

Supplementary Table 1. Detailed demographic, clinical, and histological data of the study patients and tumours at diagnosis according to the type of recurrence

	All (n = 512)	Primary tumours which gave rise to local recurrences (n = 145)	Primary tumours which gave rise to distant metastases (n = 367)
Age at diagnosis (years)			
Mean ± SD	55.8 ± 12.9	56.9 ± 14.1	55.4 ± 12.4
Median [min-max]	56.0 [25.0 - 89.0]	56.0 [26.0 - 89.0]	55.0 [25.0 - 87.0]
<i>P</i> -value			0.335
Unifocal tumour			
Yes	397 (77.5%)	123 (84.8%)	274 (79.3%)
No	115 (22.5%)	22 (15.2%)	93 (25.3%)
<i>P</i> -value			0.013
Histology			
IDC	412 (80.5%)	121 (83.4%)	291 (80.0%)
ILC	91 (17.8%)	22 (15.2%)	69 (18.8%)
Other	9 (1.8%)	2 (1.4%)	7 (1.9%)
<i>P</i> -value			0.560
Tumour Size (cm)			
Mean ± SD	2.7 ± 1.9	1.9 ± 1.4	3.0 ± 1.9
Median [min-max]	2.2 [0.1 - 10.5]	1.5 [0.1 - 10]	2.5 [0.2 - 10.5]
Missing data	6	0	6
<i>P</i> -value			< 0.001
E&E grade			
I	83 (16.4%)	38 (26.4%)	45 (12.5%)
II	264 (52.3%)	62 (43.1%)	202 (56.0%)
III	158 (31.3%)	44 (30.6%)	114 (31.6%)
Missing data	7	1	6
<i>P</i> -value			< 0.001
Glandular differentiation			
I	7 (1.4%)	6 (4.2%)	1 (0.3%)
II	146 (28.9%)	49 (34.0%)	97 (26.9%)
III	352 (69.7%)	89 (61.8%)	263 (72.9%)
Missing data	7	1	6
<i>P</i> -value			< 0.001
Nuclear grade			
I	18 (3.6%)	10 (6.9%)	8 (2.2%)
II	330 (65.3%)	93 (64.6%)	237 (65.7%)
III	157 (31.1%)	41 (28.5%)	116 (32.1%)
Missing data	7	1	6
<i>P</i> -value			0.032
Mitosis score			
I	237 (46.9%)	78 (54.2%)	159 (44.0%)
II	124 (24.6%)	25 (17.4%)	99 (27.4%)
III	144 (28.5%)	41 (28.5%)	103 (28.5%)
Missing data	7	1	6
<i>P</i> -value			0.039
Lymph node status			
N0-N0i+	235 (45.9%)	103 (71.1%)	132 (36.0%)
N1-N1mic	188 (36.7%)	37 (25.5%)	151 (41.1%)
N2-N3	89 (17.4%)	5 (3.4%)	84 (22.9%)
<i>P</i> -value			< 0.001
Disease stage			
I	165 (32.2%)	86 (59.3%)	79 (21.5%)
II	179 (35.0%)	30 (20.7%)	149 (40.6%)
III	128 (25.0%)	27 (18.6%)	101 (27.5%)
IV	40 (7.8%)	2 (1.4%)	38 (10.4%)
<i>P</i> -value			< 0.001
Oestrogen receptor expression			
Positive	413 (81.6%)	115 (79.9%)	298 (82.3%)
Negative	93 (18.4%)	29 (20.1%)	64 (17.7%)
Missing data	6	1	5
<i>P</i> -value			0.519
Progesterone receptor expression			
Positive	322 (66.4%)	98 (69.0%)	224 (76.7%)
Negative	163 (33.6%)	44 (31.0%)	119 (34.7%)
Missing data	27	3	24
<i>P</i> -value			0.432
HER2 status (IHC+/-FISH)			
0	201 (39.3%)	64 (44.1%)	137 (37.3%)

