstrated a significant improvement in PFS ($P < 0.01$), although OS did not show a notable enhancement (P = 0.60). When the chemotherapy-free interval was ≤3 months during first-line treatment, no significant differences were observed in PFS and OS between the two groups (P = 0.51 and P = 0.55, respectively, Figure 3 and Supplement Figure 2).

Safety

The adverse events were evaluated in all enrolled patients and summarized in Table 3. These adverse events were generally manageable. Hematologic toxicities were the most common adverse effects in both arms. Compared with the chemotherapy group, grade 3 or higher thrombocytopenia was significantly higher in the PD-1 ICIs re-challenge group (18.9% vs 3.4%, P =0.025). In addition, no significant differences in grade 3–4 leukopenia and neutropenia, anemia, renal dysfunction or liver dysfunction were found between the two groups.

Discussion

To our best knowledge, this is the first study to reveal that among mNPC patients experiencing disease progression following first-line chemotherapy combined with PD-1 ICIs treatment, second-line treatment with chemotherapy in combination with PD-1 ICIs yields superior PFS benefits when contrasted with chemotherapy alone.

Notably, the results from several Phase III trials, including the CAPTAIN 1ST, JUPITER 02 and RATIONALE-309 trials, have demonstrated significant PFS extensions with ICIs-based regimens when compared to chemotherapy alone in first-line recurrent/metastatic NPC treatment. Yang et al found that PD-1 ICIs plus gemcitabine with cisplatin (GP) had significantly longer progression-free survival than in the GP group (median PFS of 9.7 versus 6.9 months), while Mai

