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ORIGINAL ARTICLE

The efficacy of immunotherapy combined with capecitabine versus immunotherapy alone as maintenance therapy in patients with *de novo* metastatic nasopharyngeal carcinoma: a retrospective propensity score matching study

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Background: Chemoimmunotherapy followed by immunotherapy maintenance is recommended as the standard treatment for metastatic nasopharyngeal carcinoma (NPC) patients. While capecitabine maintenance therapy has been shown to improve outcomes in these patients, data on the efficacy of combining capecitabine with immunotherapy maintenance remain limited. This study compared the efficacy of immunotherapy combined with capecitabine maintenance therapy (Immu/Cape) versus immunotherapy maintenance alone (Immu) in patients with *de novo* metastatic NPC (dmNPC) who received first-line chemoimmunotherapy.

Patients and methods: Patients with dmNPC receiving platinum-based chemoimmunotherapy were included in this study. Propensity score matching (PSM) analysis was employed to balance the baseline characteristics between the two treatment groups.

Results: A total of 287 dmNPC patients were included in the study (100 in the Immu/Cape group and 187 in the Immu group). Patients in the Immu/Cape group demonstrated significantly prolonged progression-free survival (PFS; median PFS 41.5 versus 23.1 months, $P < 0.001$). After PSM, 83 patients remained in each group. Multivariable analysis indicated that the maintenance regimen was an independent prognostic factor for prolonged PFS (Immu/Cape versus Immu: hazard ratio 0.44, 95% confidence interval 0.26-0.73, $P = 0.001$). Subgroup analysis revealed that patients with polymetastatic disease (PMD) receiving Immu/Cape had significantly longer PFS compared with those receiving immunotherapy alone (3-year PFS rate: 49.2% versus 26.7%, $P = 0.0087$). In contrast, no significant benefit was observed in patients with oligometastatic disease (3-year PFS rate: 57.9% versus 54.2%, $P = 0.27$). Furthermore, in patients with detectable Epstein–Barr virus (EBV) $DNA_{2\text{-}6\ cycles}$, the Immu/Cape group exhibited significantly higher 3-year PFS rates compared with the Immu group (34.0% versus 19.8%, $P = 0.032$), whereas no PFS advantage was noted in patients with undetectable EBV $DNA_{2\text{-}6\ cycles}$ (65.1% versus 52.6%, $P = 0.13$).

Conclusions: Immu/Cape maintenance therapy appears to be superior to immunotherapy alone in prolonging PFS in patients with dmNPC, particularly in those with PMD and detectable EBV DNA after two to six cycles of treatment.

Key words: dmNPC patients, maintenance therapy, capecitabine, immunotherapy, prognosis

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant epithelial tumor that arises from the nasopharyngeal mucosa and exhibits a markedly heterogeneous geographical distribution, with the highest incidence observed in southern China.[1] Globally, NPC accounts for an estimated 133 354 new cases and 80 008 deaths annually, with 5%-15% of patients presenting with *de novo* metastasis at initial diagnosis.[2] While platinum-based chemotherapy remains the standard first-line systemic therapy for metastatic NPC,[3,4]

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recent phase III clinical trials have demonstrated that integrating immunotherapy with chemotherapy can significantly improve progression-free survival (PFS). However, even with these advances, the median PFS in these trials remains limited to 9.6-21.4 months. In these studies, patients received immunotherapy as maintenance treatment until radiographic progression or the development of unacceptable toxicity following four to six cycles of chemoimmunotherapy.[5-7]

Emerging retrospective evidence suggests that oral fluorouracil analogs, when administered as maintenance therapy following first-line chemotherapy, may confer survival benefits in patients with recurrent or metastatic NPC.[8-12] Notably, a landmark phase III trial by Liu et al. demonstrated that capecitabine maintenance therapy significantly improves PFS with acceptable toxicity in treatment-naïve patients with metastatic NPC.[13] However, the potential synergistic effect of combining capecitabine with immune checkpoint inhibitors in the maintenance setting remains unexplored. This retrospective study aims to compare PFS outcomes between maintenance therapy with a combination of immunotherapy and capecitabine versus immunotherapy alone in patients with *de novo* metastatic NPC (dmNPC).

PATIENTS AND METHODS

Patient selection and data collection

Patients with dmNPC treated between October 2018 and October 2022 were retrospectively analyzed. The inclusion criteria were as follows: (i) histologically confirmed NPC; (ii) radiologically or pathologically documented metastatic disease at diagnosis; (iii) completion of at least two cycles of first-line platinum-based chemoimmunotherapy; (iv) receipt of at least three cycles of maintenance therapy with either capecitabine plus immunotherapy (Immu/Cape) or immunotherapy alone (Immu); (v) comprehensive clinical documentation; and (vi) absence of prior/concurrent malignancies. The study design is presented in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105295, and a total of 287 dmNPC patients were included in the analysis.

Demographic data, TNM (tumor—node—metastasis) staging, and details of metastatic sites (including the liver, lungs, bones, and other distant areas such as the adrenal glands, spleen, and lymph nodes) were recorded based on imaging findings. Epstein—Barr virus (EBV) DNA levels were quantified using real-time PCR both at baseline and after completion of first-line chemoimmunotherapy. Treatment effectiveness was documented following chemoimmunotherapy, locoregional radiotherapy (LRRT), and local therapy to metastatic lesions (LT). Ethical approval for this retrospective study was obtained from the institutional review board of Sun Yat-sen University Cancer Center (IRB-approved number SL-B2024-371), and written informed consent was waived.

