Supplementary Appendix 1

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Supplementary Table A: List of participating centers

No	Center	Principal investigator
1	Sun Yat-sen University Cancer Centre	Yan-Qun Xiang
2	Sun Yat-sen Memorial Hospital	Yi-Min Liu
3	Maoming People's Hospital	Tian-Sheng Gao
4	Wuzhou People's Hospital	Yi-Sheng Huang

Supplementary Table B: Initial cost for each group: baseline values, ranges.

Parameters	Nab-TPC	GP
Cost of treatment, $/cycle		
Gemcitabine		559.87 (31.83-933.12)
Capecitabine	47.06 (27.18-371.39)	
Nab-paclitaxel	424.64 (318.48-1364.30)	
Cisplatin	11.25 (8.44-11.25)	16.87 (11.25-16.87)
Prophylactic leucocyte	153.77 (13.90-437.71)	
Hydration	107.42 (1.77-294.43)	
PICC/one time	1107.47 (320.87-1107.47)	
Laboratory test	111.19 (43.62-328.93)	
Imaging examination	343.53 (144.02-1910.70)	

Nab-TPC=nab-paclitaxel, cisplatin, plus capecitabine; GP=gemcitabine and cisplatin; PICC= peripherally inserted central catheter. All costs were converted to 2023 US dollars (1 USD = 7.0366 RMB).

Supplementary Table C. Tumor burden and response in patients with baseline positive or negative plasma EBV DNA level

	EBV DNA positive (n=73)	EBV DNA negative (n=8)
Number of metastases sites		
oligo	11 (15.1)	5 (62.3)
multi	62 (84.9)	3 (37.5)
Number of metastases organs		
1	29 (39.7)	4 (50)
>1	44 (60.3)	4 (50)
Tumor response		
Complete response	9 (12.3)	0
Partial response	46 (63.0)	4 (50)
Stable disease	14 (19.2)	4 (50)
Progression disease	4 (5.5)	0

Data are n (%), EBV=Epstein-Barr virus.

Supplementary Table D. Subsequent therapies after discontinuation of study treatment in all patient at the preplanned interim analysis

	No. (%)	
Therapy	Nab paclitaxel, cisplatin, plus capecitabine (n=27)	Gemcitabine and cisplatin (n=32)
Lines of therapy for progressive disease		
0	4 (15)	6 (19)
1	11 (41)	14 (44)
2	6 (22)	6 (19)
3 or more	6 (22)	6 (19)
Subsequent chemotherapy		
Gemcitabine plus cisplatin/carboplatin	12 (44)	2 (6)
Taxanes plus cisplatin/carboplatin	3 (11)	4 (13)
Taxanes plus cisplatin plus capecitabine	2 (7)	12 (38)
Other regimens	4 (15)	6 (19)
Immunotherapy*	21 (78)	20 (63)
Targeted therapy	15 (56)	12 (38)
Radiotherapy	3 (11)	4 (13)
Surgery	1 (4)	1 (3)

Data are n (%). *Immunotherapy consisted of anti-PD-1/PD-L1 antibodies monotherapy, bispecific antibodies or combination agents which could block interaction between PD-1 and PD-L1.

Supplementary Table E: Summary of tumor response

Variable	Nab-TPC group (n=41)	GP group (n=40)
Best overall response, n (%)		
Complete response	5 (12.2)	4 (10.0)
Partial response	29 (70.7)	21 (52.5)
Stable disease	6 (14.6)	12 (30.0)
Progression disease	1 (2.4)	3 (7.5)
Disease control rate	97.6 (92.6 to 100.0)	92.5 (84.0 to 100.0)
Objective response rate		
Objective response rate, (%)	82.9 (71.0 to 95.0)	62.5 (44.1 to 75.9)
P value	0.05	
Estimation of median DoR, months (95% CI)	10.8 (8.8 to 12.8)	6.9 (5.5 to 8.2)
Stratified estimate of HR (95% CI)	0.419 (0.217 to 0.807)	
P value	0.009	

