

Figure A1 A flow chart of this cohort

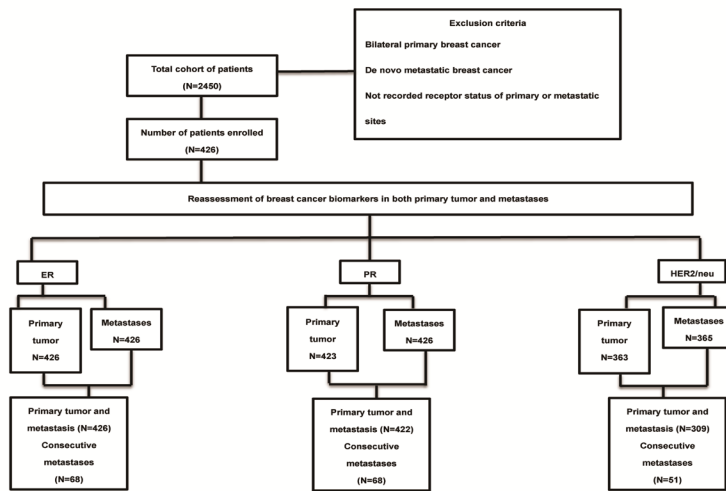
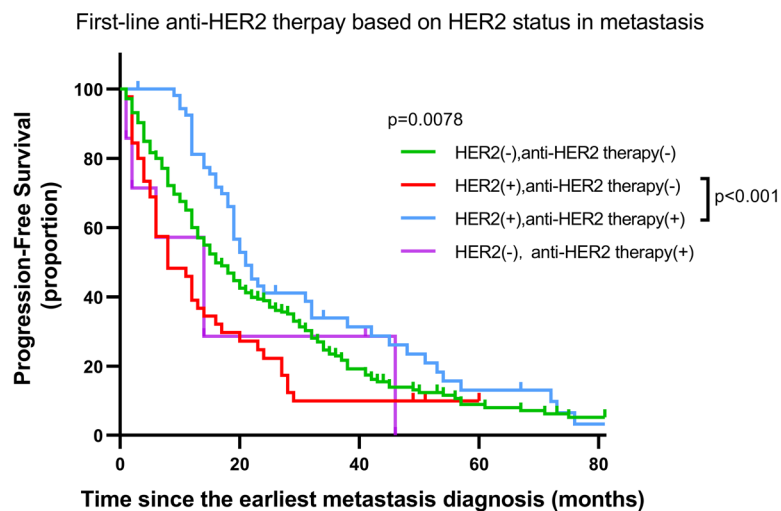


Figure. A2 Progression-free survival analysis stratified by HER2 status in metastasis and first-line anti-HER2 therapy



No. at risk

HER2(-), anti-HER2 therapy(-)	249	108	31	12	5
HER2(-), anti-HER2 targeted therapy(+)	7	4	0	0	0
HER2(+), anti-HER2 therapy(-)	45	12	4	1	0
HER2(+), anti-HER2 targeted therapy(+)	54	35	13	6	2

Table S1 Primary tumor characteristics						
	No	%				
Mean age (range), years						
At primary breast cancer diagnosis	45.9 (23–78)					
At the earliest relapse diagnosis	49.6 (24–79)					
Pathological T-stage						
Tis	5	1.2				
T1	144	33.8				
T2	222	52.1				
T3	32	7.5				
T4	3	0.7				
Tx	20	4.7				
Pathological N-stage						
N0	141	33.1				
N1	127	29.8				
N2	72	16.9				
N3	86	20.2				
Pathological type						
Invasive ductal carcinoma	365	85.7				
Invasive lobular carcinoma	15	3.5				
Other types	46	10.8				
ER status (10%)						
Positive	251	58.4				
Negative	179	41.6				
PR status (10%)						
Positive	213	50				
Negative	210	49.3				
Unknown	3	0.7				
HER2 status						
Positive	90	21.1				
Negative	273	64.1				
2+/Unknown	63	14.8				
Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2/neu, human epidermal growth factor receptor 2						

Table S2. Specific anatomical sites stratified by ER, PR, and HER2 status in primary tumor and metastasis

