

Supplementary Table 1 Clinicopathological factors and outcomes (univariate analyses)

	Cases	TR (%)	LR (%)	DOM (%)	TRD (%)
	855	79	17	62	26
Age (years)					
≤39	59	12 (20)	1 (2)	11 (19)	4 (7)
>39	796	67 (8)	16 (2)	51 (6)	22 (3)
p-values		0.005	0.851	0.001	0.149
Adjuvant therapy					
No	22	5 (23)	1 (5)	4 (18)	1 (5)
Yes	833	74 (9)	16 (2)	58 (7)	25 (3)
p-values		0.001	0.221	0.003	0.294
Radiotherapy					
No	469	54 (12)	13 (3)	41 (9)	18 (4)
Yes	386	25 (7)	4 (1)	21 (5)	8 (2)
p-values		0.013	0.076	0.065	0.154
Hormone receptor status					
Negative	141	21 (15)	6 (4)	15 (11)	12 (9)
Positive	714	58 (8)	11 (2)	47 (7)	14 (2)
p-values		0.011	0.040	0.074	<0.001
HER2 status					
Negative	732	62 (9)	15 (2)	47 (6)	19 (3)
Positive	123	17 (14)	2 (2)	15 (12)	7 (6)
p-values		0.010	0.707	0.039	0.116
Ki-67 labeling index					
<20	420	20 (5)	3 (0.7)	17 (4)	7 (2)
≥20	435	59 (14)	14 (3)	45 (10)	19 (4)
p-values		<0.001	0.017	<0.001	0.027
Intrinsic subtype					
Luminal A	334	13 (4)	1 (0.3)	12 (4)	3 (1)
Luminal B (HER2-)	314	36 (12)	8 (3)	28 (9)	9 (3)
Luminal B (HER2+)	66	9 (14)	2 (3)	7 (11)	2 (3)
HER2	54	8 (15)	0	8 (15)	5 (9)
Basal-like	87	13 (15)	6 (7)	7 (8)	7 (8)
p-values		<0.001	0.002	0.011	<0.001
Adipose tissue invasion					
Absent	55	3 (5)	1 (2)	2 (4)	0
Present	800	76 (10)	16 (2)	60 (8)	26

p-values		0.270	0.904	0.078	NA
Blood vessel invasion					
Absent	570	42 (7)	8 (1)	34 (6)	11 (2)
Present	285	37 (13)	9 (3)	28 (10)	15 (5)
p-values		0.002	0.071	0.012	0.004
Fibrotic focus					
Absent	609	31 (5)	8 (1)	23 (4)	7 (1)
Present	246	48 (20)	9 (4)	39 (16)	19 (8)
p-values		<0.001	0.026	<0.001	<0.001
Histological grade					
Grade 1	264	10 (4)	2 (0.8)	8 (3)	2 (1)
Grade 2	352	25 (7)	4 (1)	21 (6)	4 (1)
Grade 3	239	44 (18)	11 (5)	33 (14)	20 (8)
p-values		<0.001	0.432	<0.001	<0.001
Tumor-infiltrating lymphocytes (%)					
0	6	1 (17)	0	1 (17)	0
1-19	725	72 (10)	14 (2)	58 (8)	25 (4)
>19	124	6 (5)	3 (2)	3 (2)	1 (0.8)
p-values		0.063	0.689	0.020	0.164
Invasive tumor size (mm)					
≤20	326	13 (4)	5 (2)	8 (3)	1 (0.3)
>20 - ≤50	483	52 (11)	9 (2)	43 (9)	18 (4)
>50	46	14 (30)	3 (7)	11 (24)	7 (15)
p-values		<0.001	0.117	<0.001	<0.001
Lymph vessel invasion					
Absent	570	40 (7)	8 (1)	32 (6)	14 (3)
Present	285	39 (14)	9 (3)	30 (11)	12 (4)
p-values		0.007	0.106	0.028	0.256
Muscle invasion					
Absent	845	75 (9)	17 (2)	58 (7)	23 (3)
Present	10	4 (40)	0	4 (40)	3 (30)
p-values		<0.001	NA	<0.001	<0.001
Perineural invasion					
Absent	702	58 (8)	14 (2)	44 (6)	13 (2)
Present	153	21 (14)	3 (2)	18 (12)	13 (9)
p-values		0.014	0.933	0.006	<0.001
Skin invasion					
Absent	771	62 (8)	14 (2)	44 (6)	17 (2)

