Supplementary online content

Methods and results

Propensity score matching of initial CT and initial ET groups (Table S1 and Figure S1)

Patients were matched (one to one) on the logit of the propensity score using a caliper width of 0.2 of the standard deviation of the logit of the propensity score. Age, hormone receptor (HR) status, distance relapse-free interval (DRFI), visceral involvement, progression on prior (neo)adjuvant ET and number of metastatic sites were used to calculate the propensity score. Of the 1877 patients in the initial sample, 614 pairs of patients in the initial chemotherapy (CT) and endocrine therapy (ET) groups were matched, while 601 of the patients in the initial CT group were excluded from the matched sample because appropriate patients in the initial ET were not identified. Similarly, 48 of the patients in the initial ET group were excluded from the matched sample.

There were significant differences between the two groups in all confounding factors in the original sample, while there were no significant differences in the matched sample.

Propensity score matching of CT cohort and CT-ET cohort (Table S6 and Figure S2)

Patients were matched (one to one) on the logit of the propensity score using a caliper width of 0.2 of the standard deviation of the logit of the propensity score. Age, HR status, DRFI, visceral involvement, progression on prior (neo)adjuvant ET, number of metastatic sites and objective response were used to calculate the propensity score. Of the 855 patients in the initial sample, 369 pairs of patients in the CT and CT-ET cohorts were matched, while 37 patients in the CT cohort were excluded from the matched sample because appropriate patients in the CT-ET cohort were not identified. Similarly, 80 of the patients in the CT-ET cohort were excluded from the matched sample.

HR status, DRFI and visceral involvement were significantly different between the two cohorts in original sample, while there were no significant differences in any of the confounding factors in the matched sample.

Propensity score matching of CT cohort and ET cohort (Table S7 and Figure S3)

Patients were matched (one to one) on the logit of the propensity score using a caliper width of 0.2 of the standard deviation of the logit of the propensity score. Age, HR status, DRFI, visceral involvement, progression on prior (neo)adjuvant ET, number of metastatic sites were used to calculate the propensity score. Of the 933 patients in the initial sample, 305 pairs of patients in the CT cohort and CT-ET cohort were matched, while 101 patients in the CT cohort were excluded from the matched sample because appropriate patients in the ET cohort were not identified. Similarly, 222 patients in the ET cohort were excluded from the matched sample.

Age, HR status, DRFI, visceral involvement and number of metastatic sites were significantly different between the two cohorts in original sample, while there were no significant differences in any of the confounding factors in the matched sample.

Multivariate Cox regression on the clinical outcome of four first-line treatment regimens (Figure 2C and 2D)

Multivariate Cox regression was applied to evaluate the treatment effect of four different first-line regimens, among which single agent ET was used as reference group.

The PFS was 15.0 months with ET plus targeted drugs and 11.0 months with single agent ET (crude HR 0.70, p=0.04; multivariate adjusted HR 0.71, p=0.05). The PFS was 12.0 months with T-based therapy (crude HR 0.93, p=0.19; multivariate adjusted HR 0.93, p=0.20). The PFS of non T-based therapy was 8.0 months (crude HR 1.34, p＜0.01; multivariate adjusted HR 1.25, p＜0.01). There was significant difference in PFS among the four groups (P<0.01) (Figure 2C).

The OS was 52.0 months with ET plus targeted drugs and 55.0 months with single agent ET (crude HR 1.15, p=0.87; multivariate adjusted HR 1.16, p=0.51). The OS was 55.0 months with T-based therapy (crude HR 0.99, p=0.54; multivariate adjusted HR 0.94, p=0.39), while the OS of non T-based therapy was 38.0 months (crude HR 1.46, p＜0.01; multivariate adjusted HR 1.26, p＜0.01). There was significant difference in OS among the four groups (P<0.01) (Figure 2D).

Multivariate Cox regression on the clinical outcome of CT-ET cohort, CT cohort and ET cohort (Figure 2E and 2F)

Multivariate Cox regression was applied to evaluate the treatment effect of three different first-line maintenance regimens, among which the CT cohort was used as reference group.