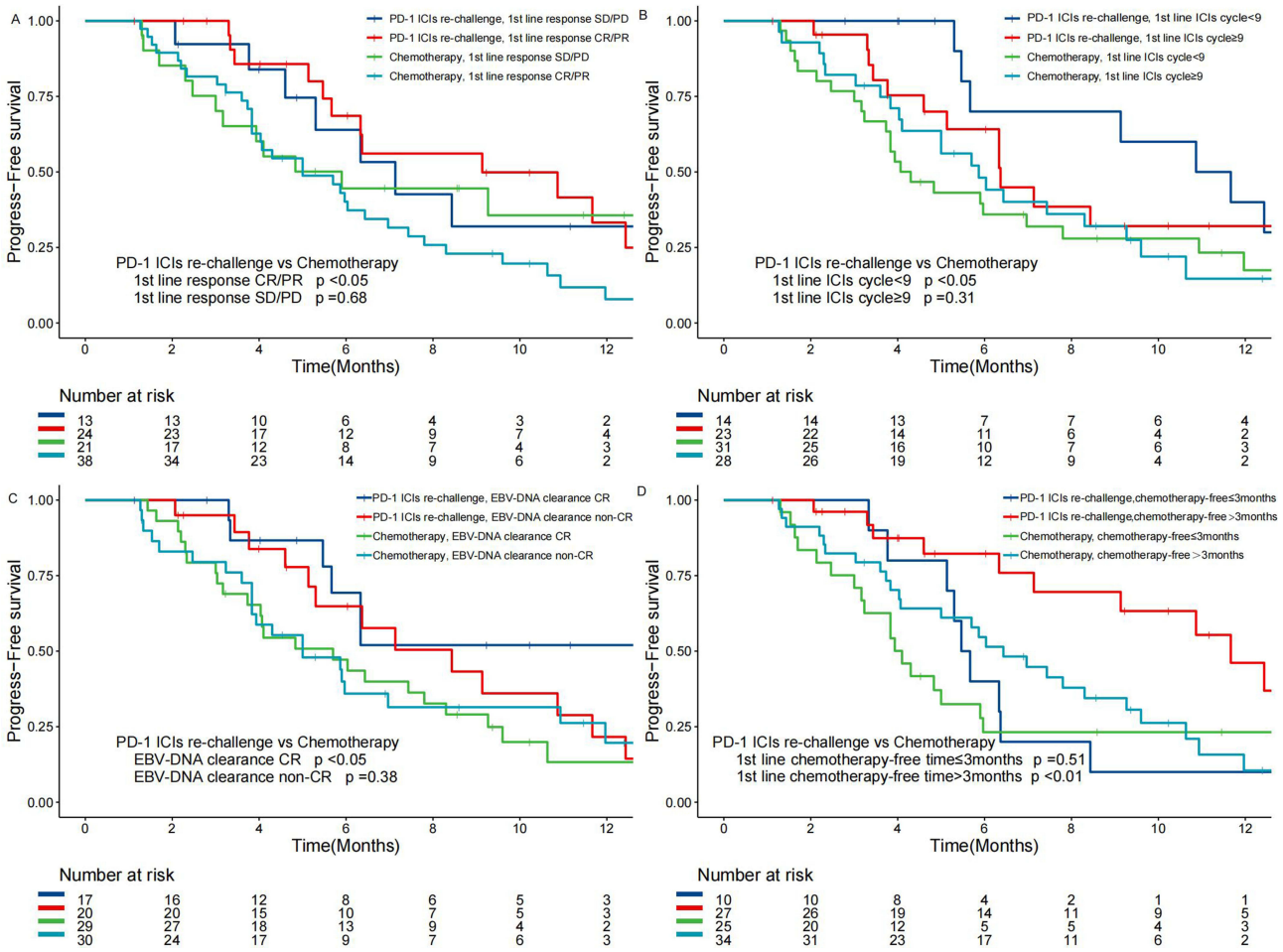

Figure 3 Kaplan–Meier estimates of progression-free survival based on first-line treatment, including (**A**) 1st line response, (**B**) 1st line ICIs cycle, (**C**) 1st line EBV-DNA clearance and (**D**) 1st line time without chemotherapy.

Abbreviations: CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ICIs: immune checkpoint inhibitors.

et al found the same result (median PFS of 11.7 versus 8.0 months), which means more effective tumor control and better prognosis.[3–5] Based on the results of these three pivotal phase III trials, the CSCO guidelines have now endorsed GP in combination with PD-1 ICIs as the preferred first-line treatment regimen for recurrent/metastatic NPC.[6] However, even after receiving first-line treatment with chemotherapy combined with PD-1 ICIs, nearly half of mNPC patients experience disease progression within one year.[3] For these patients facing disease progression, there are currently no established guidelines to determine the optimal anti-tumor approach.

Table 3 Adverse Events During Second-Line Therapy

N (%)	PD-1 ICIs Re-Challenge Group		Chemotherapy Group		*P*
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	
Leukopenia	7 (18.9)	2 (5.4)	13 (22.0)	8 (13.6)	0.308
Neutropenia	8 (21.6)	2 (5.4)	15 (25.4)	10 (17.0)	0.121
Anemia	19 (51.3)	4 (0.8)	30 (50.8)	4 (6.8)	0.707
Thrombocytopenia	1 (2.7)	7 (18.9)	10 (17)	2 (3.4)	0.025
AST/ALT increased	3 (8.1)	0	4 (6.8)	1 (1.7)	1.000
Renal dysfunction	7 (18.9)	0	4 (6.8)	0	NA

Abbreviations: ICIs, immune-checkpoint inhibitors; AST, aspartate transaminase; ALT, alanine aminotransferase.

A recent clinical data analysis encompassing over 5000 NSCLC patients who experienced disease progression after PD-1 ICIs therapy indicated that approximately 30% of patients reinitiated PD-1 ICIs treatment after changing their treatment regimens.[15] A growing body of research suggests that continuing immune treatment for patients progressing after first-line ICIs therapy may confer sustained clinical benefits, as evidenced across various studies in NSCLC, melanoma and liver cancer.[13,16,17] Notably, in liver cancer patients who progressed after ICIs treatment, those who continued ICIs treatment exhibited a prolonged PFS of 5.6 months compared to 1.9 months for those who discontinued ICIs, while those receiving combination therapy achieved even more impressive PFS figures ranging from 10.8 to 15.3 months.[17] This study underscores the potential benefits of continuing PD-1 ICIs treatment after progression and highlights the potential for enhanced efficacy with combination regimens.