Present	85	17 (20)	3 (2)	18 (12)	9 (11)
p-values		<0.001	0.933	0.006	<0.001
Tumor necrosis					
Absent	625	42 (7)	10 (2)	32 (5)	10 (2)
Present	230	37 (16)	7 (3)	30 (13)	16 (7)
p-values		<0.001	0.840	0.292	<0.001
Lymph node dissection					
SLN only	579	32 (6)	9 (2)	23 (4)	8 (1)
SLN and non-SLN	276	47 (17)	8 (3)	39 (14)	18 (7)
p-values		<0.001	0.193	<0.001	<0.001
UICC pN category					
pN0	610	35 (6)	10 (2)	25 (4)	9 (2)
pN1	163	25 (15)	4 (3)	21 (13)	7 (4)
pN2	54	10 (19)	0	10 (19)	6 (11)
pN3	28	9 (35)	3 (11)	6 (21)	4 (14)
p-values		<0.001	0.041	<0.001	<0.001
UICC pTNM stage classification					
IA/B	286	12 (4)	4 (1)	8 (3)	1 (0.4)
IIA	319	21 (7)	6 (2)	15 (5)	6 (2)
IIB	116	18 (16)	2 (2)	16 (14)	6 (5)
IIIA	42	6 (14)	1 (2)	5 (12)	1 (2)
IIIB	67	14 (21)	2 (3)	12 (18)	9 (13)
IIIC	25	8 (32)	2 (8)	6 (24)	3 (12)
p-values		<0.001	0.055	<0.001	<0.001

TR, tumor recurrence; LR, local recurrence; DOM, distant-organ metastasis; TRD, tumor-related death; NA, not available; SLN, sentinel lymph node; HER2-, HER2-negative; HER2+, HER2-positive

Supplementary Table 2 In situ HER hybridization and HER2 immunohistochemistry assessment according to the 2018 ASCO CAP recommendation

Group	Biology	HER2/CEP 17	Mean HER2 copy Number	2018 ASCO CAP recommendation
1	Classic HER2 amplified	≥ 2.0	≥ 4.0	Positive
2	Monosomy 17	≥ 2.0	< 4.0	Positive: IHC 3+
		≥ 2.0	< 4.0	Negative: IHC 1+ or 2+
3	Co-amplification, previously polysomy 17	< 2.0	≥ 6.0	Positive: IHC 2+ or 3+
		< 2.0	≥ 6.0	Negative: IHC 1+
4	Borderline	< 2.0	≥ 4.0 and < 6.0	Positive: IHC 3+
		< 2.0	≥ 4.0 and < 6.0	Negative: IHC 1+ or 2+
5	Classic HER2 nonamplified	< 2.0	< 4.0	Negative

HER, human epidermal growth factor receptor-2; IHC, immunohistochemistry

Supplementary Table 3 Multivariate analyses to identify factors predicting the clinical outcomes in patients with invasive carcinoma of no special type of the breast, according to the Ki-67 labeling index

Ki-67 labeling index, <20%					
		Tumor recurrence		Distant organ metastasis	
		Present	HR; 95% CI <i>P</i> -value	Present	HR; 95% CI <i>P</i> -value
420		20 (5)		17 (4)	
Model 1					
Conventional tumor budding grade					
Grade 1	96	0	1.0	0	1.0
Grade 2	103	4 (4)	1.0	3 (3)	1.0
Grade 3	221	16 (7)	1.1; 0.3-3.8 0.942	14 (6)	1.6; 0.4-7.0 0.527
Fibrotic focus					
Absent	329	6 (2)	1.0	5 (2)	1.0
Present	91	14 (15)	6.5; 1.6-19.3 <0.001	12 (13)	8.2; 2.8-23.7 <0.001
Invasive tumor size (mm)					
≤20	189	2 (1)	1.0	2 (1)	1.0
>20 - ≤50	216	13 (6)	4.4; 0.8-23.0 0.082	11 (5)	2.7; 0.5-14.2 0.248
>50	15	5 (33)	46.1; 5.6-367.9 <0.001	4 (27)	5.1; 1.6-17.0 0.008
Age (year)					
≤39	20	4 (20)	1.0	4 (20)	1.0
>39	400	16 (4)	0.2; 0.04-0.8 0.020	13 (3)	0.2; 0.04-0.6 0.005
Model 2					
Proposed tumor budding grading system					
Grade I	88	0	1.0	0	1.0
Grade II	288	11 (4)	1.0	9 (3)	1.0
Grade III	44	9 (21)	4.0; 1.1-14.4 0.032	8 (18)	6.9; 2.5-19.1 <0.001
Invasive tumor size (mm)					
≤20	189	2 (1)	1.0	2 (1)	1.0
>20 - ≤50	216	13 (6)	5.4; 0.9-30.1	11 (5)	5.0; 0.8-31.3