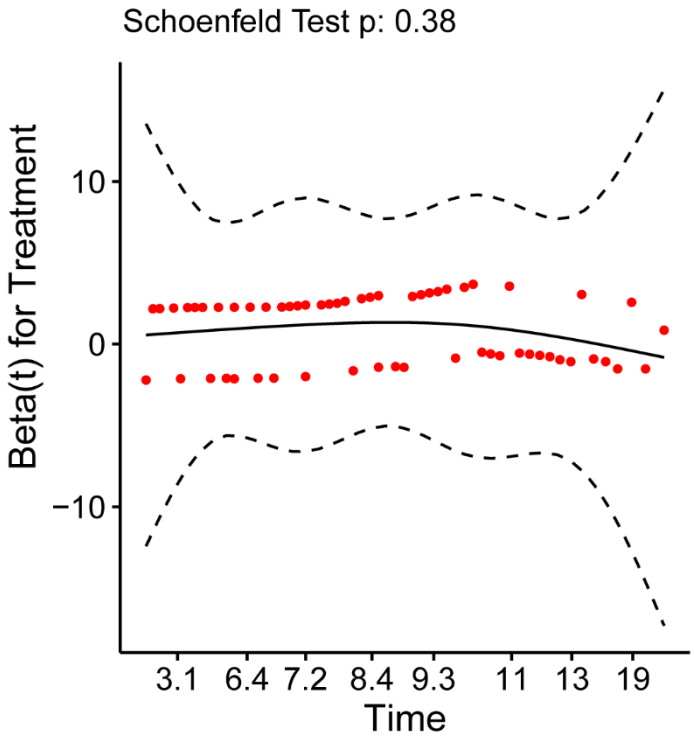
Data are n (%), % (95% CI), or median (95% CI). Nab-TPC=nab-paclitaxel, cisplatin, plus capecitabine; GP=gemcitabine and cisplatin; HR=Hazard ratio.

Supplementary Table F. Summary of prognostic factors multivariable analyses for progression-free survival

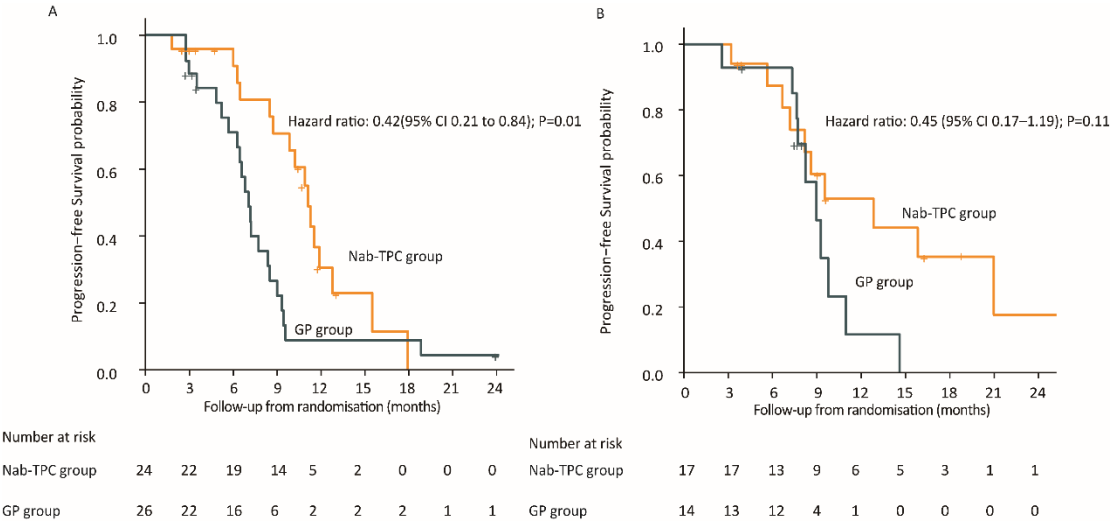
Variable	Events, n/N (%)	Hazard ratio (95% CI)	*P*
Sex			
Female	45/64 (70.3)	0.78 (0.35 to 1.74)	0.55
Male	14/17 (82.4)	1 (reference)	
Age			0.87
<50	34/47 (72.3)	0.95 (0.52 to 1.76)	
≥50	25/34 (73.5)	1 (reference)	
ECOG performance status			
0	26/33 (78.8)	1.001 (0.56 to 1.78)	1.00
1	33/48 (68.8)	1 (reference)	
Stage			
Primary metastases	24/29 (82.8)	0.75 (0.400 to 1.42)	0.38
Asynchronous metastases	35/52 (67.3)	1 (reference)	
Number of metastatic organs			
1	24/33 (72.7)	0.46 (0.16 to 1.33)	0.29
2	19/31 (61.3)	0.57 (0.25 to 1.33)	
≥3	16/17 (94.1)	1 (reference)	
Liver metastasis			
Presence	36/47 (76.6)	1.03 (0.52 to 2.04)	0.93
Absence	23/34 (67.6)	1 (reference)	
Lung metastasis			
Presence	21/30 (70.0)	0.95 (0.40 to 2.25)	0.91
Absence	38/51 (74.5)	1 (reference)	
Bone metastasis			
Presence	22/30 (73.3)	1.01 (0.42 to 2.41)	0.98
Absence	37/51 (72.5)	1 (reference)	
EBV-DNA			
≤2,000 copy/mL	21/31 (67.7)	0.75 (0.41 to 1.39)	0.36
>2,000 copy/mL	38/50 (76.0)	1 (reference)	
Treatment group			
Nab-TPC	27/41 (65.9)	0.40 (0.19 to 0.83)	0.01
GP	32/40 (80.0)	1 (reference)	