Treatment

A multidisciplinary team developed optimal treatment plans that incorporated both systemic therapies (e.g. immunochemotherapy) and local therapies (including LRRT and LT). The standard chemotherapy regimens employed included: gemcitabine and platinum; docetaxel/paclitaxel and platinum; platinum and 5-fluorouracil; docetaxel/paclitaxel, platinum, and 5-fluorouracil; and docetaxel/paclitaxel, platinum, and capecitabine. These regimens were generally administered over two to six cycles. Detailed information on the chemotherapy regimens and LT is provided in Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.esmoop.2025.105295. Commonly used immunotherapy agents included camrelizumab, toripalimab, tislelizumab, pembrolizumab, penpulimab, sintilimab, and nivolumab. Patients in the capecitabine arm received oral capecitabine (1000 mg/m^2) twice daily on days 1-14 of a 3-week cycle. For LRRT, a cumulative dose of 66-70 Gy was typically delivered in 30-35 fractions to the nasopharynx and lymph nodes. Treatment for metastatic lesions included modalities such as ablation, surgery, and radiotherapy. The detailed treatment protocols are available in the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2025.105295.

Follow-up and statistical analysis

Patients were monitored regularly, with assessments every two to three cycles during immunochemotherapy and every 3 months following the completion of all treatments. Evaluations were carried out by an experienced radiologist and a skilled radiation oncologist, using RECIST version 1.1. The primary endpoint of the study was PFS, defined as the time from the start of maintenance therapy to the first documented progression or death due to any cause. The second endpoint was overall survival (OS), defined as the time from the start of maintenance therapy to death. Oligometastatic disease (OMD) was defined according to recent consensus criteria as the presence of five or fewer metastatic lesions across two or fewer metastatic organs.[14-16]

Univariate and multivariate Cox regression models were used to assess the impact of various clinical and treatment-related factors on PFS. Propensity score matching (PSM) at a 1 : 1 ratio was implemented to balance characteristics such as demographic data, EBV DNA levels, and treatment-related information. Further analyses examined whether the therapeutic effect varied among different subgroups.

Data analysis was conducted using R (http://www.r-project.org/; R Foundation for Statistical Computing, Vienna, Austria), with continuous variables transformed into categorical variables. Categorical variables were compared using the chi-square test or Fisher's exact test. Receiver operating characteristic curve analysis identified a pretreatment EBV DNA cut-off value (area under the curve 0.65; optimal threshold 20 500 copies/ml, see Supplementary Figure S2, available at https://doi.org/10.

1016/j.esmoop.2025.105295). To optimize the cut-off value for potential clinical application, we rounded this value to the nearest integer, i.e. 20 000 copies/ml. Survival rates were estimated using the Kaplan–Meier method and compared using log-rank tests. Statistical significance was defined as $P \leq 0.05$.

RESULTS

The median age was 45 years (range 13-72 years), with a male predominance (75.3%). Metastatic involvement was most frequently observed in the bone (71.2%), followed by the liver (34.7%), lung (23.6%), and other sites (3.1%). Multiple metastatic organs (more than two) were present in 30 patients (10.4%), and more than five metastatic lesions were observed in 60.8% (175/287) of the patients. LT was administered to 66 patients (23.2%), with 6 patients receiving LT following progression of metastatic lesions. LRRT was provided to 227 (78.8%) patients. Detailed information is presented in Table 1. Within the entire cohort, the Immu/Cape group had a higher proportion of patients aged ≤45 years, a higher rate of stable disease in the nasopharyngeal and neck regions, and a higher incidence of LRRT compared with the Immu group. Following PSM, baseline characteristics were balanced between the treatment groups.

With a median follow-up of 32.0 months (interquartile range 26.1-39.8 months), multivariate Cox analysis identified the following as independent predictors for PFS: detectable EBV $DNA_{2\text{-}6\ cycles}$ [hazard ratio (HR) 3.11, 95% confidence interval (CI) 1.85-5.23, $P < 0.001$], more than five lesions (HR 2.79, 95% CI 1.59-4.88, $P < 0.001$), and Immu/Cape maintenance (HR 0.44, 95% CI 0.26-0.73, $P = 0.001$). The results of both the univariate and multivariate Cox analyses in the whole cohort and the matched cohort are summarized in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105295.

The median PFS was significantly longer in the Immu/Cape group compared with the Immu group: 41.5 months (95% CI not reached) versus 23.1 months (95% CI 19.8-26.4 months, $P = 0.00061$; Figure 1A) in the overall cohort. The 1-, 2-, and 3-year PFS rates for the two groups were 86.5% versus 71.2%, 69.3% versus 47.8%, and 54.0% versus 36.4%, respectively. Significantly prolonged OS was also observed in the Immu/Cape group compared with the Immu group (median OS not reached versus not reached, $P = 0.013$; Figure 1B). The 1-, 2-, and 3-year OS rates for the two groups were 98.0% versus 91.9%, 90.7% versus 80.8%, and 87.8% versus 73.2%, respectively. After PSM, significantly prolonged PFS was also observed in the Immu/Cape group [median PFS 41.5 months (95% CI 17.1-65.9 months) versus 23.6 months (95% CI 20.3-26.9 months), $P = 0.014$; Figure 1C]. The 1-, 2-, and 3-year PFS rates in the matched cohorts were 86.3% versus 73.0%, 70.1% versus 46.3%, and 52.9% versus 39.8%, respectively. There was no significant difference in OS between the Immu/Cape group and the Immu group in the matched cohort (median OS not reached versus not reached, $P = 0.22$; Figure 1D). The 1-, 2-, and 3-year OS rates for the two groups were 97.6% versus 93.9%, 90.2% versus 83.8%, and 86.8% versus 77.5%, respectively. In addition, when comparing PFS and OS between different chemotherapy regimens and immunotherapy drugs in both the entire and matched cohorts, no significant differences were observed (Supplementary Figure S3A-H, available at https://doi.org/10.1016/j.esmoop.2025.105295).