1+	155 (30.3%)	44 (30.3%)	111 (30.2%)
2+ non-amplified	75 (14.6%)	18 (12.4%)	57 (15.5%)
2+ amplified	14 (2.7%)	1 (0.7%)	13 (3.5%)
3+	67 (13.1%)	18 (12.4%)	49 (13.4%)
<i>P</i> -value			0.279
Time to recurrence (months)			
Mean \pm SD	72.3 \pm 50.8	88.2 \pm 56.1	66.0 \pm 47.2
Median [min-max]	60 [1.0 - 240.0]	77.0 [6.0 - 235.0]	60 [1.0 - 240.0]
<i>P</i> -value			< 0.001
HER2 status change between primary and recurrent tumour			
Stable HER2-negative	104 (20.3%)	29 (20.0%)	75 (20.4%)
Stable HER2-low	152 (29.7%)	39 (26.9%)	113 (30.8%)
Stable HER-positive	65 (12.7%)	17 (11.7%)	48 (13.1%)
HER2-negative to HER2-low	90 (17.6%)	32 (22.1%)	58 (15.8%)
HER2-negative to HER2-positive	8 (1.6%)	3 (2.1%)	5 (1.4%)
HER2-low to HER2-negative	67 (13.1%)	21 (14.5%)	46 (12.5%)
HER2-low to HER2-positive	10 (2.0%)	2 (1.4%)	8 (2.2%)
HER2-positive to HER2-negative	2 (0.4%)	1 (0.7%)	1 (0.3%)
HER2-positive to HER2-low	14 (2.7%)	1 (0.7%)	13 (3.5%)
<i>P</i> -value			0.303

E&E: Elston and Ellis; FISH: fluorescent in situ hybridisation; HER2: human epidermal growth factor receptor 2; IDC: invasive ductal carcinoma; IHC: immunohistochemistry; ILC: invasive lobular carcinoma; SD: standard deviation
In bold: *P*-values indicative of a statistical significance

Supplementary Table 2. Clinical, pathological, and immunohistochemical characteristics of breast cancer patients and tumours for the subgroup with HR-positive/HER2-negative tumours at diagnosis, by changes in the HER2 status and the type of relapse