Compared with the PFS of CT cohort, median PFS was significantly longer in the CT-ET cohort (17.0 vs 8.5 months; crude HR 0.41, P < 0.01; multivariate adjusted HR 0.43, P < 0.01) and ET cohort (14.0 months vs 8.5 months; crude HR 0.48; P < 0.01; multivariate adjusted HR 0.49, P < 0.01) (Figure 2E).

Compared with the OS of CT cohort, median OS was significantly longer in the CT-ET cohort (62.0 vs 45.0 months; crude HR 0.61, P <0.01; multivariate adjusted HR 0.66, P < 0.01) and ET cohort (61.0 vs 45.0 months; crude HR 0.65, P <0.01; multivariate adjusted HR 0.74, P < 0.01) (Figure 2F).

Table S1. Baseline characteristics of initial CT and initial ET groups in total and propensity score matched populations

	Total population				Propensity score matched population			
n (%)	Initial CT	Initial ET	Statistic	*P* value	Initial CT	Initial ET	Statistic	*P* value
	n = 1215	n = 662			n = 614	n = 614		
Age, years								
< 60	**1073 (88.3)**	**525 (79.3)**	**27.48**	**<0.01**	**503 (81.9)**	**497 (80.9)**	**0.19**	**0.66**
≥ 60	**142 (11.7)**	**137 (20.7)**			**111 (18.1)**	**117 (19.1)**		
HR status								
ER+/PR+	**871 (71.7)**	**556 (84.0)**	**36.94**	**<0.01**	**514 (83.7)**	**512 (83.4)**	**0.02**	**0.88**
ER-/PR+ and ER+/PR-	**344 (28.3)**	**106 (16.0)**			**100 (16.3)**	**102 (16.6)**		
DRFI								
< 24 months	**496 (40.8)**	**171 (25.8)**	**42.05**	**<0.01**	**170 (27.7)**	**169 (27.5)**	**0.004**	**0.95**
≥24 months	**719 (59.2)**	**491 (74.2)**			**444 (72.3)**	**445 (72.5)**		
Visceral involvement								
Yes	**646 (53.2)**	**263 (39.7)**	**31.00**	**<0.01**	**264 (43.0)**	**257 (41.9)**	**0.16**	**0.69**
No	**569 (46.8)**	**399 (60.3)**			**350 (57.0)**	**357 (58.1)**		
Progression on prior (neo)adjuvant ET*								
Yes	**561 (46.2)**	**392 (59.2)**	**28.82**	**<0.01**	**361 (58.8)**	**349 (56.8)**	**0.48**	**0.49**
No	**650 (53.5)**	**269 (40.6)**			**253 (41.2)**	**265 (43.2)**		
Number of metastatic sites								
1	**534 (44.0)**	**397 (60.0)**	**43.99**	**<0.01**	**347 (56.5)**	**354 (57.7)**	**0.16**	**0.69**
≥ 2	**681 (56.0)**	**265 (40.0)**			**267 (43.5)**	**260 (42.3)**		

***One patient in initial CT group had no information on progression on prior (neo)adjuvant ET.**

Figure S1. Progression-free survival (A) and overall survival (B) analysis of initial CT and initial ET groups in patients with HR+/HER2- MBC after propensity score matching

