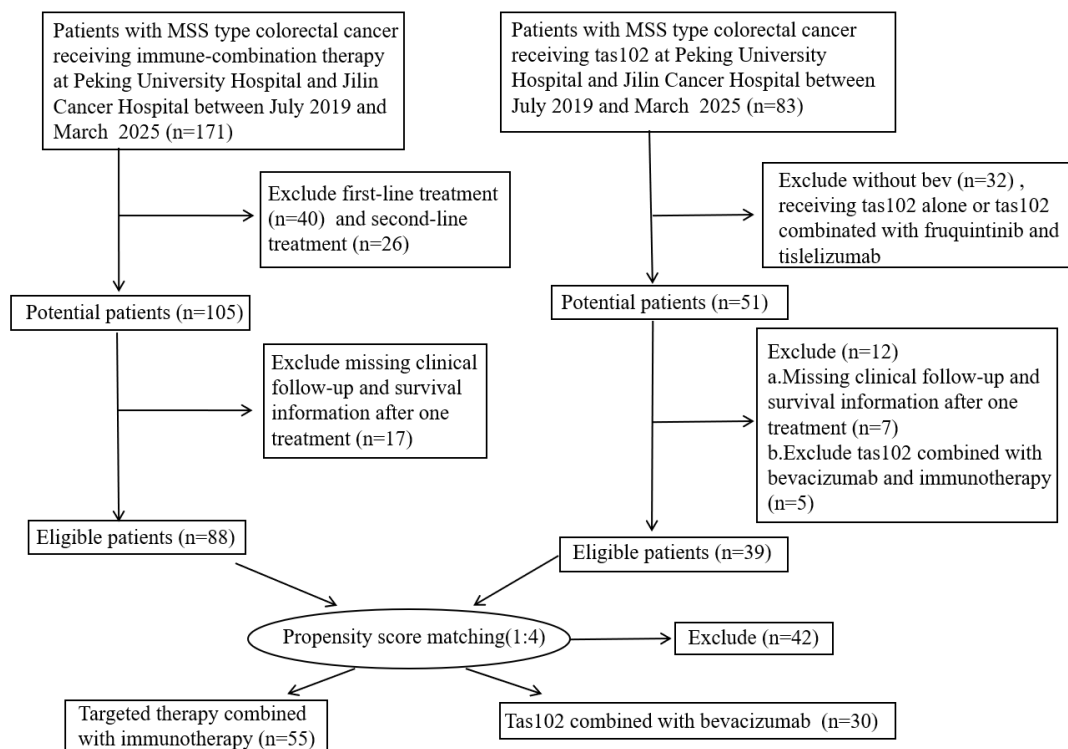
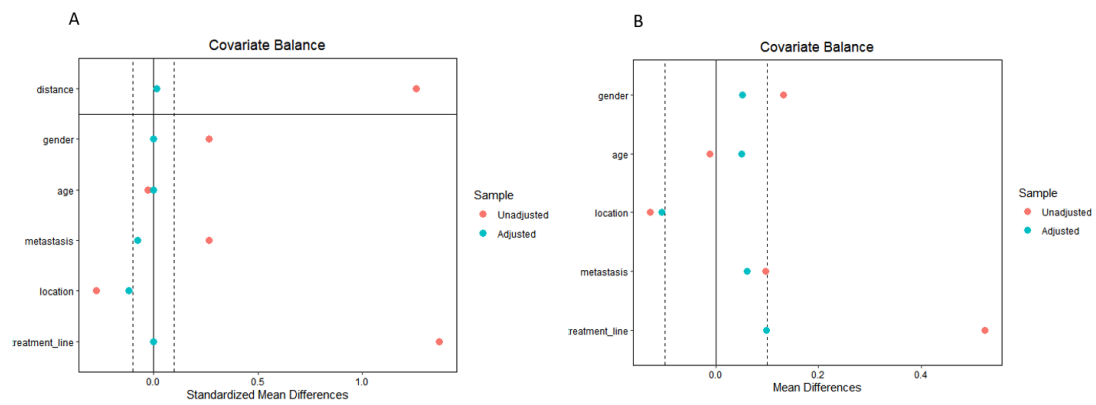


