Stromal Tumor-infiltrating Lymphocytes in NRG Oncology/NSABP B-31 Adjuvant Trial for Early-stage HER2-positive Breast Cancer

Rim S. Kim, Nan Song, Patrick G. Gavin, et al.

Table of Contents **Page**

Supplementary Table 1. Multivariate survival analyses assessment of sTILs as semi-continuous variable in NSABP B-31

		HR	LB	UB	p-value
sTILs (semi-continuous)	sTILs	0.42	0.27	0.64	<0.001
Treatment (reference: ACT)	ACTH	0.53	0.44	0.62	<0.001
ER (reference: negative)	ER positive	0.77	0.65	0.91	0.003
Node (reference: node 1-3	Node 4-9	1.35	1.11	1.64	0.003
	Node≥ 10	2.34	1.86	2.95	<0.001
Size (reference: size ≤2)	Size 2-5	1.33	1.10	1.61	0.003
	Size >5	1.51	1.12	2.03	0.006

Semi-continuous refers to assigning the % of sTILs at 0%, 5%, 10 %, 20%, 30%, etc., as seen in Supplementary Table 3.

Supplementary Table 2. Multivariate survival analyses for the combined treatment arms with dichotomized sTILs in NSABP B-31

		HR	LB	UB	p-value
sTILs (reference: ≤50)	sTILs >50	0.65	0.49	0.86	0.003
Treatment (reference: ACT)	ACTH	0.53	0.44	0.63	<0.001
ER (reference: negative)	ER positive	0.80	0.68	0.95	0.012
Node (reference: node 1-3	Node 4-9	1.34	1.10	1.62	0.004
	Node≥ 10	2.29	1.82	2.89	<0.001
Size (reference: size ≤2)	Size 2-5	1.33	1.10	1.61	0.003
	Size >5	1.54	1.15	2.07	0.004

Supplementary Table 3. Distribution of sTILs scores with other pathological variables, single-nucleotide polymorphism, mutation, subtype, or signatures in NSABP B-31

	sTILs Scores											
	0	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%	P-value
Variables												
Treatment												
ACT	36 (48%)	121 (47.5%)	217 (52%)	84 (41.8%)	105 (50.7%)	63 (56.8%)	48 (52.7%)	38 (46.9%)	48 (51.1%)	18 (43.9%)	2 (25%)	0.998
ACTH	39 (52%)	134 (52.5%)	200 (48%)	117 (58.2%)	102 (49.3%)	48 (43.2%)	43 (47.3%)	43 (53.1%)	46 (48.9%)	23 (56.1%)	6 (75%)	
Age												
Mean(SD)	50.4 (10.7%)	49.4 (10.2%)	49.1 (10.0%)	49.4 (9.4%)	50.0 (10.1%)	48.6 (11.0%)	50.4 (9.8%)	49.1 (9.0%)	50.9 (10.3%)	51.9 (9.1%)	52.9 (10.9%)	0.10
Median(range)	49 (27-74)	49 (28-76)	49 (27-77)	48 (26-76)	51 (26-78)	49 (26-75)	50 (31-75)	50 (32-70)	52 (33-74)	53 (33-73)	54 (37-70)	
Race												
White	69 (92%)	217 (85.1%)	365 (87.5%)	171 (85.1%)	171 (82.6%)	88 (79.3%)	69 (75.8%)	68 (84%)	73 (77.7%)	31 (75.6%)	4 (50%)	<0.001
Others	6 (8%)	38 (14.9%)	49 (11.8%)	30 (14.9%)	36 (17.4%)	23 (20.7%)	21 (23.1%)	12 (14.8%)	21 (22.3%)	10 (24.4%)	4 (50%)	
Unknown	0 (0%)	0 (0%)	3 (0.7%)	0 (0%)	0 (0%)	0 (0%)	1 (1.1%)	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)	
Node												
1-3	45 (60%)	157 (61.6%)	245 (58.8%)	106 (52.7%)	105 (50.7%)	61 (55%)	44 (48.4%)	45 (55.6%)	56 (59.6%)	20 (48.8%)	7 (87.5%)	0.33
4-9	18	75	123	58	70	32	33	26	33	13	1	