No	257	42	1.0	12	1.0	30	1.0	13	1.0
		(16)		(5)		(12)		(5)	
Yes	178	17	0.5	2	0.2	15	0.5	6	0.5
		(10)	0.3-0.9	(1)	0.04-0.9	(8)	0.3-1.1	(3)	0.1-1.6
			0.020		0.034		0.087		0.228
Tumor-infiltrating lymphocytes (%)									
0	1	1	1.0	0	1.0	1	0	0	1.0
		(100)				(100)			
1-19	346	54	1.0	12	1.0	42	0.2	19	1.0
		(16)		(4)		(12)	0.02-2.8	(6)	
							0.249		
>19	88	4	0.3	2	0.8	2	0.05	0	NA
		(5)	0.09-0.9	(2)	0.2-4.1	(2)	0.001-0.8		
			0.026		0.772		0.033		
Muscle invasion									
Absent	431	56	1.0	14	1.0	42	1.0	16	1.0
		(13)		(3)		(10)		(4)	
Present	4	3	4.2	0	NA	3	3.7	3	22.8
		(75)	1.1-15.8			(75)	0.9-15.3	(75)	3.1-167.2
			0.035				0.072		0.002
UICC pN category									
pN0	296	27	1.0	8	1.0	19	1.0	6	1.0
		(9)		(3)		(6)		(2)	
pN1	84	18	1.9	4	1.4	14	2.1	6	2.6
		(21)	0.6-5.7	(5)	0.4-5.1	(17)	0.6-7.7	(7)	0.8-9.2
			0.246		0.569		0.250		0.129
pN2	36	8	1.7	0	1.4	8	2.2	5	2.7
		(22)	0.4-6.5		0.4-5.1	(22)	0.5-10.7	(14)	0.5-13.9
			0.449		0.569		0.317		0.243
pN3	19	6	3.5	2	6.2	4	3.4	2	4.8
		(32)	0.9-14.2	(11)	1.3-28.5	(21)	0.6-18.7	(11)	0.7-32.2
			0.078		0.019		0.153		0.105
Perineural invasion									
Absent	360	45	1.0	13	1.0	32	1.0	8	1.0
		(13)		(4)		(9)		(2)	
Present	75	14	1.2	1	0.2	13	1.9	11	6.7
		(19)	0.6-2.4	(1)	0.02-1.6	(17)	0.8-4.2	(15)	2.0-22.1
			0.688		0.133		0.121		0.002