In the study, the ORR for the chemotherapy group was 23.7%, with a median PFS of only 5 months (95% CI: 2.8–7.2), which is consistent with prior studies.[18,19] Comparatively, the PD-1 ICIs re-challenge group demonstrated superior efficacy, with an ORR of 37.8% and a DCR of 86.5%, and median PFS and OS of 8.43 months and 28.1 months, respectively. This signifies a distinct survival benefit, with a PFS extension of 3.43 months compared to the chemotherapy group. And there existed a potential trend towards OS benefits. This evident enhancement suggests that PD-1 ICIs re-challenge may offer continued benefits. While the PFS advantage of the PD-1 ICIs rechallenge group over monotherapy is evident, the ORR remains only at 37.8%. Thus, a substantial proportion of unselected patients do not experience the anticipated benefits of immunotherapeutic rechallenge. This underscores the necessity of pinpointing the patient subgroup best suited for PD-1 ICIs rechallenge.

Yet, the potential benefits of PD-1 ICIs treatment following disease progression post-chemotherapy and PD-1 ICIs combination treatment have not been extensively studied. The potential mechanisms underlying the benefits of PD-1 ICIs re-challenge are manifold. PD-1 ICIs blockade can restore T-cell function, even in cases of disease progression, by reactivating existing T-cells within the tumor microenvironment.[20] Additionally, PD-L1 expression may fluctuate, and subsequent PD-1 ICIs therapy may decrease PD-L1 expression, enhancing treatment response.[21] Studies also suggest that PD-1 ICIs can enhance immune cell activity and infiltration within the tumor microenvironment, facilitating immune recognition and attack.[22] Moreover, a significant proportion of patients may experience atypical responses, allowing continued clinical benefits from PD-1 ICIs therapy.[23] Collectively, these various mechanisms may explain the superior efficacy observed with PD-1 ICIs re-challenge.

EBV-DNA serves as a crucial indicator for monitoring the therapeutic effectiveness of NPC. The Keynote-028 study corroborates a linkage between EBV-DNA dynamics and the efficacy of pembrolizumab.[24] Exploratory endeavors conducted by Economopoulou et al within non-endemic NPC patient cohorts divulge an association between optimal responses and reductions in post-immunotherapy EBV-DNA levels (P =0.047).[25] This extensive body of research augments the significance of plasma EBV-DNA as a pivotal determinant in assessing the efficacy of immune intervention in mNPC. This phenomenon is likely attributable to the observation that tumors exhibiting robust immunotherapeutic efficacy predominantly fall under the ambit of "hot" as opposed to "cold" malignancies. The strategic alignment of first-line chemotherapy with PD-1 ICIs engenders further amelioration of the tumor's immune microenvironment, perpetuating a state characterized by immunogenicity.[26] Accordingly, EBV-DNA clearance and evaluation of treatment response during first-line therapy may be indicators for predicting the efficacy of PD-1 ICIs rechallenge therapy.

This study has several limitations. Firstly, the sample is relatively small and the analysis was retrospective in nature, warranting further validation in a prospective cohort with larger sample sizes. Secondly, the second-line chemotherapy regimens were heterogeneous among patients, which might introduce potential bias. Thirdly, inconsistencies in the selection of specific PD-1 immune checkpoint inhibitors for first- and second-line treatments could introduce confounding factors influencing study outcomes. Fourthly, the unavailability of patient-level PD-L1 expression data constrains comprehensive prognostic analyses. Lastly, while there is potential for observed progression-free survival benefits to translate into overall survival advantages, extended follow-up assessments are crucial to establish the conversion of PFS benefits from PD-1 ICIs rechallenge into tangible OS gains.