	(24%)	(29.4%)	(29.5%)	(28.9%)	(33.8%)	(28.8%)	(36.3%)	(32.1%)	(35.1%)	(31.7%)	(12.5%)	
≥10	12 (16%)	23 (9%)	49 (11.8%)	37 (18.4%)	32 (15.5%)	18 (16.2%)	14 (15.4%)	10 (12.3%)	5 (5.3%)	8 (19.5%)	0 (0%)	
Tumor size												
≤2	31 (41.3%)	84 (32.9%)	162 (38.8%)	64 (31.8%)	79 (38.2%)	41 (36.9%)	30 (33%)	31 (38.3%)	41 (43.6%)	14 (34.1%)	6 (75%)	0.099
2-5	35 (46.7%)	143 (56.1%)	210 (50.4%)	118 (58.7%)	108 (52.2%)	62 (55.9%)	52 (57.1%)	47 (58%)	44 (46.8%)	25 (61%)	2 (25%)	
>5	9 (12%)	28 (11%)	45 (10.8%)	19 (9.5%)	20 (9.7%)	8 (7.2%)	9 (9.9%)	3 (3.7%)	9 (9.6%)	2 (4.9%)	0 (0%)	
ER												
Negative	27 (36%)	81 (31.8%)	162 (38.8%)	81 (40.3%)	100 (48.3%)	65 (58.6%)	61 (67%)	48 (59.3%)	68 (72.3%)	30 (73.2%)	6 (75%)	<0.001
Positive	48 (64%)	174 (68.2%)	254 (60.9%)	120 (59.7%)	107 (51.7%)	45 (40.5%)	30 (33%)	33 (40.7%)	26 (27.7%)	11 (26.8%)	2 (25%)	
Unknown	0 (0%)	0 (0%)	1 (0.2%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
HER2 IHC												
0	3 (4%)	7 (2.7%)	2 (0.5%)	4 (2%)	0 (0%)	0 (0%)	3 (3.3%)	3 (3.7%)	0 (0%)	1 (2.4%)	1 (12.5%)	<0.001
1	8 (10.7%)	19 (7.5%)	41 (9.8%)	10 (5%)	12 (5.8%)	4 (3.6%)	3 (3.3%)	3 (3.7%)	4 (4.3%)	1 (2.4%)	0 (0%)	
2	8 (10.7%)	26 (10.2%)	33 (7.9%)	20 (10%)	17 (8.2%)	14 (12.6%)	3 (3.3%)	4 (4.9%)	3 (3.2%)	2 (4.9%)	0 (0%)	
3	51 (68%)	189 (74.1%)	330 (79.1%)	160 (79.6%)	173 (83.6%)	86 (77.5%)	74 (81.3%)	65 (80.2%)	82 (87.2%)	36 (87.8%)	6 (75%)	
Unknown	5 (6.7%)	14 (5.5%)	11 (2.6%)	7 (3.5%)	5 (2.4%)	7 (6.3%)	8 (8.8%)	6 (7.4%)	5 (5.3%)	1 (2.4%)	1 (12.5%)	
HER2 FISH												