**Supplementary Figure 1 Kaplan-Meier curve of original cohort.** (A) KM curve of original cohort (OS). (B) After propensity score-matching analysis in OS (ratio=4); (C) After propensity score-matching analysis in OS (ratio=3); (D) After propensity score-matching analysis in OS (ratio=2); (E) After propensity score-matching analysis in OS (ratio=1); (F) After inverse probability of treatment weighting analysis (OS).



**Supplementary Figure 2 Flow chart of patient inclusion and propensity score matching.**



**Supplementary Figure 3 Standardized mean difference before and after PSM and IPTW.** (A) Standardized mean difference before and after PSM; (B) Standardized mean difference before and after IPTW.

**Supplementary Table 1 Details of medication treatment received in TP group**

Treatment modality		Number of patients
PD-1 inhibitors	Sintilimab	41
	Pembrolizumab	14
	Camrelizumab	12
	Nivolumab	8
	Tislelizumab	5
	Toripalimab	4
	Serplulimab	4
Targeted agent	Regorafenib	46
	Fruquintinib	42

TP group: Targeted drug+PD1.

**Supplementary Table 2 Univariate and multivariate cox analysis of the effect of prognostic factors in the original cohort**

Dependent: Surv (OS/30, status OS)	All	HR (univariable)	HR (multivariable)
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Gender	Male	80 (63.0%)		1.4491 (0.3307-6.349, p=0.6227)
	Female	47 (37.0%)	1.96 (0.46-8.24, p=0.360)	
Age	≤ 60	51 (40.2%)		
	> 60	76 (59.8%)	1.95 (0.39-9.66, p=0.414)	1.3220 (0.2481-7.044, p=0.7436)
ECOG	0-1	110 (86.6%)		
	2	17 (13.4%)	0.90 (0.11-7.34, p=0.924)	
Number of metastatic organs	1	28 (22.0%)		
	≥2	99 (78.0%)	3.40 (0.42-27.78, p=0.254)	
Primary tumor location	Right colon	31 (24.4%)		
	Left colon and rectum	96 (75.6%)	0.20 (0.05-0.84, p=0.027)	0.2479 (0.0532-1.157, p=0.0759)
Liver metastasis	No	48 (37.8%)		

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	Yes	79 (62.2%)	5.31 (0.65-43.39, p=0.119)	
Lung metastasis	No	47 (37.0%)		
	Yes	80 (63.0%)	1.71 (0.34-8.46, p=0.512)	
RAS	Wild-type	34 (26.8%)		
	Mutation	69 (54.3%)	3.89 (0.47-32.36, p=0.209)	
	Unknown	24 (18.9%)	2.35 (0.15-37.80, p=0.546)	
Treatment regimen	Targeted drug+PD1	88 (69.3%)		1.6023 (0.3900-6.582, p=0.5132)
	TAS102+bevacizumab	39 (30.7%)	2.00 (0.50-8.01, p=0.328)	
n=127, events=8, Likelihood ratio test=5.01 on 1 df (p=0.025)				
Abbreviations: ECOG, Eastern Cooperative Oncology Group.				

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**Supplementary Table 3 Propensity score-adjusted multivariable cox regression analysis of prognostic factors associated with PFS in the original cohort**

Dependent: Surv(OS, status OS)		All	HR (multivariable)
Gender	Male	80 (63.0%)	0.93 (0.14-6.24, p=0.937)
	Female	47 (37.0%)	
Age	≤ 60	51 (40.2%)	1.37 (0.22-8.52, p=0.733)
	> 60	76 (59.8%)	
ECOG	0-1	110 (86.6%)	2.56 (0.23-28.58, p=0.444)
	2	17 (13.4%)	
Number of metastatic organs	1	28 (22.0%)	0.57 (0.03-10.54, p=0.707)
	≥2	99 (78.0%)	
Primary tumor location	Right colon	31 (24.4%)	0.40 (0.06-2.50, p=0.324)
	Left colon and rectum	96 (75.6%)	
Liver metastasis	No	48 (37.8%)	