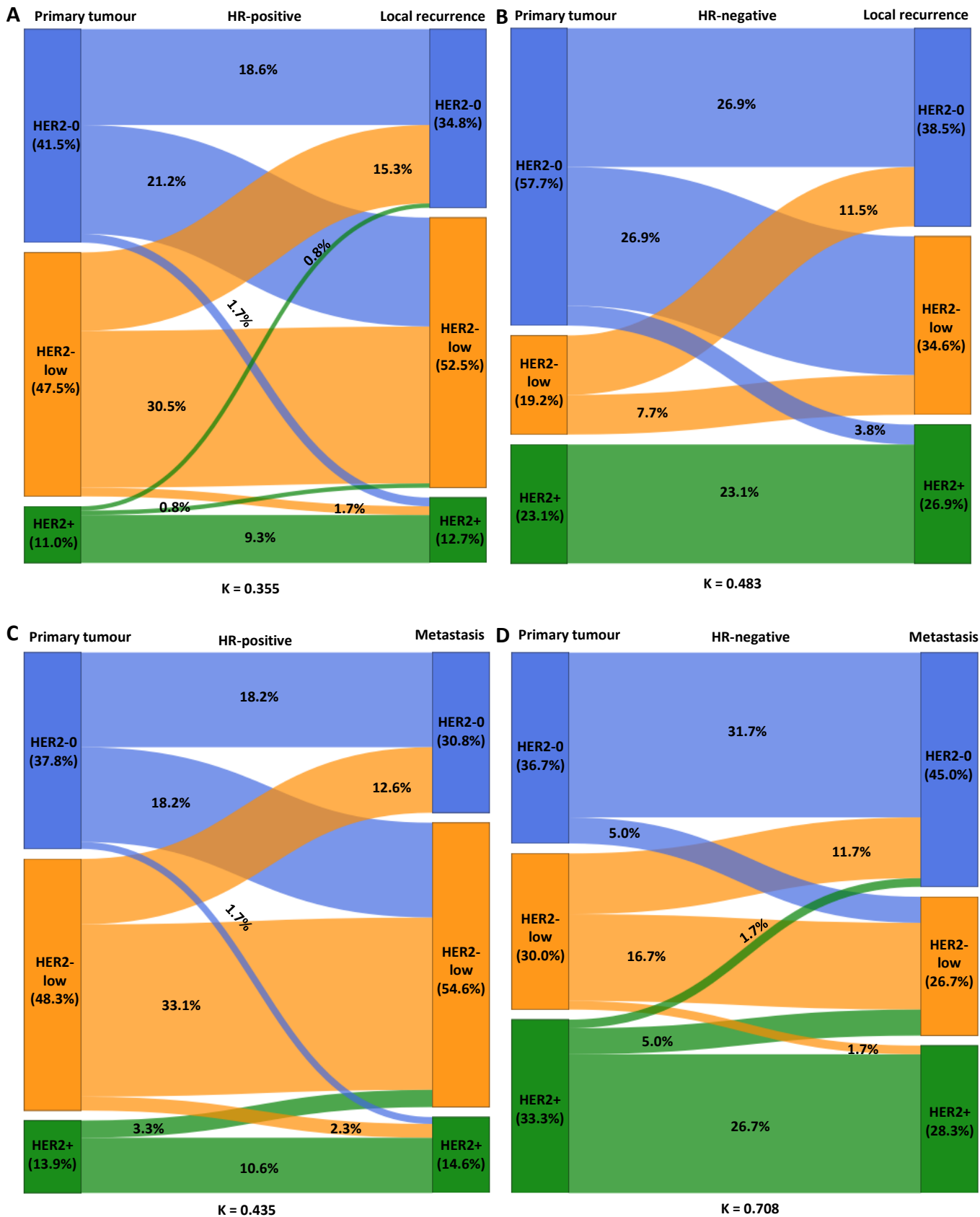
Parameter	All		Local recurrences		Distant metastases	
	Tumours which relapsed as HER2-low (n = 80)	Tumours which relapsed as HER2-negative (unchanged HER2 status) (n = 77)	Tumours which relapsed as HER2-low (n = 25)	Tumours which relapsed as HER2-negative (unchanged HER2 status) (n = 22)	Tumours which relapsed as HER2-low (n = 55)	Tumours which relapsed as HER2-negative (unchanged HER2 status) (n = 55)
Age at diagnosis (years)						
Mean ± SD	55.2 ± 10.9	57.8 ± 14.0	55.8 ± 10.1	63.2 ± 17.5	55.0 ± 11.3	55.6 ± 11.8
Median [min-max]	56.0 [29.0 - 81.0]	57.0 [34.0 - 89.0]	56.0 [38.0 - 79.0]	70.5 [34.0 - 89.0]	56.0 [29.0 - 81.0]	55.0 [36.0 - 87.0]
P-values		0.207		0.075		0.780
Unifocal tumour						
Yes	66 (82.5%)	62 (80.5%)	22 (88.0%)	20 (90.9%)	44 (80.0%)	42 (76.4%)
No	14 (17.5%)	15 (19.5%)	3 (12.0%)	2 (9.1%)	11 (20.0%)	13 (23.6%)
P-values		0.749		1.000		0.644
Histology						
IDC	56 (70.0%)	54 (70.1%)	19 (76.0%)	16 (72.7%)	37 (67.3%)	38 (69.1%)
ILC	22 (27.5%)	20 (26.0%)	6 (24.0%)	5 (22.7%)	16 (29.1%)	15 (27.3%)
Other	2 (2.5%)	3 (3.9%)	0 (0.0%)	1 (4.5%)	2 (3.6%)	2 (3.6%)
P-values		0.909		0.859		1.000
Tumour Size (cm)						