To identify which patients may benefit from Immu/Cape maintenance therapy, its efficacy was compared between patients with OMD and polymetastatic disease (PMD). Immu/Cape did not significantly improve PFS or OS in patients with OMD (Figure 2A and B). In contrast, among patients with PMD, the Immu/Cape group showed a significant advantage in the median PFS compared with the Immu group [26.4 months (95% CI 7.3-45.6 months) versus 16.4 months (95% CI 12.9-19.9 months), $P = 0.0087$; Figure 2C], with corresponding 3-year PFS rates of 49.2% versus 26.7%. However, no significant difference was observed in OS between the two groups (Figure 2D). Comprehensive survival outcomes across all subgroups, including 3-year rates and median survival times, are detailed in Supplementary Tables S4 (PFS) and S5 (OS), available at https://doi.org/10.1016/j.esmoop.2025.105295, with extended Kaplan–Meier curves provided in Supplementary Figures S4-S6, available at https://doi.org/10.1016/j.esmoop.2025.105295.

We then compared the efficacy of different maintenance therapies in patients stratified by EBV DNA levels. Among patients with pretreatment EBV DNA <20 000 copies/ml, the Immu/Cape group exhibited a significantly longer median PFS compared with the Immu group [41.5 months (95% CI 18.4-64.6 months) versus 25.4 months (95% CI 19.6-31.2 months), $P = 0.077$; Figure 3A]. The 3-year PFS rates were 54.7% for Immu/Cape versus 43.7% for Immu. In patients with pretreatment EBV DNA >20 000 copies/ml, the Immu/Cape group achieved a significantly longer median PFS compared with the Immu group [not reached versus 11.9 months (95% CI 4.0-19.8 months), $P = 0.014$; Figure 3C], with 3-year PFS rates of 55.0% versus 24.2%. However, regardless of whether the pretreatment EBV DNA levels exceeded 20 000 copies/ml, no significant improvement in OS was observed in the Immu/Cape group compared with the Immu group (Figure 3B and D).

For patients with undetectable EBV $DNA_{2\text{-}6\ cycles}$, no significant improvements in PFS were observed with Immu/Cape compared with Immu (median PFS not reached in both groups, $P = 0.13$; Figure 3E), with 3-year PFS rates of 65.1% versus 52.6%. However, among patients with detectable EBV $DNA_{2\text{-}6\ cycles}$, those receiving Immu/Cape maintenance therapy achieved a significantly longer median PFS than those receiving Immu alone [26.4 months (95% CI 24.1-28.7 months) versus 14.7 months (95% CI 9.5-19.9 months), $P = 0.032$; Figure 3G], with corresponding 3-year PFS rates of 34.0% versus 19.8%. With respect to OS, no significant benefits were observed with Immu/Cape maintenance therapy compared with Immu alone, irrespective of post-treatment EBV DNA detectability (Figure 3F and H).

We further compared the efficacy of different maintenance regimens in patients who did or did not receive local