Conclusion

In conclusion, mNPC patients who progressed from prior anti-PD1 therapy could benefit from the anti-PD1 rechallenge in combination with chemotherapy. However, further validation through prospective large-sample clinical trials is urgently required.

Data Sharing Statement

All data generated or analyzed during this study are available via the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Institutional Review Board of Sun Yat-Sen University Cancer Center, with Institution Review Board (IRB) Number of B2023-245-01. The study was performed in accordance with the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of this study and the anonymous processing of patient data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

References

1. Chen Y-P, Chan ATC, Le Q-T, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. *Lancet*. 2019;394(10192):64–80. doi:10.1016/s0140-6736(19)30956-0
2. Lee AWM, Ng WT, Chan JYW, et al. Management of locally recurrent nasopharyngeal carcinoma. *Cancer Treat Rev*. 2019;79:101890. doi:10.1016/j.ctrv.2019.101890
3. Yang Y, Qu S, Li J, et al. Camrelizumab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN-1st): a multicentre, randomised, double-blind, Phase 3 trial. *Lancet Oncol*. 2021. doi:10.1016/s1470-2045(21)00302-8
4. Zhang L, Yang Y, Pan J-J, et al. RATIONALE-309: updated progression-free survival (PFS), PFS after next line of treatment, and overall survival from a phase 3 double-blind trial of tislelizumab versus placebo, plus chemotherapy, as first-line treatment for recurrent/metastatic nasopharyngeal cancer. *J Clin Oncol*. 2022;40(36_suppl):384950. doi:10.1200/JCO.2022.40.36_suppl.384950
5. Mai HQ, Chen QY, Chen D, et al. Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicenter randomized phase 3 trial. *Nat Med*. 2021;27(9):1536–1543. doi:10.1038/s41591-021-01444-0
6. Tang LL, Chen YP, Chen CB, et al. The Chinese Society of Clinical Oncology (CSCO) clinical guidelines for the diagnosis and treatment of nasopharyngeal carcinoma. *Cancer Commun*. 2021;41(11):1195–1227. doi:10.1002/cac2.12218
7. Zhang L, Zhang Y, Huang PY, Xu F, Peng PJ, Guan ZZ. Phase II clinical study of gemcitabine in the treatment of patients with advanced nasopharyngeal carcinoma after the failure of platinum-based chemotherapy. *Cancer Chemother Pharmacol*. 2008;61(1):33–38. doi:10.1007/s00280-007-0441-8
8. Fang W, Yang Y, Ma Y, et al. Camrelizumab (SHR-1210) alone or in combination with gemcitabine plus cisplatin for nasopharyngeal carcinoma: results from two single-arm, Phase 1 trials. *Lancet Oncol*. 2018;19(10):1338–1350. doi:10.1016/s1470-2045(18)30495-9
9. Wang FH, Wei XL, Feng J, et al. Efficacy, safety, and correlative biomarkers of toripalimab in previously treated recurrent or metastatic nasopharyngeal carcinoma: a phase II Clinical Trial (POLARIS-02). *J Clin Oncol*. 2021;39(7):704–712. doi:10.1200/jco.20.02712
10. Hsu C, Lee SH, Ejadi S, et al. Safety and antitumor activity of pembrolizumab in patients with programmed death-ligand 1-positive nasopharyngeal carcinoma: results of the KEYNOTE-028 Study. *J Clin Oncol*. 2017;35(36):4050–4056. doi:10.1200/jco.2017.73.3675

