Supplementary Figures

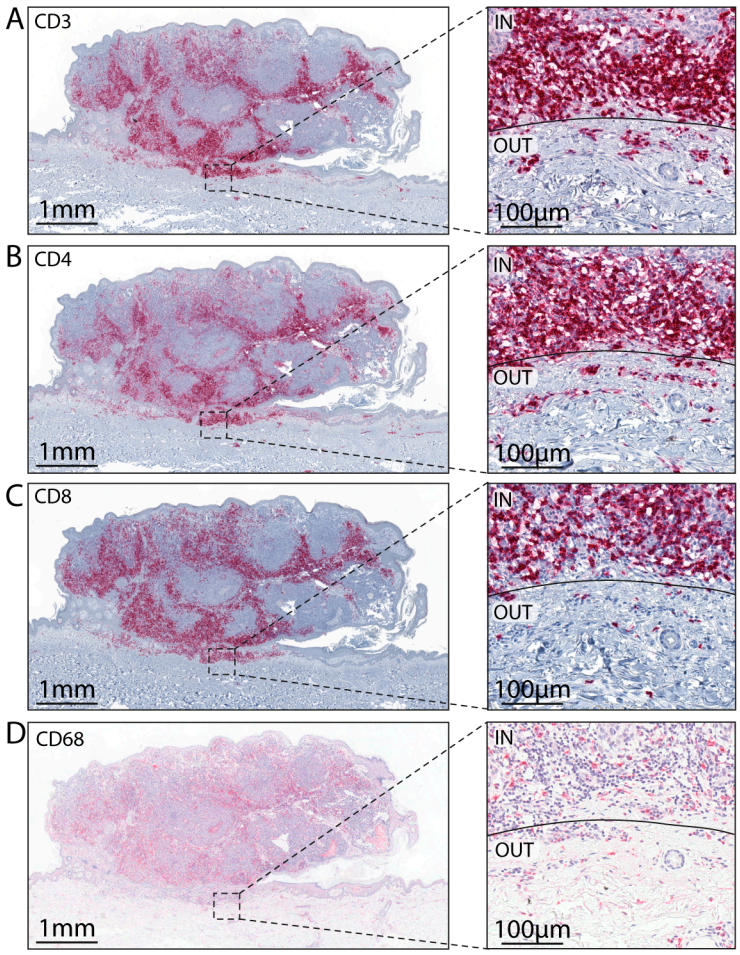


Figure S1. Representative immunohistochemical images of CD3 (A), CD4 (B), CD8 (C) and CD68 (D) in melanoma tissue. IN, indicates the inner portion of the peritumoral area, OUT, indicates the outer portion of the peritumoral area.