ECOG=Eastern Cooperative Oncology Group; EBV=Epstein-Barr virus; Nab-TPC=nab-paclitaxel, cisplatin, plus capecitabine; GP=gemcitabine and cisplatin.

Supplementary Figure A. The examination of Schoenfeld residuals from stratified Cox proportional regression model for progression-free survival.

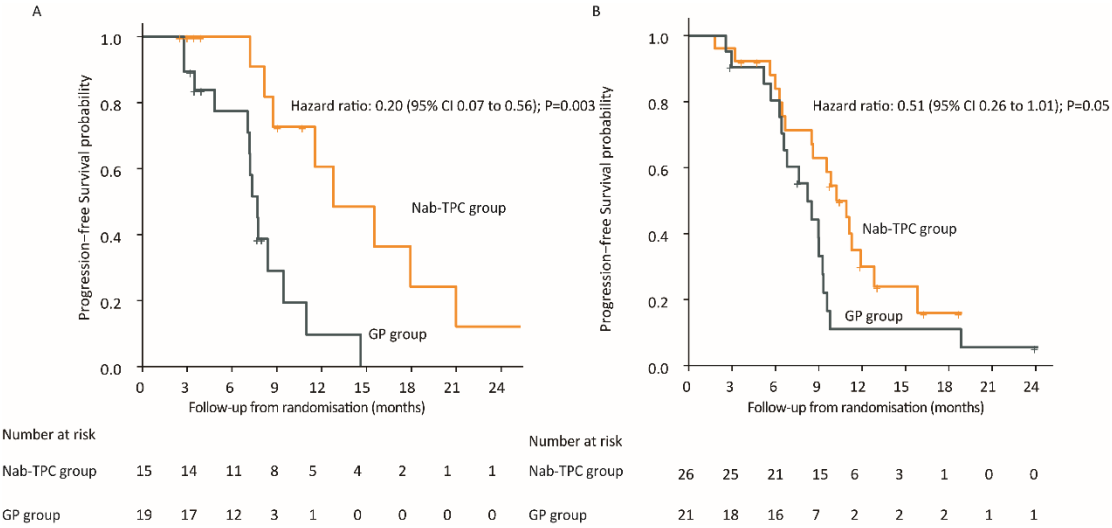


Supplementary Figure B. Kaplan–Meier Analysis of progression-free survival according to baseline plasma EBV DNA level. (A) Progression-free survival in patients with high EBV DNA level. (B) Progression-free survival in patients with low EBV DNA level at baseline.