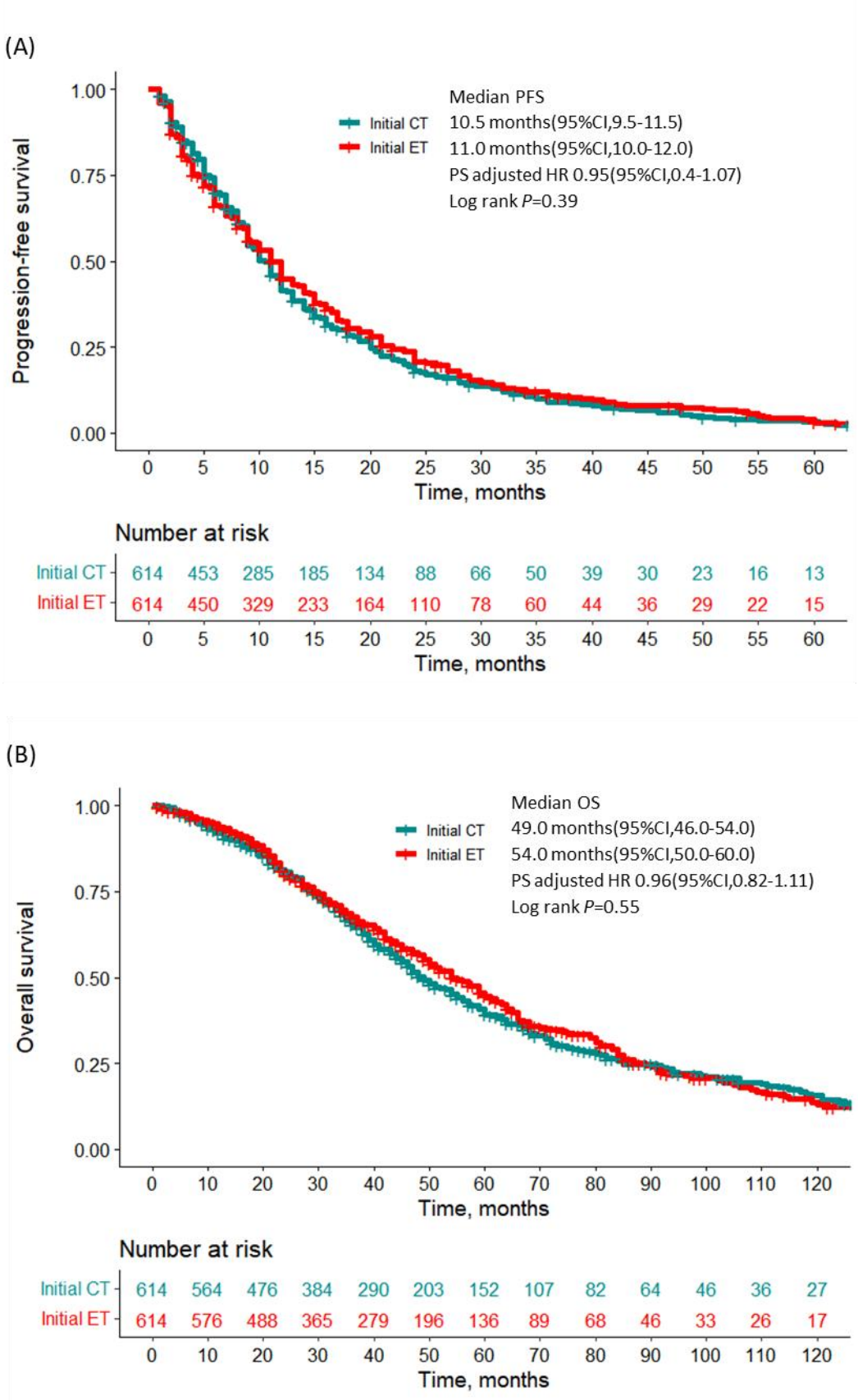

Table S2. Baseline characteristics of the four initial first-line regimens.