	Yes	79 (62.2%)	3.69 (0.21-64.18, p=0.371)
Lung metastasis	No	47 (37.0%)	
	Yes	80 (63.0%)	1.71 (0.29-10.09, p=0.553)
RAS	Wild-type	34 (26.8%)	
	Mutation	69 (54.3%)	3.08 (0.23-40.70, p=0.393)
	Unknown	24 (18.9%)	3.55 (0.15-81.91, p=0.428)
Treatment regimen	Targeted drug+PD1	88 (69.3%)	
	TAS102+bevacizumab	39 (30.7%)	1.14 (0.20-6.43, p=0.886)
ps	Mean ± SD	0.3 ± 0.2	11.07 (0.10-1276.27, p=0.321)
n=127, events=8, Likelihood ratio test=9.7 on 11 df (p=0.558)			

**Supplementary Table 4 Univariate and multivariate cox regression analysis of the prognostic impact of factors (including prior therapeutic agents) on progression-free survival in the original cohort**

Dependent: Surv (PFS/30, status PFS)	All	HR (univariable)	HR (multivariable)
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Gender	Male	80 (63.0%)		
	Female	47 (37.0%)	1.11 (0.74-1.66, p=0.619)	0.97 (0.64-1.46, p=0.869)
Age	≤ 60	51 (40.2%)		
	> 60	76 (59.8%)	0.87 (0.58-1.31, p=0.514)	0.91 (0.60-1.37, p=0.649)
ECOG	0-1	110 (86.6%)		
	2	17 (13.4%)	0.54 (0.28-1.01, p=0.055)	0.53 (0.27-1.02, p=0.057)
Primary tumor location	Right colon	31 (24.4%)		
	Left colon and rectum	96 (75.6%)	0.94 (0.59-1.49, p=0.800)	
Number of metastatic organs	1	28 (22.0%)		
	≥2	99 (78.0%)	2.22 (1.34-3.68, p=0.002)	2.32 (1.31-4.08, p=0.004)
Liver metastasis	No	48 (37.8%)		
	Yes	79 (62.2%)	1.39 (0.91-2.11, p=0.126)	
Lung metastasis	No	47 (37.0%)		



	Yes	80 (63.0%)	1.01 (0.67-1.52, p=0.966)	
RAS	Wild type	34 (26.8%)		
	Mutation	69 (54.3%)	1.02 (0.65-1.59, p=0.932)	
	Unknown	24 (18.9%)	0.63 (0.33-1.20, p=0.159)	
Treatment regimen	TP group	88 (69.3%)		
	TB group	39 (30.7%)	1.43 (0.94-2.18, p=0.094)	1.07 (0.68-1.67, p=0.769)
Prior fluorouraci	No	78 (61.4%)		
	Yes	49 (38.6%)	0.90 (0.60-1.35, p=0.598)	
Prior oxaliplatin	No	19 (15.0%)		
	Yes	108 (85.0%)	1.33 (0.74-2.38, p=0.348)	
Prior irinotecan	No	19 (15.0%)		
	Yes	108 (85.0%)	0.87 (0.49-1.53, p=0.619)	
Prior capecitabine	No	26 (20.5%)		
	Yes	101 (79.5%)	1.63 (0.98-2.72, p=0.062)	0.99 (0.56-1.75, p=0.960)
Prior raltitrexed	No	86 (67.7%)		

	Yes	41 (32.3%)	0.75 (0.48-1.16, p=0.193)	
Prior bevacizumab	No	18 (14.2%)		
	Yes	109 (85.8%)	1.72 (0.92-3.24, p=0.091)	1.86 (0.96-3.59, p=0.065)
Prior cetuximab	No	95 (74.8%)		
	Yes	32 (25.2%)	0.80 (0.51-1.26, p=0.337)	

n=127, events=100, Likelihood ratio test=19.91 on 5 df (p=0.001)

TP group: Targeted drug+PD1

TB group: TAS102+bevacizumab.