Table 1. Baseline characteristics of patients in the whole and matched cohorts

Variable	Before PSM analysis			After PSM analysis		*P* value
	Immu	Immu/Cape	*P* value	Immu	Immu/Cape	
Sex			0.688			1
Male	140 (74.87)	77 (77.00)		63 (75.90)	63 (75.90)	
Female	47 (25.13)	23 (23.00)		20 (24.10)	20 (24.10)	
Age (years)			0.005			1
≤45	85 (45.45)	63 (63.00)		49 (59.04)	49 (59.04)	
>45	102 (54.55)	37 (37.00)		34 (40.96)	34 (40.96)	
T stage			0.854			0.599
1/2	20 (10.70)	10 (10.00)		7 (8.43)	9 (10.84)	
3/4	167 (89.30)	90 (90.00)		76 (91.57)	74 (89.16)	
N stage			0.143			0.828
0/1	35 (18.72)	12 (12.00)		13 (15.66)	12 (14.46)	
2/3	152 (81.28)	88 (88.00)		70 (84.34)	71 (85.54)	
Pre-EBV DNA			0.119			0.791
<20 000 copies/ml	114 (60.96)	73 (73.00)		61 (73.49)	59 (71.08)	
≥20 000 copies/ml	66 (35.29)	25 (25.00)		20 (24.10)	23 (27.71)	
NA	7 (3.74)	2 (2.00)		2 (2.41)	1 (1.20)	
EBV $DNA_{2\text{-}6\ cycles}$			0.572			0.718
Undetectable	113 (60.43)	63 (63.00)		53 (63.86)	58 (69.88)	
Detectable	56 (29.95)	31 (31.00)		26 (31.33)	22 (26.51)	
NA	18 (9.63)	6 (6.00)		4 (4.82)	3 (3.61)	
Liver metastasis			0.46			0.617
No	119 (63.64)	68 (68.00)		58 (69.88)	55 (66.27)	
Yes	68 (36.36)	32 (32.00)		25 (30.12)	28 (33.73)	
Bone metastasis			0.127			0.46
No	59 (31.55)	23 (23.00)		17 (20.48)	21 (25.30)	
Yes	128 (68.45)	77 (77.00)		66 (79.52)	62 (74.70)	
Lung metastasis			0.171			1
No	138 (73.80)	81 (81.00)		66 (79.52)	66 (79.52)	
Yes	49 (26.20)	19 (19.00)		17 (20.48)	17 (20.48)	
Other metastasis			0.651			1
No	180 (96.26)	98 (98.00)		82 (98.80)	81 (97.59)	
Yes	7 (3.74)	2 (2.00)		1 (1.20)	2 (2.41)	
Number of metastatic sites			0.321			0.755
≤2	165 (88.24)	92 (92.00)		78 (93.98)	77 (92.77)	
>2	22 (11.76)	8 (8.00)		5 (6.02)	6 (7.23)	
Number of metastatic lesions			0.804			0.533
≤5	72 (38.50)	40 (40.00)		40 (48.19)	36 (43.37)	
>5	115 (61.50)	60 (60.00)		43 (51.81)	47 (56.63)	
NP response			0.05			1
CR/PR	178 (95.19)	89 (89.00)		77 (92.77)	77 (92.77)	
SD	9 (4.81)	11 (11.00)		6 (7.23)	6 (7.23)	
LN response			0.092			1
CR/PR	178 (95.19)	90 (90.00)		78 (93.98)	78 (93.98)	
SD	9 (4.81)	10 (10.00)		5 (6.02)	5 (6.02)	
ML response			0.009			0.729
CR/PR	151 (80.75)	67 (67.00)		59 (71.08)	61 (73.49)	
SD	36 (19.25)	33 (33.00)		24 (28.92)	22 (26.51)	
LRRT			<0.001			0.417
No	54 (28.88)	6 (6.00)		9 (10.84)	6 (7.23)	
Yes	133 (71.12)	94 (94.00)		74 (89.16)	77 (92.77)	
LT			0.398			0.601
No	148 (79.14)	73 (73.00)		59 (71.08)	63 (75.90)	
Yes	36 (19.25)	24 (24.00)		23 (27.71)	18 (21.69)	
Yes after progression	3 (1.60)	3 (3.00)		1 (1.20)	2 (2.41)	
Cycles of chemotherapy			0.091			0.06
2-3	8 (4.28)	1 (1.00)		3 (3.61)	0 (0.00)	
4-6	177 (94.65)	95 (95.00)		80 (96.39)	80 (96.39)	
>6	2 (1.07)	4 (4.00)		0 (0.00)	3 (3.61)	

Cape, capecitabine; CR, complete response; EBV $DNA_{2\text{-}6\ cycles}$, Epstein—Barr virus DNA levels after two to six cycles of chemotherapy; Immu, immunotherapy; LN, lymph node; LRRT, locoregional radiotherapy; LT, local therapy to metastatic lesions; ML, metastatic lesion; NA, not available; NP, nasopharynx; PD, disease progression; PR, partial response; pre-EBV DNA, pretreatment Epstein—Barr virus DNA; PSM, propensity score matching; SD, stable disease.

therapies. After PSM, 151 patients received LRRT and 41 patients received LT. Among patients receiving LRRT, the Immu/Cape group exhibited a significantly longer median PFS compared with the Immu group [41.5 months (95% CI 18.3-64.7 months) versus 23.6 months (95% CI 19.9-27.4 months), $P = 0.024$; Figure 4A]. The 3-year PFS rates were 53.1% for Immu/Cape versus 39.9% for Immu. However, no significant OS benefit was observed (Figure 4B). Among patients who did not receive LRRT, only six patients received Immu/Cape maintenance and nine patients