Mean ± SD	2.1 ± 1.3	2.7 ± 2.3	1.2 ± 0.6	1.6 ± 1.0	2.5 ± 1.4	3.2 ± 2.5
Median [min-max]	1.8 [0.4 - 6.5]	2.0 [0.1 - 10.5]	1.1 [0.4 - 2.8]	1.4 [0.1 - 4.3]	2.0 [0.7 - 6.5]	2.3 [0.2 - 10.5]
Missing data	3	1	0	0	3	1
P-value		0.162		0.253		0.351
E&E grade						
I	20 (25.0%)	17 (22.6%)	8 (32.0%)	7 (31.8%)	12 (21.8%)	10 (18.9%)
II	45 (56.3%)	38 (50.7%)	13 (52.0%)	10 (45.5%)	32 (58.2%)	28 (52.8%)
III	15 (18.8%)	20 (26.7%)	4 (16.0%)	5 (22.7%)	11 (20.0%)	15 (28.3%)
Missing data	0	2	0	0	0	2
P-values		0.500		0.926		0.598
Glandular differentiation						
I	2 (2.5%)	2 (2.6%)	2 (8.2%)	2 (9.1%)	0 (0.0%)	0 (0.0%)
II	26 (32.5%)	21 (27.6%)	8 (32.0%)	6 (27.3%)	18 (32.7%)	15 (27.8%)
III	52 (65.0%)	53 (69.7%)	15 (60.0%)	14 (63.6%)	37 (67.3%)	39 (72.2%)
Missing data	0	1	0	0	0	1
P-values		0.848		1.000		0.574
Nuclear grade						
I	6 (7.5%)	7 (9.2%)	3 (12.0%)	4 (18.2%)	3 (5.5%)	3 (5.6%)
II	58 (72.5%)	52 (68.4%)	19 (76.0%)	13 (59.1%)	39 (70.9%)	39 (72.2%)
III	16 (20.0%)	17 (22.4%)	3 (12.0%)	5 (22.7%)	13 (23.6%)	12 (22.2%)
Missing data	0	1	0	0	0	1
P-values		0.847		1.000		1.000
Mitosis score						
I	48 (60.0%)	39 (51.3%)	16 (64.0%)	15 (68.2%)	32 (58.2%)	24 (44.4%)
II-III	32 (40.0%)	37 (48.7%)	9 (36.0%)	7 (31.8%)	23 (41.8%)	30 (55.6%)