0	15 (20%)	34 (13.3%)	56 (13.4%)	28 (13.9%)	17 (8.2%)	8 (7.2%)	6 (6.6%)	8 (9.9%)	5 (5.3%)	3 (7.3%)	1 (12.5%)	<0.001
1	56 (74.7%)	208 (81.6%)	350 (83.9%)	166 (82.6%)	186 (89.9%)	96 (86.5%)	77 (84.6%)	67 (82.7%)	84 (89.4%)	37 (90.2%)	6 (75%)	
Unknown	4 (5.3%)	13 (5.1%)	11 (2.6%)	7 (3.5%)	4 (1.9%)	7 (6.3%)	8 (8.8%)	6 (7.4%)	5 (5.3%)	1 (2.4%)	1 (12.5%)	
HER2 Copy Number												
0	7 (9.3%)	10 (3.9%)	17 (4.1%)	10 (5%)	5 (2.4%)	1 (0.9%)	3 (3.3%)	2 (2.5%)	0 (0%)	1 (2.4%)	1 (12.5%)	0.006
1	8 (10.7%)	23 (9%)	38 (9.1%)	17 (8.5%)	13 (6.3%)	7 (6.3%)	3 (3.3%)	6 (7.4%)	5 (5.3%)	2 (4.9%)	0 (0%)	
2	11 (14.7%)	49 (19.2%)	90 (21.6%)	35 (17.4%)	40 (19.3%)	30 (27%)	14 (15.4%)	13 (16%)	13 (13.8%)	9 (22%)	3 (37.5%)	
3	45 (60%)	160 (62.7%)	261 (62.6%)	132 (65.7%)	145 (70%)	66 (59.5%)	63 (69.2%)	54 (66.7%)	71 (75.5%)	28 (68.3%)	3 (37.5%)	
Unknown	4 (5.3%)	13 (5.1%)	11 (2.6%)	7 (3.5%)	4 (1.9%)	7 (6.3%)	8 (8.8%)	6 (7.4%)	5 (5.3%)	1 (2.4%)	1 (12.5%)	
FCGR2A												
131 H/H	13 (17.3%)	50 (19.6%)	71 (17%)	43 (21.4%)	37 (17.9%)	23 (20.7%)	21 (23.1%)	16 (19.8%)	20 (21.3%)	12 (29.3%)	1 (12.5%)	0.37
131 H/R	32 (42.7%)	89 (34.9%)	156 (37.4%)	72 (35.8%)	84 (40.6%)	41 (36.9%)	34 (37.4%)	32 (39.5%)	37 (39.4%)	15 (36.6%)	2 (25%)	
131 R/R	11 (14.7%)	49 (19.2%)	83 (19.9%)	41 (20.4%)	35 (16.9%)	19 (17.1%)	15 (16.5%)	19 (23.5%)	11 (11.7%)	8 (19.5%)	2 (25%)	
Unknown	19 (25.3%)	67 (26.3%)	107 (25.7%)	45 (22.4%)	51 (24.6%)	28 (25.2%)	21 (23.1%)	14 (17.3%)	26 (27.7%)	6 (14.6%)	3 (37.5%)	
FCGR2A												
131 high	43 (57.3%)	138 (54.1%)	239 (57.3%)	113 (56.2%)	119 (57.5%)	60 (54.1%)	49 (53.8%)	51 (63%)	48 (51.1%)	23 (56.1%)	4 (50%)	0.22