11. Ma BBY, Lim WT, Goh BC, et al. Antitumor activity of nivolumab in recurrent and metastatic nasopharyngeal carcinoma: an international, multicenter study of the mayo clinic phase 2 consortium (NCI-9742). *J Clin Oncol*. 2018;36(14):1412–1418. doi:10.1200/jco.2017.77.0388
12. Herbst RS, Garon EB, Kim DW, et al. Long-term outcomes and retreatment among patients with previously treated, programmed death-ligand 1–positive, advanced non–small-cell lung cancer in the KEYNOTE-010 Study. *J Clin Oncol*. 2020;38(14):1580–1590. doi:10.1200/jco.19.02446
13. Gandara DR, von Pawel J, Mazieres J, et al. Atezolizumab treatment beyond progression in advanced NSCLC: results from the randomized, phase III OAK study. *J Thorac Oncol*. 2018;13(12):1906–1918. doi:10.1016/j.jtho.2018.08.2027
14. Beaver JA, Hazarika M, Mulkey F, et al. Patients with melanoma treated with an anti-PD-1 antibody beyond RECIST progression: a US Food and Drug Administration pooled analysis. *Lancet Oncol*. 2018;19(2):229–239. doi:10.1016/s1470-2045(17)30846-x
15. Giaj Levra M, Cotté FE, Corre R, et al. Immunotherapy rechallenge after nivolumab treatment in advanced non-small cell lung cancer in the real-world setting: a national data base analysis. *Lung Cancer*. 2020;140:99–106. doi:10.1016/j.lungcan.2019.12.017
16. Reinhorn D, Jacobi O, Icht O, et al. Treatment beyond progression with immune checkpoint inhibitors in non-small-cell lung cancer. *Immunotherapy*. 2020;12(4):235–243. doi:10.2217/imt-2019-0131
17. Talbot T, D'Alessio A, Pinter M, et al. Progression patterns and therapeutic sequencing following immune checkpoint inhibition for hepatocellular carcinoma: an international observational study. *Liver Int*. 2023;43(3):695–707. doi:10.1111/liv.15502
18. Chua D, Wei W, Sham J, Au G. Capecitabine monotherapy for recurrent and metastatic nasopharyngeal cancer. *Japan J Clin Oncol*. 2008;38(4):244–249. doi:10.1093/jjco/hyn022
19. Peng P, Cheng H, Ou X, et al. Safety and efficacy of S-1 chemotherapy in recurrent and metastatic nasopharyngeal carcinoma patients after failure of platinum-based chemotherapy: multi-institutional retrospective analysis. *Drug Des Devel Ther*. 2014;8:1083–1087. doi:10.2147/dddt.S67592
20. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature*. 2014;515(7528):568–571. doi:10.1038/nature13954
21. Havel JJ, Chowell D, Chan TA. The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. *Nat Rev Cancer*. 2019;19(3):133–150. doi:10.1038/s41568-019-0116-x
22. Ma W, Gilligan BM, Yuan J, Li T. Current status and perspectives in translational biomarker research for PD-1/PD-L1 immune checkpoint blockade therapy. *J Hematol Oncol*. 2016;9(1):47. doi:10.1186/s13045-016-0277-y
23. Jia W, Gao Q, Han A, Zhu H, Yu J. The potential mechanism, recognition and clinical significance of tumor pseudoprogression after immunotherapy. *Cancer Biol Med*. 2019;16(4):655–670. doi:10.20892/j.issn.2095-3941.2019.0144
24. Kao HF, Hsu C, Huang HC, Cheng J. Correlation between plasma EBV DNA and clinical response to pembrolizu mab in patients with advanced or metastatic nasopharyngeal carcinoma. *Ann Oncol*. 2015;26:5. doi:10.1093/annonc/mdv514.07
25. Economopoulou P, Pantazopoulos A, Spathis A, et al. Immunotherapy in nonendemic nasopharyngeal carcinoma: real-world data from two nonendemic regions. *Cells*. 2021;11(1). doi:10.3390/cells11010032
26. Liu YT, Sun ZJ. Turning cold tumors into hot tumors by improving T-cell infiltration. *Theranostics*. 2021;11(11):5365–5386. doi:10.7150/thno.58390