		ER							PR							HER2						
		Stable§		primary(+)/metastasis(-)		primary(-)/metastasis(+)		Total	Stable§		primary(+)/metastasis(-)		primary(-)/metastasis(+)		Total	Stable§		primary(+)/metastasis(-)		primary(-)/metastasis(+)		Total
		No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.
All sites		336	78.9	63	14.8	27	6.3	426	282	66.8	117	27.7	23	5.5	422	273	88.3	17	5.5	19	6.1	309
Lymphonode	Local	55	84.6	8	12.3	2	3.1	65	43	67.2	19	29.7	2	3.1	64	44	86.3	4	7.8	3	5.9	51
	Distant	38	67.9	14	25	4	7.1	56	38	67.9	17	30.3	1	1.8	56	33	78.6	4	9.5	5	11.9	42
Skin/soft tissue	Local	101	83.5	11	9.1	9	7.4	121	78	65	31	25.8	11	9.2	120	87	93.6	3	3.2	3	3.2	93
	Distant	3	60	2	40	0	0	5	2	40	3	60	0	0	5	2	66.7	1	33.3	0	0	3
Breast	Ipsilateral	12	100	0	0	0	0	12	8	66.7	4	33.3	0	0	12	8	88.9	0	0	1	11.1	9
	Contralateral	20	66.5	5	16.7	5	16.7	30	25	83.3	3	10	2	6.7	30	15	93.8	1	6.2	0	0	16
Bone		9	90	1	10	0	0	10	5	50	4	40	1	10	10	6	75	1	12.5	1	12.5	8
Lung		35	77.8	6	13.3	4	8.9	45	28	63.6	12	27.3	4	9.1	44	30	96.8	1	3.2	0	0	31
Liver		42	75	12	21.4	2	3.6	56	35	62.5	19	33.9	2	3.6	56	34	82.9	1	2.5	6	14.6	41
CNS		7	100	0	0	0	0	7	5	71.4	2	28.6	0	0	7	5	100	0	0	0	0	5
Pleuar		6	85.7	1	14.3	0	0	7	5	71.4	2	28.6	0	0	7	3	100	0	0	0	0	3
Other		8	66.7	3	25	1	8.3	12	10	83.4	1	8.3	1	8.3	12	5	71.4	1	14.3	1	14.3	7

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2

§, persistant positive/negative in primary and metastatic sites

Table S3. Association between the conversion of hormone receptor and clinicopathological variables (Multivariate Logistic Regression model)

Clinicopathological variables†	ER conversion									PR conversion								
	Any discordance‡			primary(+)-relapse(-)			primary(-)-relapse(+)			Any discordance‡			primary(+)-relapse(-)			primary(-)-relapse(+)		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Age at diagnosis (continuous)			0.726			0.482			0.113			0.067			0.142			0.468
Tumor size			0.606			0.855			0.654			0.13			0.457			0.359
T1 v Tis			0.1			0.327			0.199			0.384			0.737			0.239
T2 v Tis			0.182			0.659			0.121			0.684			0.522			0.968
T3 vTis			0.794			0.894			0.548			0.012			0.061			0.054
T4 vTis			0.403			0.53			0.616			0.258			0.322			0.651
Tx vTis			0.666			0.357			0.659			0.399			0.68			0.43
Lymphnode status			0.056			0.421			0.074			0.192			0.9			0.06
N1 v N0			0.096			0.174			0.413			0.088			0.708			0.031
N2 v N0			0.201			0.812			0.108			0.447			0.634			0.385
N3 v N0			0.04			0.179			0.13			0.199			0.94			0.403
Adjuvant chemotherapy (positive v negative)			0.148			0.447			0.176	2.841	1.015 to 7.952	0.047	4.268	1.217 to 14.965	0.023			0.738
Adjuvant endocrine therapy (positive v neg)	2.211	1.342 to 3.643	0.002	5.967	2.861 to 12.445	0.000	0.381	0.167 to 0.868	0.022	5.491	3.400 to 8.870	0.000	8.627	4.845 to 15.361	0.000			0.543
Adjuvant targeted therapy (positive v negative)			0.56			0.065			0.181			0.12			0.307			0.29
Adjuvant radiotherapy (positive v negative)			0.476			0.962			0.285			0.072			0.064			0.738
Abbreviations: ER, estrogen receptor; PR, progesterone receptor; OR, odds ratio, CI, confidence interval																		
‡Persistent positive/negative in primary and metastatic sites																		
† In Multivariate Logistic Regression model (forward stepwise procedure), the variables not included in the equation do not have Odds Ratio and Confidence Interval																		

Table S4. Progression-free survival analysis stratified by HER2 status in metastasis and first-line anti-HER2 therapy (Multivariable Model)

PFS (time since the earliest metastasis diagnosis)	No. of patients	No. of progression	Adjusted HR * 95% CI	P value
HER2 status in metastasis and first-line anti-HER2 therapy				
HER2 (-), anti-HER2 therapy (-)	256	205	1.754 (1.254 - 2.454)	0.001
HER2 (-), anti-HER2 therapy (+)	7	6	1.540 (0.639 - 3.542)	0.35
HER2 (+), anti-HER2 therapy (-)	46	40	1.821 (1.181 - 2.807)	0.007
HER2 (+), anti-HER2 therapy (+)	56	45	1.000(reference)	

*After adjustment for age of first metastasis diagnosis (continuous), ER and PR status in metastatic site, site of metastasis (local and distant metastasis) first-line therapy (chemotherapy and endocrine therapy)

Abbreviations: HER2 human epidermal growth factor receptor 2; HR hazard ratio; CI confidential Interval; PFS progression-free survival

Supporting information

Figure. A1 Flow chart of the study

Figure. A2 Progression-free survival analysis stratified by HER2 status in metastasis and first-line anti-HER2 therapy

Table. S1 Primary tumor characteristics

Table. S2 Specific anatomical sites stratified by ER, PR, and HER2 status in primary tumor and metastasis

Table. S3 Association between the conversion of hormone receptor status and clinicopathological variables (multivariable model)

Table. S4 Progression-free survival analysis stratified by HER2 status in metastasis and first-line anti-HER2 therapy (Multivariable Model)

Abbreviations: HER2 human epidermal growth factor receptor 2; HR hazard ratio; CI confidential Interval; PFS progression-free survival