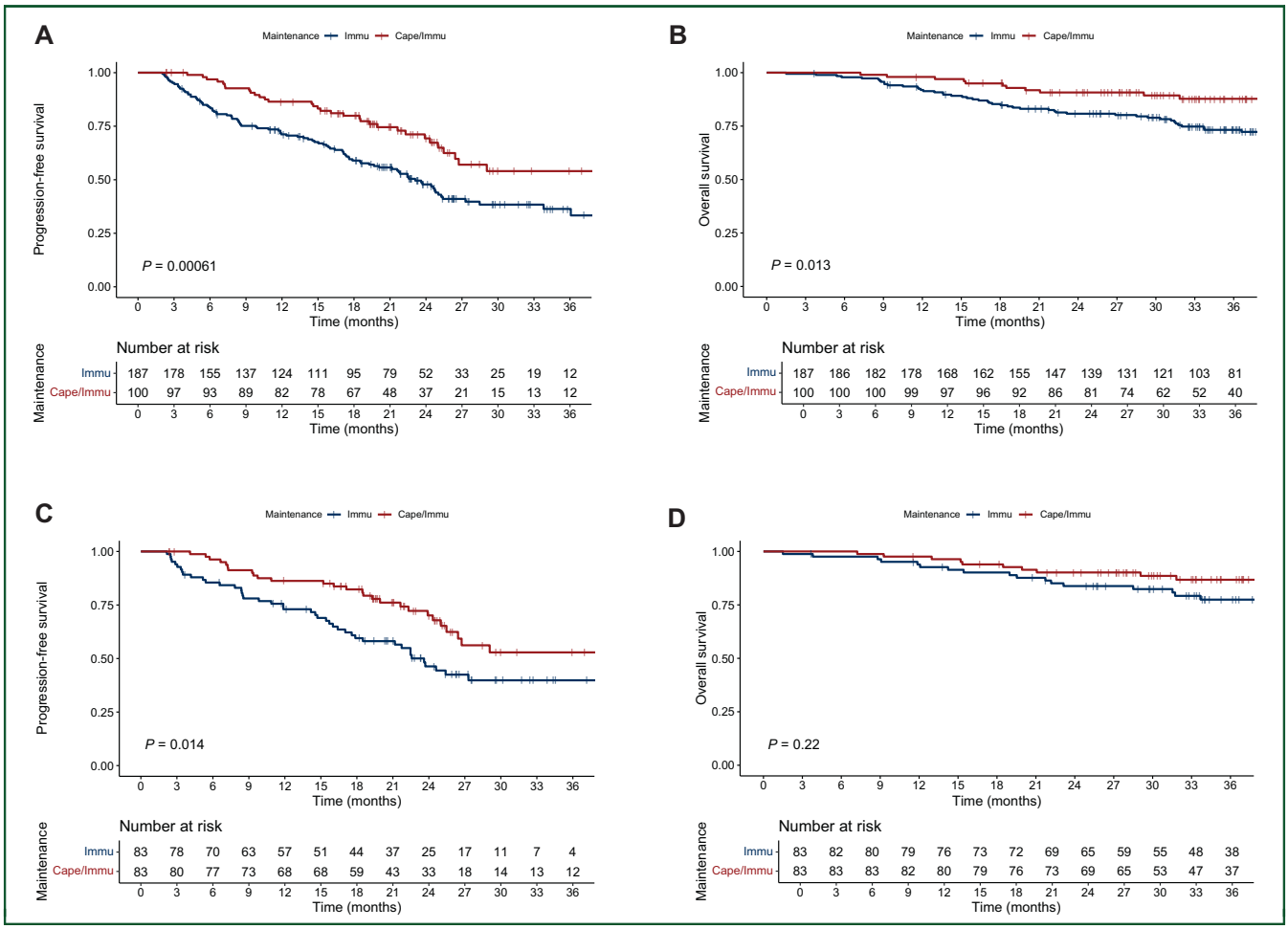

Figure 1. Overall survival (OS) and progression-free survival (PFS) curves for *de novo* metastatic nasopharyngeal carcinoma (dmNPC) patients receiving different maintenance regimens in the whole and matched cohorts. (A) PFS in the whole cohort; (B) OS in the whole cohort; (C) PFS in the matched cohort; (D) OS in the matched cohort.
Cape, capecitabine; Immu, immunotherapy.

received Immu maintenance therapy (Figure 4C and D). In patients receiving LT, no significant differences in PFS (median PFS 26.7 months versus not reached, $P = 0.92$; Figure 4E) or OS (Figure 4F) were observed between Immu/Cape and Immu maintenance therapies. However, in patients who did not receive LT, the Immu/Cape group was associated with a significantly longer median PFS compared with the Immu group (median PFS not reached versus 21.7 months, $P = 0.0017$; Figure 4G), with 3-year PFS rates of 61.0% versus 36.3%. Similarly, Immu/Cape showed a nearly significant improvement in OS (median OS not reached versus not reached, $P = 0.053$; Figure 4H).

DISCUSSION

Capecitabine is an oral fluoropyrimidine that has demonstrated single-agent activity in metastatic NPC.[17-21] Its efficacy as a maintenance therapy has also been reported in other metastatic malignancies, including colorectal cancer[22] and breast cancer.[23,24] The observed PFS advantage with Immu/Cape maintenance may be attributed to capecitabine's dual mechanisms. Firstly, several studies have indicated that when administered as metronomic chemotherapy, oral fluoropyrimidines can exert antivascular effects by targeting the endothelial cells of tumor blood vessels.[25,26] Secondly, capecitabine maintenance therapy appears to delay the growth of distant micrometastatic disease by reducing tumor burden and eliminating micrometastatic lesions.[27] Thirdly, low-dose maintenance chemotherapy may induce angiogenic dormancy by inhibiting tumor angiogenesis and enhancing the immune response against tumor-associated antigens.[28,29] Supporting this, He et al. reported that locally advanced NPC patients receiving capecitabine metronomic therapy exhibited higher levels of CD8+ cells, CD28+CD8+ cells, and activated CD8+ cells compared with those who did not receive such treatment.[30] This immunomodulatory effect induced by metronomic capecitabine may, at least in part, explain the prolonged PFS observed in patients undergoing Immu/Cape maintenance therapy in our study.

NPC is highly sensitive to platinum-based chemoimmunotherapy, with clinical trials reporting response rates ranging from 55% to 87%.[5-7] Our results indicate that immunotherapy combined with capecitabine significantly prolongs PFS in dmNPC patients, particularly in those with PMD, detectable EBV $DNA_{2\text{-}6}$ cycles, and those who did not