131 low	13 (17.3%)	50 (19.6%)	71 (17%)	43 (21.4%)	37 (17.9%)	23 (20.7%)	21 (23.1%)	16 (19.8%)	20 (21.3%)	12 (29.3%)	1 (12.5%)	
Unknown	19 (25.3%)	67 (26.3%)	107 (25.7%)	45 (22.4%)	51 (24.6%)	28 (25.2%)	21 (23.1%)	14 (17.3%)	26 (27.7%)	6 (14.6%)	3 (37.5%)	
FCGR3A												
158 F/F	29 (38.7%)	71 (27.8%)	116 (27.8%)	69 (34.3%)	70 (33.8%)	30 (27%)	30 (33%)	31 (38.3%)	30 (31.9%)	13 (31.7%)	1 (12.5%)	0.89
158 F/V	18 (24%)	73 (28.6%)	129 (30.9%)	53 (26.4%)	54 (26.1%)	32 (28.8%)	26 (28.6%)	31 (38.3%)	25 (26.6%)	11 (26.8%)	1 (12.5%)	
158 V/V	3 (4%)	27 (10.6%)	37 (8.9%)	19 (9.5%)	16 (7.7%)	11 (9.9%)	11 (12.1%)	5 (6.2%)	7 (7.4%)	4 (9.8%)	2 (25%)	
Unknown	25 (33.3%)	84 (32.9%)	135 (32.4%)	60 (29.9%)	67 (32.4%)	38 (34.2%)	24 (26.4%)	14 (17.3%)	32 (34%)	13 (31.7%)	4 (50%)	
FCGR3A												
High	21 (28%)	100 (39.2%)	166 (39.8%)	72 (35.8%)	70 (33.8%)	43 (38.7%)	37 (40.7%)	36 (44.4%)	32 (34%)	15 (36.6%)	3 (37.5%)	0.63
Low	29 (38.7%)	71 (27.8%)	116 (27.8%)	69 (34.3%)	70 (33.8%)	30 (27%)	30 (33%)	31 (38.3%)	30 (31.9%)	13 (31.7%)	1 (12.5%)	
Unknown	25 (33.3%)	84 (32.9%)	135 (32.4%)	60 (29.9%)	67 (32.4%)	38 (34.2%)	24 (26.4%)	14 (17.3%)	32 (34%)	13 (31.7%)	4 (50%)	
8-gene												
Low	12 (16%)	30 (11.8%)	52 (12.5%)	23 (11.4%)	19 (9.2%)	6 (5.4%)	3 (3.3%)	8 (9.9%)	6 (6.4%)	2 (4.9%)	0 (0%)	<0.001
Med	16 (21.3%)	81 (31.8%)	148 (35.5%)	73 (36.3%)	71 (34.3%)	47 (42.3%)	39 (42.9%)	31 (38.3%)	47 (50%)	17 (41.5%)	7 (87.5%)	
High	31 (41.3%)	94 (36.9%)	156 (37.4%)	78 (38.8%)	87 (42%)	40 (36%)	32 (35.2%)	32 (39.5%)	26 (27.7%)	15 (36.6%)	1 (12.5%)	
Unknown	16 (21.3%)	50 (19.6%)	61 (14.6%)	27 (13.4%)	30 (14.5%)	18 (16.2%)	17 (18.7%)	10 (12.3%)	15 (16%)	7 (17.1%)	0 (0%)	