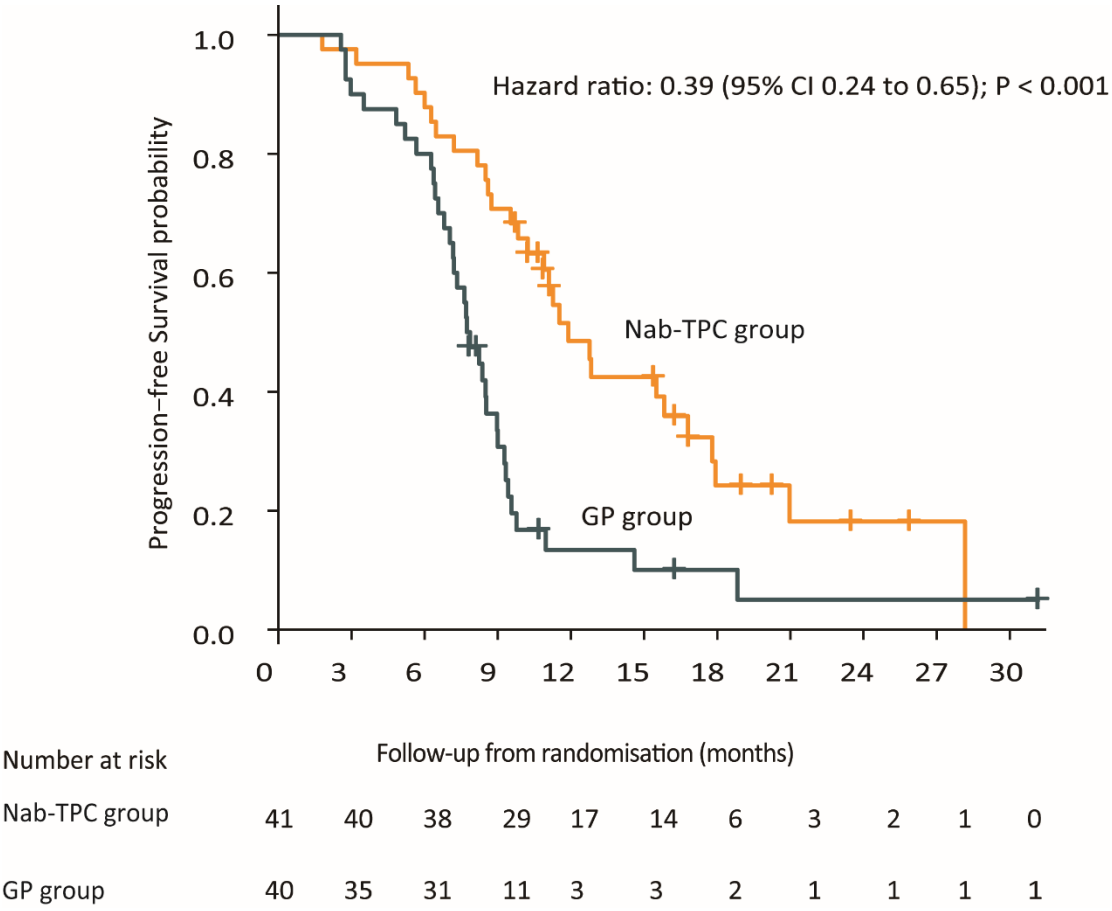
EBV=Epstein-Barr virus; Nab-TPC=nab-paclitaxel, cisplatin, plus capecitabine; GP=gemcitabine and cisplatin.

Supplementary Figure C. Independent review committee-assessed progression-free survival according to liver metastases at the updated analysis. (A) Progression-free survival in patients without liver metastases. (B) Progression-free survival in patients with liver metastases.



Nab-TPC=nab-paclitaxel, cisplatin, plus capecitabine; GP=gemcitabine and cisplatin.

Supplementary Figure D. Independent review committee-assessed progression-free survival at updated analysis.



Nab-TPC=Nab-paclitaxel, cisplatin, plus capecitabine; GP=gemcitabine and cisplatin.