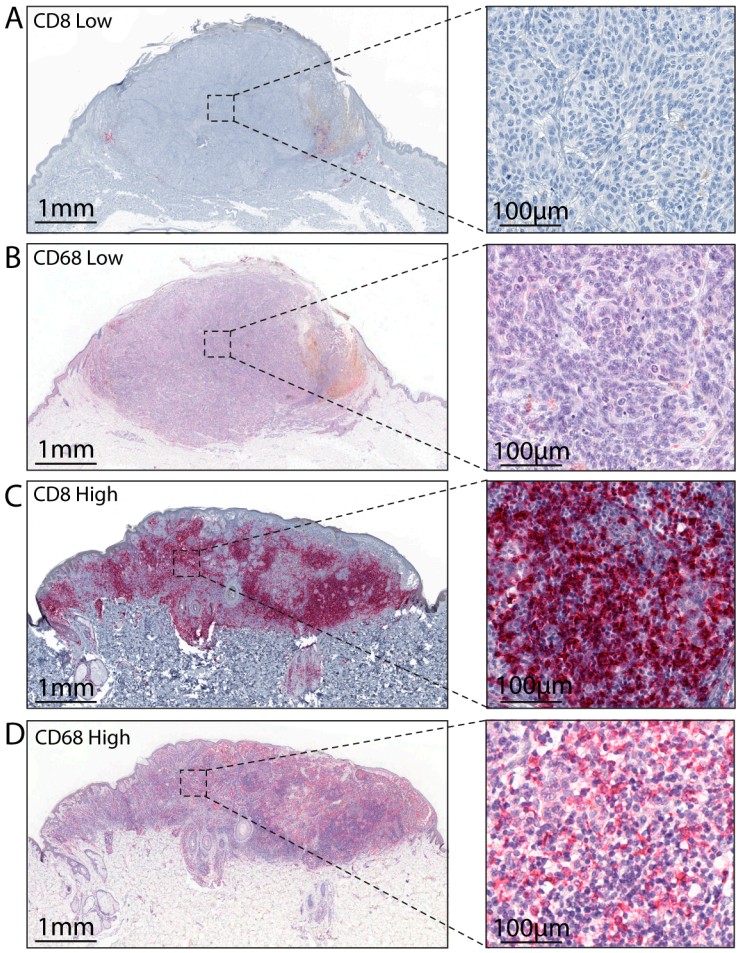


Figure S2. Representative images of melanoma tissue with low CD8 (A) and low CD68 (B). Representative images of melanoma tissue with high CD8 (C) and high CD68 (D).

Supplementary Tables

Table S1. Biomarkers associations in the training cohort. Spearman correlation index.

	CD3+			CD4+			CD8+			CD68+			CD163+			FOXP3			PD1			PD-L1		
	Intra	**IN**	**OUT**	**Intra**	**IN**	**OUT**	**Intra**	**IN**	**OUT**	**Intra**	**IN**	**OUT**	**Intra**	**IN**	**OUT**	**Intra**	**IN**	**OUT**	**Intra**	**IN**	**OUT**	**Intra**	**IN**	**OUT**
CD3+																								
Intra	1	**0.80**	0.60	**0.75**	0.56	0.48	**0.71**	0.60	0.52	0.31	0.31	0.14	0.44	0.32	0.30	0.50	0.41	0.34	0.57	0.51	0.35	0.42	0.40	0.26
IN		1	**0.75**	0.69	**0.77**	0.59	**0.71**	**0.80**	**0.73**	0.38	0.45	0.28	0.45	0.53	0.46	0.41	0.45	0.43	0.59	0.67	0.49	0.46	0.60	0.44
OUT			1	0.45	0.62	0.69	0.43	0.57	**0.80**	0.34	0.45	0.38	0.32	0.46	0.45	0.33	0.41	0.49	0.49	0.60	0.52	0.38	0.52	0.47
CD4+																								
Intra				1	**0.76**	0.55	0.67	0.59	0.50	0.36	0.40	0.18	0.59	0.46	0.42	0.38	0.34	0.28	0.57	0.52	0.40	0.62	0.61	0.42
IN					1	**0.78**	0.54	**0.72**	0.69	0.28	0.45	0.32	0.46	0.56	0.51	0.37	0.42	0.43	0.50	0.63	0.46	0.51	0.67	0.53
OUT						1	0.31	0.47	0.68	0.25	0.45	0.46	0.28	0.45	0.55	0.41	0.46	0.52	0.36	0.47	0.44	0.40	0.56	0.58
CD8+																								
Intra							1	**0.85**	0.65	0.50	0.40	0.40	0.56	0.44	0.40	0.13	0.16	0.15	**0.80**	**0.73**	0.59	0.61	0.56	0.40
IN								1	**0.84**	0.45	0.51	0.53	0.44	0.52	0.45	0.22	0.29	0.31	**0.71**	**0.82**	0.63	0.55	0.68	0.51
OUT									1	0.12	0.25	0.40	0.34	0.53	0.53	0.25	0.34	0.42	0.63	**0.76**	**0.70**	0.53	0.67	0.57
CD68+																								
Intra										1	**0.80**	0.61	0.29	0.28	0.38	-0.09	0.00	0.01	0.55	0.47	0.49	0.43	0.46	0.34
IN											1	**0.78**	0.24	0.38	0.50	0.03	0.14	0.19	0.51	0.54	0.56	0.39	0.52	0.39
OUT												1	0.02	0.22	0.44	0.14	0.20	0.26	0.25	0.30	0.45	0.17	0.33	0.35
CD163+																								
Intra													1	**0.82**	0.61	0.16	0.18	0.18	0.58	0.42	0.32	0.61	0.52	0.34
IN														1	**0.80**	0.21	0.35	0.38	0.47	0.45	0.38	0.47	0.60	0.45