Intrinsic subtype												
Basal	2 (2.7%)	8 (3.1%)	11 (2.6%)	10 (5%)	17 (8.2%)	6 (5.4%)	6 (6.6%)	6 (7.4%)	9 (9.6%)	3 (7.3%)	1 (12.5%)	<0.001
HER2	25 (33.3%)	84 (32.9%)	149 (35.7%)	82 (40.8%)	87 (42%)	56 (50.5%)	47 (51.6%)	39 (48.1%)	53 (56.4%)	24 (58.5%)	4 (50%)	
Lum A	18 (24%)	75 (29.4%)	128 (30.7%)	44 (21.9%)	45 (21.7%)	16 (14.4%)	11 (12.1%)	14 (17.3%)	4 (4.3%)	4 (9.8%)	1 (12.5%)	
Lum B	13 (17.3%)	34 (13.3%)	52 (12.5%)	33 (16.4%)	21 (10.1%)	11 (9.9%)	3 (3.3%)	8 (9.9%)	9 (9.6%)	2 (4.9%)	0 (0%)	
Normal	1 (1.3%)	4 (1.6%)	16 (3.8%)	5 (2.5%)	7 (3.4%)	4 (3.6%)	7 (7.7%)	4 (4.9%)	4 (4.3%)	1 (2.4%)	2 (25%)	
Unknown	16 (21.3%)	50 (19.6%)	61 (14.6%)	27 (13.4%)	30 (14.5%)	18 (16.2%)	17 (18.7%)	10 (12.3%)	15 (16%)	7 (17.1%)	0 (0%)	
Intrinsic subtype												
HER2	25 (33.3%)	84 (32.9%)	149 (35.7%)	82 (40.8%)	87 (42%)	56 (50.5%)	47 (51.6%)	39 (48.1%)	53 (56.4%)	24 (58.5%)	4 (50%)	<0.001
Non-HER2	34 (45.3%)	121 (47.5%)	207 (49.6%)	92 (45.8%)	90 (43.5%)	37 (33.3%)	27 (29.7%)	32 (39.5%)	26 (27.7%)	10 (24.4%)	4 (50%)	
Unknown	16 (21.3%)	50 (19.6%)	61 (14.6%)	27 (13.4%)	30 (14.5%)	18 (16.2%)	17 (18.7%)	10 (12.3%)	15 (16%)	7 (17.1%)	0 (0%)	
PIK3CA Mutation												
WT	26 (34.7%)	69 (27.1%)	106 (25.4%)	53 (26.4%)	61 (29.5%)	31 (27.9%)	32 (35.2%)	23 (28.4%)	23 (24.5%)	15 (36.6%)	2 (25%)	0.66
MT	4 (5.3%)	20 (7.8%)	38 (9.1%)	24 (11.9%)	24 (11.6%)	6 (5.4%)	11 (12.1%)	9 (11.1%)	4 (4.3%)	3 (7.3%)	1 (12.5%)	
Unknown	45 (60%)	166 (65.1%)	273 (65.5%)	124 (61.7%)	122 (58.9%)	74 (66.7%)	48 (52.7%)	49 (60.5%)	67 (71.3%)	23 (56.1%)	5 (62.5%)	

Note: Associations of sTILs scores and other variables were analyzed by ANOVA test without including samples with missing values. Study methods and results for molecular variables are as previously described.[13, 17, 21]

Supplementary Table 4. Multivariate survival analyses with clinicopathological and molecular variables in NSABP B-31

		ACT Arm				ACTH Arm			
		HR	**LB**	**UB**	**p-value**	**HR**	**LB**	**UB**	**p-value**
sTILs (reference: ≤50)	sTILs >50	0.64	0.39	1.06	0.082	0.36	0.19	0.67	0.001
ER (reference: negative)	ER Positive	0.94	0.62	1.43	0.777	0.71	0.44	1.13	0.145
Node (reference: Node 1-3)	Node 4-9	1.10	0.76	1.59	0.620	1.62	1.10	2.38	0.015
	Node ≥10	2.57	1.67	3.95	<0.001	3.00	1.87	4.81	<0.001
Size (reference: size ≤2)	Size 2-5	1.29	0.91	1.83	0.149	1.50	1.01	2.23	0.043
	Size >5	1.92	1.08	3.40	0.026	1.48	0.81	2.68	0.201
FCGR3 (reference: low)	FCGR3 high affinity	1.47	1.07	2.02	0.018	0.98	0.69	1.39	0.916
8-gene (reference: low)	Med	1.14	0.63	2.07	0.656	0.60	0.35	1.03	0.065
	High	1.59	0.87	2.88	0.129	0.40	0.23	0.71	0.002
Intrinsic subtype (reference: Lum A)	Lum B	0.69	0.40	1.19	0.179	1.28	0.74	2.21	0.381
	HER2	1.07	0.67	1.72	0.779	1.18	0.69	2.02	0.535
	Basal	1.01	0.47	2.18	0.981	1.67	0.62	4.46	0.310
	Normal like	0.61	0.22	1.72	0.349	0.80	0.29	2.25	0.678

Note: Models included all listed variables with the exception of PIK3CA, which was excluded from multivariate analysis, because PIK3CA mutations were profiled only in a subset of B-31.

Supp Fig 1. NSABP B-31 sTILs Remark Diagram