Missing data	0		1		0		0		0		1
<i>P</i> -values		0.275			0.763				0.151		
Mitotic index (/mm ²)											
Mean ± SD	3.5 ± 4.3		5.3 ± 6.8		4.7 ± 5.4		3.7 ± 4.4		3.0 ± 3.7		6.0 ± 7.6
Median [min-max]	1.9 [0.4 - 16.0]		0.4 [0.4 - 33.0]		1.7 [0.4 - 15.5]		1.7 [0.4 - 16.5]		1.9 [0.4 - 16.0]		3.8 [0.4 - 33.0]
Missing data	33		24		11		6		22		18
<i>P</i> -values		0.117			0.786				0.057		
Lymph node status											
N0-N0i+	47 (58.8%)		39 (50.7%)		20 (80.0%)		16 (72.7%)		27 (49.1%)		23 (41.8%)
N1-N1mic	20 (25.0%)		23 (29.9%)		4 (16.0%)		6 (27.3%)		16 (29.1%)		17 (30.9%)
N2-N3	13 (16.2%)		15 (19.4%)		1 (4.0%)		0 (0.0%)		12 (21.8%)		15 (27.3%)
<i>P</i> -values		0.595			0.851				0.710		
Disease stage											
I	37 (46.3%)		31 (40.3%)		19 (76.0%)		14 (63.7%)		18 (32.7%)		17 (30.9%)
II	26 (32.5%)		19 (24.7%)		5 (20.0%)		5 (22.7%)		21 (38.2%)		14 (25.5%)
III	16 (20.0%)		19 (24.7%)		1 (4.0%)		3 (13.6%)		15 (27.3%)		16 (29.1%)
IV	1 (1.3%)		8 (10.4%)		0 (0.0%)		0 (0.0%)		1 (1.8%)		8 (14.5%)
<i>P</i> -values		0.062			0.406				0.075		
Oestrogen receptor expression											
Negative	0 (0.0%)		1 (1.3%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		1 (1.8%)
Positive	80 (100%)		76 (98.7%)		25 (100%)		22 (100%)		55 (100%)		54 (98.2%)
Missing data	0		1		0		0		0		1
<i>P</i> -values		0.490			1.000				1.000		
Progesterone receptor expression											
Negative	15 (21.1%)		9 (12.5%)		1 (4.0%)		4 (19.0%)		14 (30.4%)		5 (9.8%)
Positive	56 (78.9%)		63 (87.5%)		24 (96.0%)		17 (81.0%)		32 (69.6%)		46 (90.2%)
Missing data	9		5		0		1		9		4
<i>P</i> -values		0.168			0.163				0.010		
Ki67 expression											
Mean ± SD	22.9 ± 14.5		27.8 ± 19.4		30.0 ± 9.4		25.3 ± 25.7		20.5 ± 15.3		29.7 ± 14.0
Median [min-max]	23.5 [1.0 - 50.0]		25.0 [1.0 - 90.0]		25.0 [20.0 - 40.0]		20.0 [8.0 - 90.0]		15.0 [1.0 - 50.0]		30.0 [1.0 - 50.0]
Missing data	60		56		20		13		40		43
<i>P</i> -values		0.479			0.177				0.123		
Metastatic site											
Liver	-		-		-		-		16 (29.1%)		14 (25.5%)
Bone	-		-		-		-		9 (16.4%)		16 (29.1%)
Skin and muscle	-		-		-		-		9 (16.4%)		7 (12.7%)
Lymph nodes	-		-		-		-		10 (18.2%)		6 (10.9%)
Lung and pleura	-		-		-		-		4 (7.3%)		4 (7.3%)
Gynaecological tract	-		-		-		-		3 (5.5%)		4 (7.3%)
Gastrointestinal tract	-		-		-		-		3 (5.5%)		0 (0.0%)
Brain	-		-		-		-		0 (0.0%)		0 (0.0%)
Other	-		-		-		-		1 (1.8%)		4 (7.3%)
<i>P</i> -values		-			-				0.344		

Time to recurrence (months)						
Mean \pm SD	93.7 \pm 52.8	73.8 \pm 52.2	108.4 \pm 57.8	67.0 \pm 52.5	87.0 \pm 49.5	76.5 \pm 52.3
Median [min-max]	84.0 [2.0 - 240.0]	60.0 [1.0 - 212.0]	110.0 [18.0 - 215.0]	49.0 [6.0 - 212.0]	84.0 [2.0 - 240.0]	60.0 [1.0 - 204.0]
<i>P</i> -values		0.014		0.006		0.275

BC: breast cancer; E&E: Elston and Ellis; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; SD: standard deviation

In bold: *P*-values indicative of a statistical significance



Supplementary Figure 1. Changes in the HER2 status between primary breast tumours and matched relapses (local or distant recurrence), stratified by the hormone receptor (HR) expression. Sankey diagrams illustrating the HER2 status changes for local recurrence (A-B) and distant metastases (C-D) according to the HR status, with specific percentages. HER2-0: HER2-negative, HER2+: HER2-positive