Hormone receptor status									
Negative	118	18	1.0	4	1.0	14	1.0	9	1.0
		(15)		(3)		(12)		(8)	
Positive	317	41	0.8	10	0.9	31	0.7	10	0.2
		(13)	0.4-1.5	(3)	0.2-4.1	(10)	0.4-1.5	(3)	0.04-0.7
			0.437		0.944		0.346		0.014
Histological grade									
Grade 1	54	4	1.0	2	1.0	2	1.0	0	1.0
		(7)		(4)		(4)			
Grade 2	175	15	0.8	2	0.3	13	1.2	2	1.0
		(9)	0.3-2.5	(1)	0.04-2.0	(7)	0.3-5.7	(1)	
			0.667		0.196		0.806		
Grade 3	206	40	1.4	10	3.1	30	1.6	17	9.5
		(19)	0.4-4.5	(5)	0.9-10.9	(15)	0.3-7.8	(8)	1.4-65.4
			0.560		0.074		0.543		0.021
Model 2									
Proposed tumor budding grading system									
Grade I	76	1	1.0	0	1.0	1	1.0	1	1.0
		(1)				(1)		(1)	
Grade II	293	35	6.9	10	1.0	25	5.0	8	0.8
		(12)	0.9-52.8	(3)		(9)	0.6-39.2	(3)	0.1-7.2
			0.060				0.126		0.865
Grade III	66	23	17.1	4	2.2	19	14.0	10	4.3
		(35)	2.0-123.9	(6)	0.6-7.9	(29)	1.7-118.7	(15)	1.3-15.4
			0.008		0.224		0.016		0.019
Adjuvant therapy									
No	12	4	1.0	1	1.0	3	1.0	0	1.0
		(33)		(8)		(25)			
Yes	423	55	0.1	13	0.2	42	0.1	19	NA
		(13)	0.04-0.4	(3)	0.03-2.3	(10)	0.02-0.4	(5)	
			0.001		0.200		0.002		
Tumor-infiltrating lymphocytes (%)									
0	1	1	1.0	0	1.0	1	1.0	0	1.0
		(100)				(100)			
1-19	346	54	1.0	12	1.0	42	0.1	19	1.0
		(16)		(4)		(12)	0.001-1.5	(6)	
							0.101		
>19	88	4	0.3	2	0.6	2	0.02	0	NA

		(5)	0.09-0.9 0.026	(2)	0.1-3.1 0.579	(2)	0.001-0.4 0.010		
Muscle invasion									
Absent	431	56 (13)	1.0	14 (3)	1.0	42 (10)	1.0	16 (4)	1.0
Present	4	3 (75)	4.7 1.2-18.2 0.024	0	NA	3 (75)	4.4 1.0-19.1 0.045	3 (75)	40.2 4.7-349.3 <0.001
Radiotherapy									
No	257	42 (16)	1.0	12 (5)	1.0	30 (12)	1.0	13 (5)	1.0
Yes	178	17 (10)	0.5 0.3-0.9 0.029	2 (1)	0.2 0.05-1.1 0.053	15 (8)	0.6 0.3-1.1 0.107	6 (3)	0.6 0.2-1.9 0.388
Perineural invasion									
Absent	360	45 (13)	1.0	13 (4)	1.0	32 (9)	1.0	8 (2)	1.0
Present	75	14 (19)	1.0 0.5-2.1 0.955	1 (1)	0.2 0.02-1.6 0.125	13 (17)	1.6 0.7-3.7 0.256	11 (15)	6.1 1.7-21.4 0.005
Hormone receptor status									
Negative	118	18 (15)	1.0	4 (3)	1.0	14 (12)	1.0	9 (8)	1.0
Positive	317	41 (13)	0.7 0.3-1.3 0.243	10 (3)	0.9 0.2-4.0 0.854	31 (10)	0.5 0.2-1.3 0.149	10 (3)	0.1 0.03-0.6 0.007
Histological grade									
Grade 1	54	4 (7)	1.0	2 (4)	1.0	2 (4)	1.0	0	1.0
Grade 2	175	15 (9)	0.8 0.2-2.4 0.622	2 (1)	0.3 0.04-2.2 0.240	13 (7)	1.1 0.3-5.2 0.867	2 (1)	1.0
Grade 3	206	40 (19)	1.3 0.4-4.1 0.628	10 (5)	3.7 1.0-13.8 0.045	30 (15)	1.5 0.3-7.0 0.632	17 (8)	9.6 1.5-64.2 0.020

HR, hazard ratio; CI, confidence interval; TR, tumor recurrence; LR, local recurrence; DOM, distant-organ metastasis; TRD, tumor-related death; +, present

Supplementary Table 4 Multivariate analyses to identify predictors of the clinical outcomes in patients with invasive carcinoma of no special type of the breast according to the tumor histological grade