n (%)	T-based (n = 803)	Non T-based CT (n = 412)	ET + targeted drugs (n = 53)	ET (n = 609)
Age, years				
< 60	705 (87.8)	368 (89.3)	39 (73.6)	486 (79.8)
≥ 60	98 (12.2)	44 (10.7)	14 (26.4)	123 (20.2)
HR status				
ER+/PR+	581 (72.4)	290 (70.4)	47 (88.7)	509 (83.6)
ER+/PR-	159 (19.8)	90 (21.8)	5 (9.4)	90 (14.8)
ER-/PR+	63 (7.8)	32 (7.8)	1 (1.9)	10 (1.6)
Distant relapse-free interval				
De novo stage Ⅳ	157 (19.6)	40 (9.7)	0	25 (4.1)
< 24 months	142 (17.7)	157 (38.1)	12 (22.6)	134 (22.0)
≥ 24 months	504 (62.8)	215 (52.2)	41 (77.4)	450 (73.9)
Visceral disease				
No	384 (47.8)	185 (44.9)	31 (58.5)	368 (60.4)
Yes	419 (52.2)	227 (55.1)	22 (41.5)	241 (39.6)
Metastasis site				
Bone	420 (52.3)	183 (44.4)	30 (56.6)	360 (59.1)
Liver	175 (21.8)	119 (28.9)	8 (15.1)	77 (12.6)
Lung	294 (36.6)	132 (32.0)	16 (30.2)	169 (27.8)
Brain	25 (3.1)	12 (2.9)	0	22 (3.6)
Prior (neo)adjuvant ET disease-free interval *				
ET naïve	321 (40.0)	136 (33.0)	2 (3.8)	127 (20.9)
> 12 months	147 (18.3)	39 (9.5)	12 (22.6)	123 (20.2)
≤12 months	331 (41.2)	237 (57.5)	39 (73.6)	358 (58.8)
Comorbidity †				
No	635 (79.1)	340 (82.5)	45 (84.9)	454 (74.5)
Yes	168 (20.9)	72 (17.5)	8 (15.1)	155 (25.5)

CT, chemotherapy; ET, endocrine therapy; HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor.

***Defined as the time from the end of (neo)adjuvant endocrine therapy to relapse. Four patients receiving T-based CT and one patient receiving ET had no information on Prior (neo)adjuvant ET disease-free interval.**

† Systemic diseases that were diagnosed before first-line treatment for metastatic breast cancer, including kidney disease, cardiovascular disease, pulmonary disease, hematological system disease, immune system disease, and mental illness.

Table S3. Baseline characteristics of CT cohort, CT-ET cohort, and ET cohort.

n (%)	CT cohort (n = 406)	CT-ET cohort (n = 449)	ET cohort (n = 527)
Age, years			
< 60	352 (86.7)	403 (89.8)	423 (80.3)
≥ 60	54 (13.3)	46 (10.2)	104 (19.7)
HR status			
ER+/PR+	283 (69.7)	345 (76.8)	452 (85.8)
ER+/PR-	93 (22.9)	84 (18.7)	68 (12.9)
ER-/PR+	30 (7.4)	20 (4.5)	7 (1.3)
Distant relapse-free interval			
De novo stage Ⅳ	76 (18.7)	82 (18.3)	20 (3.8)
< 24 months	95 (23.4)	78 (17.4)	115 (21.8)
≥ 24 months	235 (57.9)	289 (64.4)	392 (74.4)
Visceral disease			
No	165 (40.6)	233 (51.9)	332 (63.0)
Yes	241 (59.4)	216 (48.1)	195 (37.0)
Metastasis site			
Bone	195 (48.0)	244 (54.3)	313 (59.4)
Liver	117 (28.8)	93 (20.7)	50 (9.5)
Lung	152 (37.4)	146 (32.5)	143 (27.1)
Brain	15 (3.7)	15 (3.3)	18 (3.4)
Prior (neo)adjuvant ET disease-free interval *			
ET naïve	160 (39.4)	165 (36.7)	111 (21.1)
> 12 months	48 (11.8)	88 (19.6)	121 (23.0)
≤12 months	197 (48.5)	196 (43.7)	294 (55.8)
Comorbidity †			
No	329 (81.0)	359 (80.0)	394 (74.8)
Yes	77 (19.0)	90 (20.0)	133 (25.2)

CT, chemotherapy; ET, endocrine therapy; HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor.

*** Defined as the time from the end of (neo)adjuvant endocrine therapy to relapse. One patient in CT cohort and one patient in ET cohort had no information on Prior (neo)adjuvant ET disease-free interval.**

† Systemic diseases that were diagnosed before first-line treatment for metastatic breast cancer, including kidney disease, blood system, immune system, and mental illness.