	CD3+			CD4+			CD8+			CD68+			CD163+			FOXP3			PD1			PD-L1		
	Intra	**IN**	**OUT**	**Intra**	**IN**	**OUT**	**Intra**	**IN**	**OUT**	**Intra**	**IN**	**OUT**	**Intra**	**IN**	**OUT**	**Intra**	**IN**	**OUT**	**Intra**	**IN**	**OUT**	**Intra**	**IN**	**OUT**
OUT															1	0.31	0.44	0.46	0.42	0.40	0.44	0.44	0.61	0.58
FOXP3																								
Intra																1	**0.91**	**0.84**	0.02	0.11	0.04	0.28	0.40	0.43
IN																	1	**0.95**	0.07	0.23	0.11	0.25	0.46	0.47
OUT																		1	0.10	0.26	0.18	0.24	0.47	0.49
PD1																								
Intra																			1	**0.86**	**0.74**	0.65	0.60	0.43
IN																				1	**0.77**	0.56	0.65	0.48
OUT																					1	0.47	0.54	0.51
PD-L1																								
Intra																						1	**0.83**	0.69
IN																							1	**0.85**
OUT																								1

Legend. Intra: intratumoral. IN: peritumoral IN. OUT: peritumoral OUT.

Table S2. Associations between biomarkers and clinical characteristics in the training cohort. Chi-square and Wilcoxon test.

	Stage at diagnosis – n (%)			**Breslow thickness (mm)**		**Ulceration** – n (%)		
	Stage II	**Stage III**	**P-value**	**Median (Q1-Q3)**	**P-value**	**Absent**	**Present**	**P-value**
Intratumoral			0.432		0.533			0.666
Low CD3+	23 (53.5)	17 (44.7)		5.0 (3.0-6.8)		10 (45.5)	30 (50.8)	
High CD3+	20 (46.5)	21 (55.3)		3.8 (3.0-6.5)		12 (54.5)	29 (49.2)	
Peritumoral IN			0.603		0.749			0.865
Low CD3+	24 (47.1)	20 (52.6)		4.0 (2.7-6.0)		12 (48.0)	32 (50.0)	
High CD3+	27 (52.9)	18 (47.4)		4.0 (3.1-6.0)		13 (52.0)	32 (50.0)	
Peritumoral OUT			0.927		0.318			0.086
Low CD3+	25 (49.0)	19 (50.0)		3.5 (2.7-6.0)		16 (64.0)	28 (43.8)	
High CD3+	26 (51.0)	19 (50.0)		4.0 (3.2-6.0)		9 (36.0)	36 (56.3)	
Intratumoral			0.536		0.684			0.496
Low CD4+	26 (47.3)	22 (53.7)		4.7 (3.0-6.4)		12 (44.4)	36 (52.2)	
High CD4+	29 (52.7)	19 (46.3)		3.8 (2.9-6.5)		15 (55.6)	33 (47.8)	
Peritumoral IN			0.071		0.613			0.865
Low CD4+	21 (41.2)	23 (60.5)		4.0 (2.7-6.0)		12 (48.0)	32 (50.0)	
High CD4+	30 (58.8)	15 (39.5)		4.0 (3.0-6.0)		13 (52.0)	32 (50.0)	
Peritumoral OUT			0.603		0.215			**0.029***
Low CD4+	24 (47.1)	20 (52.6)		3.5 (2.7-6.0)		17 (68.0)	27 (42.2)	
High CD4+	27 (52.9)	18 (47.4)		4.3 (3.2-6.3)		8 (32.0)	37 (57.8)	
Intratumoral			0.124		0.381			0.871
Low CD8+	23 (42.6)	24 (58.5)		5.0 (2.7-8.0)		13 (48.1)	34 (50.0)	
High CD8+	31 (57.4)	17 (41.5)		3.8 (3.0-6.0)		14 (51.9)	34 (50.0)	
Peritumoral IN			**0.025***		0.690			0.865
Low CD8+	20 (39.2)	24 (63.2)		4.0 (2.7-6.2)		12 (48.0)	32 (50.0)	
High CD8+	31 (60.8)	14 (36.8)		4.0 (3.1-6.0)		13 (52.0)	32 (50.0)	
Peritumoral OUT			0.168		0.438			0.439