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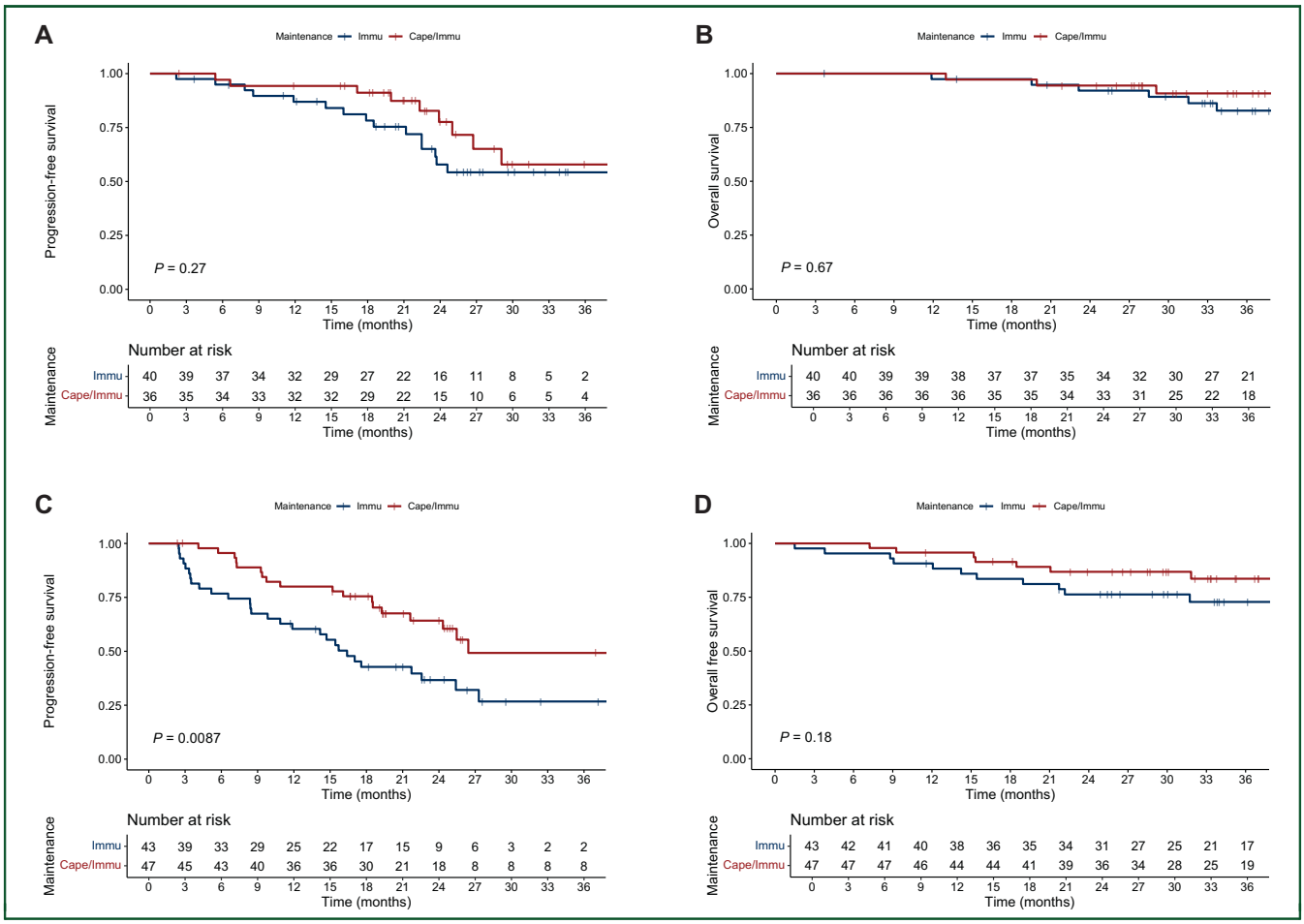

Figure 2. Survival curves for *de novo* metastatic nasopharyngeal carcinoma (dmNPC) patients receiving different maintenance regimens across subgroups in the matched cohort. (A) Progression-free survival (PFS) in patients with oligometastatic disease; (B) overall survival (OS) in patients with oligometastatic disease; (C) PFS in patients with polymetastatic disease; (D) OS in patients with polymetastatic disease.
Cape, capecitabine; Immu, immunotherapy.

receive LT. Currently, programmed cell death protein 1 (PD-1) inhibitors are recommended as maintenance therapy in clinical trials; however, capecitabine is also recommended by treatment guidelines for use after progression following first-line therapy.

In this study, 135 patients experienced disease progression, and subsequent treatment information was available for 93 patients (see Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2025.105295). Only 10 patients in the Immu group received subsequent treatments that included capecitabine after progression, and only one of these patients received single-agent capecitabine treatment (with a PFS of 2.3 months since the addition of capecitabine; Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2025.105295). Due to the small sample size, we were unable to compare PFS or OS between patients who received capecitabine as maintenance therapy and those who received it upon progression. Two ongoing clinical trials focusing on the subsequent treatment of recurrent/metastatic NPC patients have included capecitabine monotherapy (NCT05717764 and NCT05126719), but the survival data have not yet been reported.

Our results show that patients in the Immu/Cape group had significantly higher OS rates across all populations; however, this difference did not reach statistical significance in the matched population. The lack of OS difference after PSM likely reflects the impact of effective salvage therapies (e.g. BL-B01D1[31] and MRG003[32]) in progressive disease. Thus, whether PFS is an appropriate surrogate endpoint for OS in this setting remains to be further investigated.