**Supplementary Table 5 Univariate and multivariate cox regression analysis of prognostic factors in TP group patients receiving only regorafenib as targeted therapy for PFS**

Dependent: Surv (PFS/30, status PFS)		All	HR (univariable)	HR (multivariable)
Gender	Male	50 (58.8%)		
	Female	35 (41.2%)	1.10 (0.68-1.79, p=0.701)	1.02 (0.62-1.68, p=0.926)
Age	≤ 60	36 (42.4%)		

ECOG		> 60	49 (57.6%)	1.08 (0.67-1.76, p=0.745)	1.19 (0.72-1.95, p=0.496)
		0-1	76 (89.4%)		
		2	9 (10.6%)	0.42 (0.17-1.06, p=0.066)	0.47 (0.18-1.21, p=0.117)
Primary tumor location		Right colon	21 (24.7%)		
		Left colon and rectum	64 (75.3%)	0.79 (0.46-1.36, p=0.396)	
Number of metastatic organs		1	17 (20.0%)		
		≥2	68 (80.0%)	2.54 (1.34-4.83, p=0.004)	2.33 (1.16-4.69, p=0.018)
Liver metastasis		No	32 (37.6%)		
		Yes	53 (62.4%)	1.66 (0.99-2.81, p=0.057)	1.10 (0.62-1.94, p=0.752)
Lung metastasis		No	30 (35.3%)		
		Yes	55 (64.7%)	1.08 (0.65-1.79, p=0.763)	
RAS		Wild type	19 (22.4%)		
		Mutation	54 (63.5%)	1.05 (0.60-1.82, p=0.869)	

	Unknown	12 (14.1%)	0.59 (0.23-1.51, p=0.270)	
Treatment regimen	TP group	46 (54.1%)		
	TB group	39 (45.9%)	1.50 (0.91-2.47, p=0.110)	1.21 (0.72-2.03, p=0.471)

n=85, events=69, Likelihood ratio test=13.34 on 3 df (p=0.004)

TP group: Targeted drug+PD1

TB group: TAS102+bevacizumab

**Supplementary Table 6 Univariate and multivariate cox regression analysis of prognostic factors in TP group patients receiving only fruquintinib as targeted therapy for PFS**

Dependent: Surv (PFS/30, status PFS)		All	HR (univariable)	HR (multivariable)
Gender	Male	51 (63.0%)		
	Female	30 (37.0%)	1.23 (0.74-2.03, p=0.420)	1.04 (0.61-1.75, p=0.892)
Age	≤ 60	31 (38.3%)		
	> 60	50 (61.7%)	0.66 (0.40-1.09, p=0.101)	0.73 (0.44-1.22, p=0.229)

ECOG	0-1	71 (87.7%)		
	2	10 (12.3%)	0.50 (0.22-1.11, p=0.088)	0.57 (0.25-1.34, p=0.198)
Primary tumor location	Right colon	23 (28.4%)		
	Left colon and rectum	58 (71.6%)	1.31 (0.75-2.28, p=0.343)	
Number of metastatic organs	1	17 (21.0%)		
	≥2	64 (79.0%)	1.60 (0.87-2.96, p=0.130)	
Liver metastasis	No	28 (34.6%)		
	Yes	53 (65.4%)	0.91 (0.54-1.52, p=0.708)	
Lung metastasis	No	31 (38.3%)		
	Yes	50 (61.7%)	0.93 (0.56-1.52, p=0.758)	
RAS	Wild type	27 (33.3%)		
	Mutation	39 (48.1%)	1.07 (0.63-1.81, p=0.808)	
	Unknown	15 (18.5%)	0.69 (0.32-1.49, p=0.346)	
Treatment regimen	TP group	42 (51.9%)		