Histological grade 1					
Tumor recurrence					
	Cases	TRR (%)	HR	95% CI	p-value
	264	10 (4)			
Model 1					
Conventional tumor budding grade					
Grade 1	94	0	1.0		
Grade 2	71	2 (3)	1.0		
Grade 3	99	8 (8)	2.8	0.4-17.5	0.278
Fibrotic focus					
Absent	231	4 (2)	1.0		
Present	33	6 (18)	5.3	1.3-22.0	0.024
Model 2					
Proposed tumor budding grading system					
Grade I	90	0	1.0		
Grade II	160	6 (4)	1.0		
Grade III	14	4 (19)	3.4	0.7-16.4	0.136
Blood vessel invasion					
Absent	184	3 (2)	1.0		
Present	80	7 (9)	6.0	1.5-23.6	0.010
Radiotherapy					
No	133	8 (6)	1.0		
Yes	131	2 (2)	0.1	0.02-0.9	0.048
UICC pN category					
pN0	215	8 (4)	1.0		
pN1	40	0	1.0		
pN2	7	1 (14)	3.6	0.2-81.9	0.427
pN3	2	1 (50)	15.0	1.1-205.7	0.044
Histological grade 2					
	Tumor recurrence			Distant organ metastasis	
		Present	HR; 95% CI	Present	HR; 95% CI
			P-value		P-value
	420	20 (5)		17 (4)	
Model 1					
Conventional tumor budding grade					
Grade 1	96	0	1.0	0	1.0

Grade 2	103	4 (4)	1.0	3 (3)	1.0
Grade 3	221	16 (7)	3.0; 0.8-10.4	14 (6)	3.2; 0.7-14.2
			0.090		0.114
Fibrotic focus					
Absent	329	6 (2)	1.0	5 (2)	1.0
Present	91	14 (15)	2.8; 1.3-6.4	12 (13)	3.7; 1.5-9.0
			0.010		0.004
Muscle invasion					
Absent	349	23 (7)	1.0	19 (5)	1.0
Present	3	2 (67)	10.4; 2.5-47.9	2 (67)	13.5; 3.0-59.7
			0.001		<0.001
Invasive tumor size (mm)					
≤20	189	2 (1)	1.0	2 (1)	1.0
>20 - ≤50	216	13 (6)	2.8; 0.6-12.6	11 (5)	1.5; 0.3-7.0
			0.182		0.591
>50	15	5 (33)	5.2; 1.7-15.6	4 (27)	4.5; 1.3-15.6
			0.003		0.017
Model 2					
Proposed tumor budding grading system					
Grade I	41	0	1.0	0	1.0
Grade II	260	5 (4)	1.0	10 (4)	1.0
Grade III	51	12 (24)	5.4; 2.4-12.1	11 (22)	6.6; 2.8-16.2
			<0.001		<0.001
Muscle invasion					
Absent	349	23 (7)	1.0	19 (5)	1.0
Present	3	2 (67)	7.2; 1.5-13.7	2 (67)	8.4; 1.8-38.8
			0.007		0.006
Invasive tumor size (mm)					
≤20	189	2 (1)	1.0	2 (1)	1.0
>20 - ≤50	216	13 (6)	2.9; 0.6-13.7	11 (5)	1.7; 1.4-7.9
			0.160		0.536
>50	15	5 (33)	4.5; 1.5-13.7	4 (27)	4.0; 1.1-14.1
			0.007		0.030
Histological grade 3					
Cases			No. of patients (%)		
		TR		LR	DOM
	+	HR	+	HR	+
		95%CI		95%CI	
		P-value		P-value	
239	44		11	33	20
	(18)		(5)	(14)	(8)