Undetectable levels of circulating tumor DNA following treatment have been associated with better PFS across various cancers.[33,34] Subgroup analysis further indicated that only patients with detectable EBV $DNA_{2\text{-}6\ cycles}$ benefited from Immu/Cape maintenance therapy, consistent with the findings from Lu et al.'s study.[35] While our findings align with Sun et al.'s report on capecitabine efficacy in patients with low pretreatment EBV DNA levels,[10] the universal PFS improvement across pretreatment EBV DNA strata suggests that immunotherapy may potentiate capecitabine's activity irrespective of baseline viral load (Supplementary Figure S5A and C, available at https://doi.org/10.1016/j.esmoop.2025.105295; Figure 3A and C). Moreover, subgroup analysis indicated that patients with OMD did not benefit from Immu/Cape maintenance

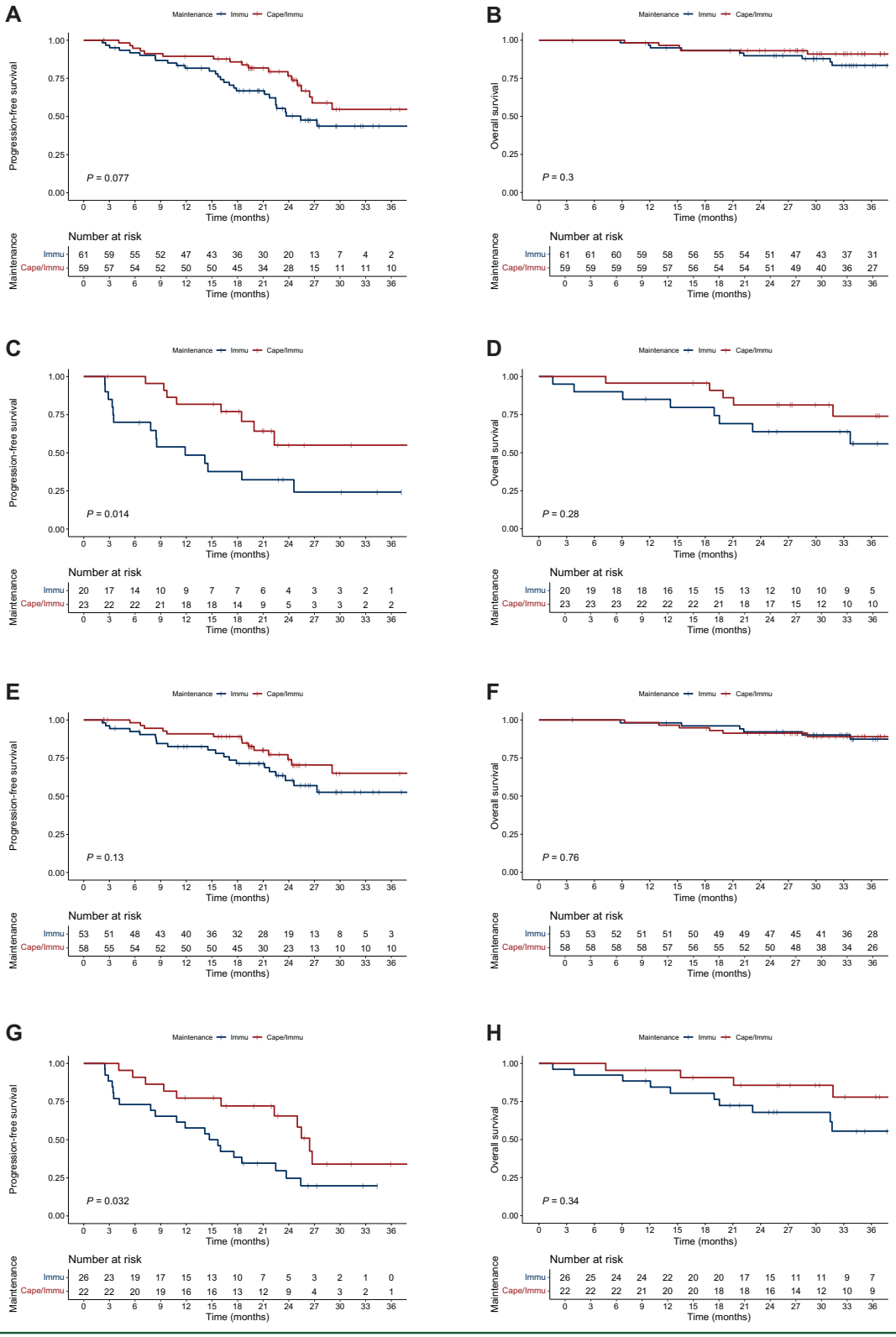

Figure 3. Survival curves for *de novo* metastatic nasopharyngeal carcinoma (dmNPC) patients receiving different maintenance regimens across subgroups in the matched cohort. (A) Progression-free survival (PFS) in patients with baseline Epstein–Barr virus (EBV) DNA <20 000 copies/ml; (B) overall survival (OS) in patients with baseline EBV DNA <20 000 copies/ml; (C) PFS in patients with baseline EBV DNA >20 000 copies/ml; (D) OS in patients with baseline EBV DNA >20 000 copies/ml; (E) PFS in patients with undetectable EBV DNA after two to six cycles of treatment; (F) OS in patients with undetectable EBV DNA after two to six cycles of treatment; (G) PFS in patients with detectable EBV DNA after two to six cycles of treatment; (H) OS in patients with detectable EBV DNA after two to six cycles of treatment.
Cape, capecitabine; Immu, immunotherapy.