	Stage at diagnosis – n (%)			**Breslow thickness (mm)**		**Ulceration** – n (%)		
	Stage II	**Stage III**	**P-value**	**Median (Q1-Q3)**	**P-value**	**Absent**	**Present**	**P-value**
Low CD8+	22 (43.1)	22 (57.9)		3.5 (2.7-6.2)		14 (56.0)	30 (46.9)	
High CD8+	29 (56.9)	16 (42.1)		4.3 (3.1-6.0)		11 (44.0)	34 (53.1)	
Intratumoral			0.095		0.323			0.254
Low CD68+	23 (42.6)	24 (60.0)		3.8 (2.6-6.5)		11 (40.7)	36 (53.7)	
High CD68+	31 (57.4)	16 (40.0)		4.5 (3.3-6.0)		16 (59.3)	31 (46.3)	
Peritumoral IN			0.343		0.380			0.763
Low CD68+	23 (45.1)	21 (55.3)		3.6 (2.4-6.4)		13 (52.0)	31 (48.4)	
High CD68+	28 (54.9)	17 (44.7)		4.0 (3.2-5.0)		12 (48.0)	33 (51.6)	
Peritumoral OUT			0.444		0.075			0.521
Low CD68+	24 (47.1)	21 (55.3)		3.5 (2.6-5.9)		14 (56.0)	31 (48.4)	
High CD68+	27 (52.9)	17 (44.7)		4.5 (3.3-6.2)		11 (44.0)	33 (51.6)	
Intratumoral			**0.023***		0.196			0.496
Low CD163+	22 (40.0)	26 (63.4)		5.0 (3.0-7.0)		12 (44.4)	36 (52.2)	
High CD163+	33 (60.0)	15 (36.6)		3.9 (2.9-6.0)		15 (55.6)	33 (47.8)	
Peritumoral IN			0.105		0.506			0.865
Low CD163+	22 (43.1)	23 (60.5)		4.8 (2.7-6.0)		13 (52.0)	32 (50.0)	
High CD163+	29 (56.9)	15 (39.5)		3.9 (3.0-5.4)		12 (48.0)	32 (50.0)	
Peritumoral OUT			0.343		0.582			0.439
Low CD163+	23 (45.1)	21 (55.3)		3.6 (2.5-6.0)		14 (56.0)	30 (46.9)	
High CD163+	28 (54.9)	17 (44.7)		4.0 (3.2-6.0)		11 (44.0)	34 (53.1)	
Intratumoral			0.063		0.111			0.496
Low FOXP3	32 (58.2)	16 (39.0)		3.9 (2.5-6.0)		15 (55.6)	33 (47.8)	
High FOXP3	23 (41.8)	25 (61.0)		4.7 (3.3-6.8)		12 (44.4)	36 (52.2)	
Peritumoral IN			0.105		0.175			0.865
Low FOXP3	29 (56.9)	15 (39.5)		3.7 (2.5-5.7)		12 (48.0)	32 (50.0)	
High FOXP3	22 (43.1)	23 (60.5)		4.2 (3.2-6.4)		13 (52.0)	32 (50.0)	