0	1	1	1.0	0	1.0	1	1.0	0	1.0
		(100)				(100)			
1-19	124	38	0.5	8	1.0	30	0.5	19	1.0
		(24)	0.04-5.2	(5)		(19)	0.03-5.9	(12)	
			0.530				0.560		
>19	76	5	0.3	3	0.9	2	0.2	1	0.1
		(7)	0.1-0.9	(4)	0.2-3.9	(3)	0.04-0.8	(1)	0.02-1.2
			0.046		0.950		0.020		0.077
Blood vessel invasion									
Absent	161	23	1.0	4	1.0	19	1.0	9	1.0
		(14)		(3)		(12)		(6)	
Present	78	21	1.5	7	4.5	14	0.9	11	1.1
		(27)	0.7-3.2	(9)	1.2-16.8	(18)	0.3-2.4	(14)	0.3-3.7
			0.321		0.025		0.812		0.884
Muscle invasion									
Absent	235	42	1.0	11	1.0	31	1.0	18	1.0
		(18)		(5)		(13)		(8)	
Present	4	2	2.9	0	NA	2	4.7	2	6.3
		(50)	0.6-15.1			(50)	1.1-21.1	(50)	1.2-32.0
			0.201				0.042		0.027
Perineural invasion									
Absent	201	32	1.0	10	1.0	22	1.0	10	1.0
		(16)		(5)		(11)		(5)	
Present	38	12	1.3	1	0.2	11	2.3	10	12.5
		(32)	0.6-2.9	(3)	0.02-1.6	(29)	0.9-5.9	(26)	2.2-15.6
			0.498		0.114		0.079		<0.001
Hormone receptor status									
Negative	115	18	1.0	5	1.0	13	1.0	10	1.0
		(16)		(4)		(11)		(9)	
Positive	124	26	0.8	6	0.8	20	0.9	10	0.3
		(21)	0.4-1.8	(5)	0.2-3.3	(16)	0.4-2.5	(8)	0.1-0.9
			0.609		0.800		0.929		0.029
Model 2									
Proposed tumor budding grading system									
Grade I	33	1	1.0	0	1.0	1	1.0	1	1.0
		(3)				(3)		(3)	
Grade II	161	27	2.9	7	1.0	20	2.0	10	0.8
		(17)	0.4-22.5	(4)		(12)	0.2-17.6	(6)	0.1-7.3
			0.313				0.518		0.873
Grade III	45	16	5.5	4	2.8	12	3.2	9	3.8
		(36)	0.6-45.9	(9)	0.6-12.8	(27)	0.3-32.2	(20)	1.4-10.1

Absent	201	32	1.0	10	1.0	22	1.0	10	1.0
		(16)		(5)		(11)		(5)	
Present	38	12	1.2	1	0.2	11	2.1	10	5.4
		(32)	0.5-2.8	(3)	0.02-1.4	(29)	0.8-5.5	(26)	2.2-13.6
			0.643		0.101		0.113		<0.001
Hormone receptor status									
Negative	115	18	1.0	5	1.0	13	1.0	10	1.0
		(16)		(4)		(11)		(9)	
Positive	124	26	0.8	6	0.8	20	0.9	10	0.4
		(21)	0.4-1.8	(5)	0.2-3.8	(16)	0.4-2.4	(8)	0.1-0.9
			0.593		0.817		0.855		0.044

HR, hazard ratio; CI, confidence interval; TR, tumor recurrence; LR, local recurrence; DOM, distant-organ metastasis; TRD, tumor-related death; +, present

Supplementary Table 5 Analyses to identify the prognostic power of the conventional tumor budding grade in cases of invasive carcinoma of no special type of the breast (Overall)

Univariate analyses					
	Cases	TR (%)	p-values	TRD (%)	p-values
	855	79		26	
Peripheral tumor budding (PTB)					
Grade 1	183	3 (2)		1 (0.6)	
Grade 2	208	13(6)	0.022	4 (2)	0.233
Grade 3	464	63 (14)	0.003	21 (5)	0.059
P for trend			<0.001		0.005
Intra-tumor tumor budding (ITB)					
Grade 1	225	10(4)		4 (2)	
Grade 2	218	5 (2)	0.335	1 (0.5)	0.261
Grade 3	412	64 (16)	<0.001	21 (6)	0.004
P for trend			<0.001		0.006
Multivariate analyses					
		HR for trend	95 % CI for trend		p for trend
Tumor recurrence					
PTB grade (1, 2, 3)		1.9	1.1–3.0		0.015
ITB grade (1, 2, 3)		1.7	1.1–2.7		0.011
Tumor-related death					
PTB grade (1, 2, 3)		2.0	0.9–5.0		0.098
ITB grade (1, 2, 3)		1.6	0.8–3.2		0.215

TR, tumor recurrence; TRD, tumor-related death; HR, hazard ratio; CI, confidence interval.