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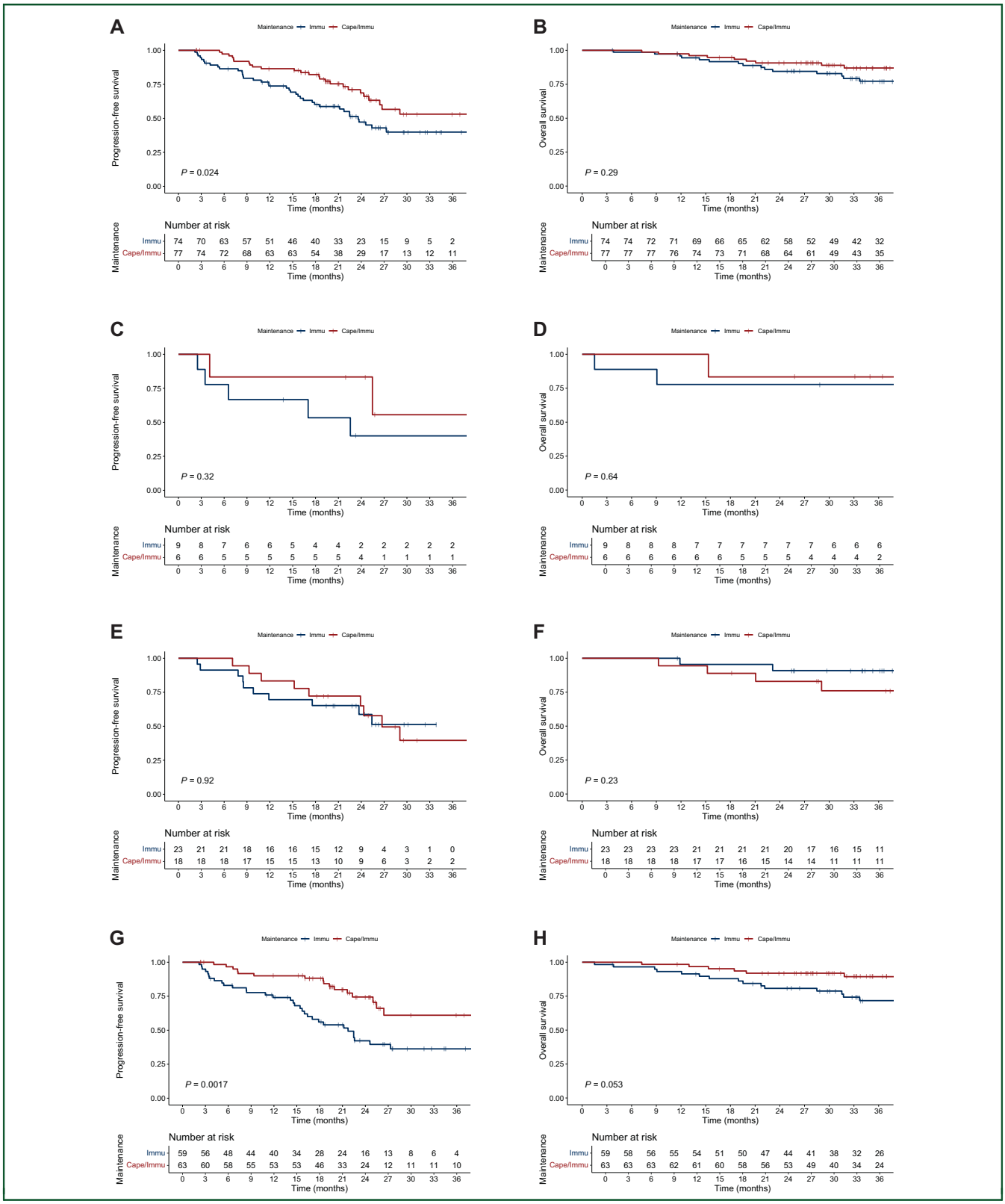

Figure 4. Progression-free survival (PFS) curves for *de novo* metastatic nasopharyngeal carcinoma (dmNPC) patients receiving different maintenance regimens across subgroups in the matched cohort. (A) PFS in patients who received locoregional radiotherapy (LRRT); (B) overall survival (OS) in patients who received LRRT; (C) PFS in patients who did not receive LRRT; (D) OS in patients who did not receive LRRT; (E) PFS in patients who received local therapy to metastatic lesions (LT); (F) OS in patients who received LT; (G) PFS in patients who did not receive LT; (H) OS in patients who did not receive LT.
Cape, capecitabine; Immu, immunotherapy.

therapy, whereas those with PMD did. This may be because patients with OMD tend to respond more favorably to treatment and may even achieve remission,[36] whereas immunotherapy alone may be insufficient to manage tumor progression in PMD patients. In addition, we observed that patients who did not receive LT derived a PFS benefit from

the addition of capecitabine, while those who underwent LT did not. Several studies have demonstrated that local therapies for metastatic disease can offer OS advantages,[37-39] suggesting that Immu/Cape maintenance therapy may enhance disease control in patients who have not received LT.

There are several limitations to our study. Firstly, it was a retrospective, single-center analysis conducted in an academic setting. Although PSM and multivariate Cox regression analyses were employed to minimize bias, selection biases could not be eliminated entirely. Secondly, the study included only 287 patients due to the low incidence of dmNPC. Thirdly, variability in first-line chemotherapy regimens and anti-PD-1 agents may have impacted PFS benefits, even though no significant PFS and OS differences were observed across different chemotherapy regimens and immunotherapy agents (Supplementary Figure S3A-H, available at https://doi.org/10.1016/j.esmoop.2025.105295). Furthermore, our findings may not be generalizable to patients with primary chemo-refractory disease, as maintenance therapy is typically reserved for those who derive clinical benefit from initial chemotherapy. Finally, adverse events related to capecitabine were difficult to accurately assess due to the retrospective nature of the study. Therefore, a multicenter, prospective clinical trial is necessary to validate our findings in the future.

Conclusion

Maintenance therapy with immunotherapy combined with capecitabine significantly prolongs PFS compared with immunotherapy alone in dmNPC patients, particularly in those with PMD and detectable post-treatment EBV DNA levels. These findings warrant validation in prospective randomized trials to further establish capecitabine's role in immunotherapy-based maintenance paradigms.

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DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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