Table S4. First-line initial and maintenance treatment of patients with HR+/HER2- MBC

	Initial regimen	n (%)	Maintenance regimen	n (%)
CT-ET cohort (n=449)	T-based	340 (75.7)	AI	340 (75.7)
	N-based	39 (8.7)	Fulvestrant	18 (4.0)
	Capecitabine	10 (2.2)	ET + targeted drugs	9 (2.0)
	G-based	25 (5.6)	Other-ET	82 (18.3)
	Other-CT	35 (7.8)		
CT cohort (n=406)	T-based	257 (63.3)	343 continued initial CT regimen 63 switched to other CT regimen	
	N-based	58 (14.3)		
	Capecitabine	38 (9.4)		
	G-based	23 (5.7)		
	Other-CT	30 (7.4)		
ET cohort (n=527)	AI	362 (68.7)	515 continued initial ET regimen 12 switched to other ET regimen	
	Fulvestrant	63 (12.0)		
	ET + targeted drugs	46 (8.7)		
	Other-ET	56 (10.6)		

T-based: single-agent taxane, taxane plus cisplatin, capecitabine, gemcitabine, bevacizumab or adriamycin /doxorubicin, taxane plus adriamycin/doxorubicin and cyclophosphamide; N-based: single-agent vinorelbine, vinorelbine plus capecitabine or cisplatin; G-based: single-agent gemcitabine, gemcitabine plus capecitabine or cisplatin; Other CT: etoposide, 5-fluorouracil, single-agent anthracycline(adriamycin/epirubicin), adriamycin/doxorubicin plus cyclophosphamide; targeted drugs: CDK4/6 inhibitors, everolimus, tucidinostat; Others ET: Tamoxifen; toremifene; progesterone.

Table S5. Treatment exposure time in CT cohort, CT-ET cohort, and ET cohort

Months	n	Mean±SD	Median	Min; Max	Q1;Q3
CT cohort	406	8.04±6.68	5.5	3.0; 60.0	4.0; 9.0
CT-ET cohort	449	20.76±15.73	16.0	4.0; 149.0	10.0; 26.0
Initial CT		5.59±3.48	5.0	3.0; 35.5	4.0; 6.0
Maintenance ET		15.17±15.51	10.0	1.0; 146.0	5.0; 20.0
ET cohort	527	17.87±15.13	13.0	3.0; 120.0	8.0; 23.0

SD: standard deviation; Max: maximum; min: minimum; Q1: first quartile; Q3: third quartile.

Table S6. Baseline characteristics of the total and propensity score matched populations in CT cohort and CT-ET cohort

	Total population				Propensity score matched population			
	CT cohort (n = 406)	CT-ET cohort (n = 449)	Statistic	*P* value	CT cohort (n = 369)	CT-ET cohort (n = 369)	Statistic	*P* value
Age, years								
< 60	352 (86.7)	403 (89.8)	1.93	0.17	328 (88.9)	326 (88.3)	0.05	0.82
≥ 60	54 (13.3)	46 (10.2)			41 (11.1)	43 (11.7)		
HR status								
ER+/PR+	283 (69.7)	345 (76.8)	5.56	0.02	270 (73.2)	268 (72.6)	0.03	0.87
ER-/PR+ and ER+/PR-	123 (30.3)	104 (23.2)			99 (26.8)	101 (27.4)		
DRFI								
< 24 months	171 (42.1)	160 (35.6)	3.78	0.05	147 (39.8)	156 (42.3)	0.45	0.50
≥ 24 months	235 (57.9)	289 (64.4)			222 (60.2)	213 (57.7)		
Visceral involvement								
Yes	241 (59.4)	216 (48.1)	10.85	<0.01	208 (56.4)	203 (55.0)	0.14	0.71
No	165 (40.6)	233 (51.9)			161 (43.6)	166 (45.0)		
Progression on prior (neo)adjuvant ET*			2.29	0.13			0.35	0.55
Yes	195 (48.0)	193 (43.0)			173 (46.9)	165 (44.7)		
No	210 (51.7)	256 (57.0)			196 (53.1)	204 (55.3)		
Number of metastatic sites	161 (39.7)	204 (45.4)	2.91	0.09	153 (41.5)	158 (42.8)	0.14	0.71
1	245 (60.3)	245 (54.6)			216 (58.5)	211 (57.2)		
≥ 2								
Objective response								
Yes	234 (57.6)	267 (59.5)	0.29	0.59	213 (57.7)	208 (56.4)	0.14	0.71
No	172 (42.4)	182 (40.5)			156 (42.3)	161 (43.6)		

*One patient in CT cohort had no information on prior (neo)adjuvant ET.