TB group	39 (48.1%)	1.44 (0.88-2.37, p=0.149)	1.28 (0.77-2.13, p=0.343)
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n=81, events=67, Likelihood ratio test=3.44 on 1 df (p=0.063)

TP group: Targeted drug+PD1

TB group: TAS102+bevacizumab

**Supplementary Table 7 Baseline demographic and clinical characteristics of patients with PFS > 90 days**

Characteristics	Levels	Targeted drug+PD1 (N=26)	TAS102+bevacizumab (N=17)	p
Age	≤ 60	12 (46.2%)	8 (47.1%)	1.000
	> 60	14 (53.8%)	9 (52.9%)	
Gender	Male	13 (50%)	9 (52.9%)	1.000
	Female	13 (50%)	8 (47.1%)	
ECOG	0-1	22 (84.6%)	16 (94.1%)	0.643
	2	4 (15.4%)	1 (5.9%)	

Primary location	tumor	Right colon	8 (30.8%)	3 (17.6%)	0.544
		Left colon and rectum	18 (69.2%)	14 (82.4%)	
Primary surgery	tumor	No	1 (3.8%)	1 (5.9%)	1.000
		Yes	25 (96.2%)	16 (94.1%)	
Number of metastatic organs		1	7 (26.9%)	6 (35.3%)	0.807
		≥2	19 (73.1%)	11 (64.7%)	
Liver metastasis		No	10 (38.5%)	6 (35.3%)	1.000
		Yes	16 (61.5%)	11 (64.7%)	
Lung metastasis		No	11 (42.3%)	7 (41.2%)	1.000
		Yes	15 (57.7%)	10 (58.8%)	
RAS		Wild-type	9 (34.6%)	6 (35.3%)	0.215
		KRAS mutation	10 (38.5%)	9 (52.9%)	
		NRAS mutation	0 (0%)	1 (5.9%)	

	Unknown	7 (26.9%)	1 (5.9%)	
Treatment line	3 line	13 (50%)	3 (17.6%)	0.068
	>3 line	13 (50%)	14 (82.4%)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

**Supplementary Table 8 Baseline demographic and clinical characteristics of patients with PFS > 120 days**

Characteristics		Levels	Targeted (N=22)	drug+PD1 TAS102+bevacizumab (N=13)	p
Age		≤ 60	9 (40.9%)	7 (53.8%)	0.696
		> 60	13 (59.1%)	6 (46.2%)	
Gender		Male	11 (50%)	7 (53.8%)	1.000
		Female	11 (50%)	6 (46.2%)	
ECOG		0-1	18 (81.8%)	12 (92.3%)	0.721
		2	4 (18.2%)	1 (7.7%)	
Primary tumor location		Right colon	6 (27.3%)	2 (15.4%)	0.695



		Left colon and rectum	16 (72.7%)	11 (84.6%)	
Primary tumor surgery	No		1 (4.5%)	0 (0%)	1.000
	Yes		21 (95.5%)	13 (100%)	
Number of metastatic organs	1		6 (27.3%)	5 (38.5%)	0.755
	≥2		16 (72.7%)	8 (61.5%)	
Liver metastasis	No		8 (36.4%)	3 (23.1%)	0.659
	Yes		14 (63.6%)	10 (76.9%)	
Lung metastasis	No		10 (45.5%)	6 (46.2%)	1.000
	Yes		12 (54.5%)	7 (53.8%)	
RAS	Wild-type		8 (36.4%)	6 (46.2%)	1.000
	KRAS mutation		8 (36.4%)	7 (53.8%)	
	NRAS mutation		0 (0%)	0 (0%)	
	Unknown		6 (27.3%)	0 (0%)	
Treatment line	3 line		10 (45.5%)	3 (23.1%)	0.336

>3 line	12 (54.5%)	10 (76.9%)
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