Figure S2. Progression-free survival (A) and overall survival (B) in CT-ET cohort versus CT cohort after propensity score matching

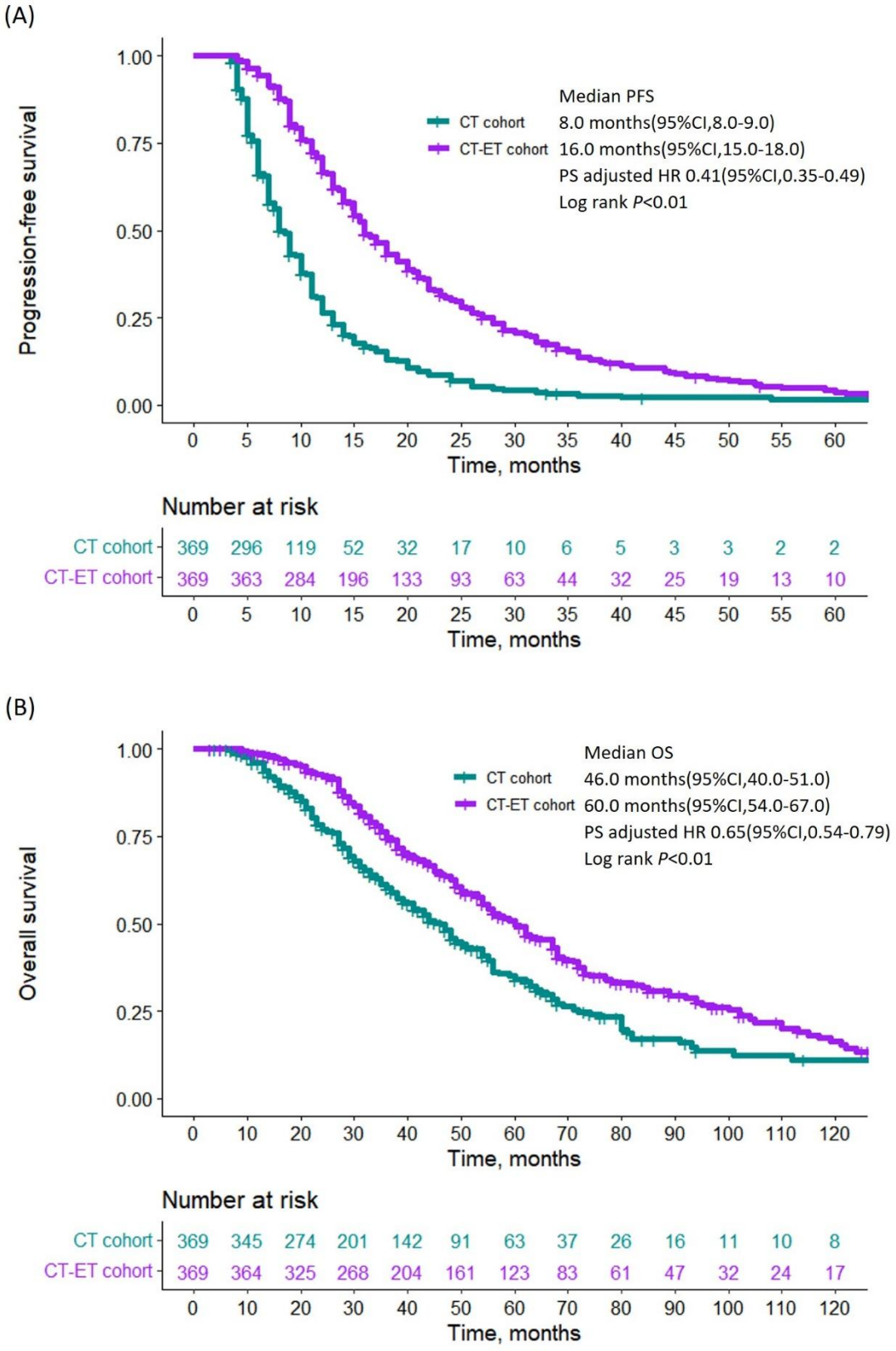

Table S7. Baseline characteristics of the total and propensity score matched populations in CT cohort and ET cohort

	Total population				Propensity score matched population			
	CT cohort (n = 406)	ET cohort (n = 527)	Statistic	*P* value	CT cohort (n = 305)	ET cohort (n = 305)	Statistic	*P* value
Age, years								
< 60	352 (86.7)	423 (80.3)	6.75	0.01	258 (84.6)	244 (80.0)	2.21	0.14
≥ 60	54 (13.3)	104 (19.7)			47 (15.4)	61 (20.0)		
HR status								
ER+/PR+	283 (69.7)	453 (86.0)	36 37	<0.01	233 (76.4)	238 (78.0)	0.23	0.63
ER-/PR+ and ER+/PR-	123 (30.3)	74 (14.0)			72 (23.6)	67 (22.0)		
DRFI								
< 24 months	171 (42.1)	135 (25.6)	28.33	< 0.01	100 (32.8)	95 (31.2)	0.19	0.66
≥ 24 months	235 (57.9)	392 (74.4)			205 (67.2)	210 (68.8)		
Visceral involvement								
Yes	241 (59.4)	195 (37.0)	46.05	<0.01	160 (52.5)	171 (56.1)	0.80	0.37
No	165 (40.6)	332 (63.0)			145 (47.5)	134 (43.9)		
Progression on prior (neo)adjuvant ET*								
No	210 (51.7)	237 (45.0)	4.23	0.04	150 (49.2)	155 (50.8)	0.16	0.69
Yes	195 (48.0)	289 (54.8)			155 (50.8)	150 (49.2)		
~~Unknown~~	~~1 (0.3)~~	~~1 (0.2)~~			~~0 (0)~~	~~0 (0)~~		
Number of metastatic sites	161 (39.7)	327 (62.1)	46.10	<0.01	144 (47.2)	132 (43.3)	0.95	0.33
1	245 (60.3)	200 (37.9)			161 (52.8)	173 (56.7)		
≥ 2								

*One patient in CT cohort and one patient in ET cohort had no information on prior (neo)adjuvant ET.

Figure S3. Progression-free survival (A) and overall survival (B) in ET cohort versus CT cohort after propensity score matching

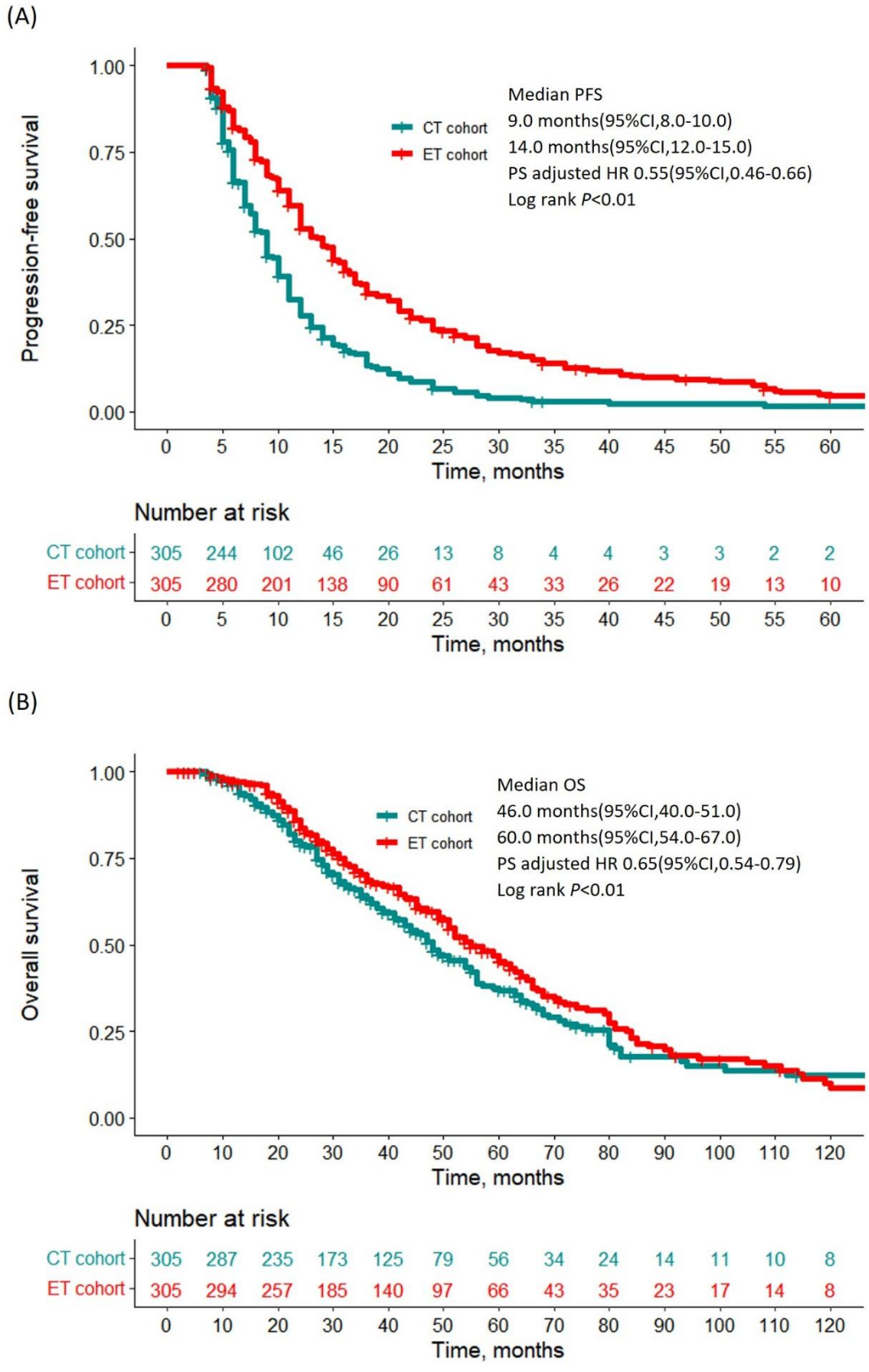

Table S8. Second and third line systemic treatment of patients with HR+/HER2- MBC

Subsequent treatment	Initial CT (n = 1215)		Initial ET (n = 662)	
	Second-line n (%)	Third-line n (%)	Second-line n (%)	Third-line n (%)
Any	923	513	406	283
Chemotherapy	583	266	260	148
T-based	255 (43.7)	98 (36.8)	156 (60.0)	72 (48.6)
N-based	123 (21.1)	68 (25.6)	35 (13.5)	29 (19.6)
Capecitabine	92 (15.8)	36 (13.5)	53 (20.4)	25 (16.9)
Gem-based	60 (10.3)	27 (10.2)	8 (3.1)	7 (4.7)
Others CT	53 (9.1)	37 (13.9)	8 (3.1)	15 (10.1)
Endocrine therapy	340	247	146	135
AI	202 (59.4)	148 (59.9)	76 (52.1)	68 (50.4)
Fulvestrant	48 (14.1)	39 (15.8)	23 (15.8)	26 (19.3)
Others	60 (17.6)	31 (12.6)	37 (25.3)	29 (21.5)
ET+ everolimus	17 (5.0)	24 (9.7)	8 (5.5)	6 (4.4)
ET+ CDK4/6 inhibitor	13 (3.8)	5 (2.0)	2 (1.4)	6 (4.4)