	Stage at diagnosis – n (%)			**Breslow thickness (mm)**		**Ulceration** – n (%)		
	Stage II	**Stage III**	**P-value**	**Median (Q1-Q3)**	**P-value**	**Absent**	**Present**	**P-value**
Peritumoral OUT			0.232		**0.021***			0.763
Low FOXP3	28 (54.9)	16 (42.1)		3.3 (2.4-5.3)		13 (52.0)	31 (48.4)	
High FOXP3	23 (45.1)	22 (57.9)		4.5 (3.4-6.4)		12 (48.0)	33 (51.6)	
Intratumoral			0.063		0.313			0.820
Low PD1	23 (41.8)	25 (61.0)		5.0 (3.0-7.5)		13 (48.1)	35 (50.7)	
High PD1	32 (58.2)	16 (39.0)		4.0 (2.9-5.9)		14 (51.9)	34 (49.3)	
Peritumoral IN			**0.013***		0.709			0.266
Low PD1	20 (39.2)	25 (65.8)		4.2 (2.8-6.5)		15 (60.0)	30 (46.9)	
High PD1	31 (60.8)	13 (34.2)		3.9 (2.9-5.9)		10 (40.0)	34 (53.1)	
Peritumoral OUT			**0.008***		0.347			0.213
Low PD1	19 (37.3)	25 (65.8)		3.7 (2.5-6.2)		15 (60.0)	29 (45.3)	
High PD1	32 (62.7)	13 (34.2)		4.0 (3.2-6.0)		10 (40.0)	35 (54.7)	
Intratumoral			0.063		0.486			0.496
Low PD-L1	23 (41.8)	25 (61.0)		4.4 (2.5-6.8)		15 (55.6)	33 (47.8)	
High PD-L1	32 (58.2)	16 (39.0)		4.3 (3.3-6.0)		12 (44.4)	36 (52.2)	
Peritumoral IN			**0.008***		0.345			0.763
Low PD-L1	19 (37.3)	25 (65.8)		3.6 (2.4-6.3)		13 (52.0)	31 (48.4)	
High PD-L1	32 (62.7)	13 (34.2)		4.0 (3.3-6.0)		12 (48.0)	33 (51.6)	
Peritumoral OUT			0.736		0.511			0.113
Low PD-L1	25 (49.0)	20 (52.6)		3.8 (2.6-6.0)		16 (64.0)	29 (45.3)	
High PD-L1	26 (51.0)	18 (47.4)		4.0 (3.2-6.0)		9 (36.0)	35 (54.7)	

* Significant p-value at 0.05 level.

Table S3. Spatial distribution of biomarkers.

Density (cells/mm^2) - Mean (SD)	Training cohort N=100					Validation cohort N=74				
	Intratumoral	Peritumoral IN	Peritumoral OUT	Overall F-test p-value	T-test p-value	Intratumoral	Peritumoral IN	Peritumoral OUT	Overall F-test p-value	T-test p-value
CD3+	1543.9 (1448.4)	2281.1 (1483.6)	1916.9 (1363.2)	<0.001	A:0.001 B:0.087 C:0.090	1202.7 (1051.8)	1765.0 (1492.4)	379.5 (335.5)	<0.0001	A:0.010 B:<0.001 C:<0.001
CD4+	1675.2 (1379.9)	2622.3 (1662.8)	2177.9 (1467.5)	<0.001	A:<0.001 B:0.017 C:0.060	1532.3 (1422.1)	1882.2 (1247.8)	601.4 (440.3)	<0.0001	A:0.120 B:<0.001 C:<0.001
CD8+	868.8 (1028.3)	1429.1 (1335.5)	1119.8 (1122.1)	<0.001	A:0.002 B:0.115 C:0.096	751.4 (719.6)	1054.4 (1062.0)	227.0 (287.3)	<0.0001	A:0.047 B:<0.001 C:<0.001
CD68+	367.2 (398.5)	469.7 (494.6)	337.9 (312.6)	0.002	A:0.126 B:0.580 C:0.035	583.7 (633.1)	611.7 (658.4)	88.7 (120.3)	<0.0001	A:0.794 B:<0.001 C:<0.001
CD163+	1188.9 (1073.4)	1472.6 (1090.4)	1061.4 (691.7)	<0.001	A: 0.076 B:0.335 C: 0.003					
FOXP3	528.5 (1297.7)	430.1 (1031.0)	292.4 (602.4)	0.098	-					

A: Intratumoral vs Peritumoral IN. B: Intratumoral vs Peritumoral OUT. C: Peritumoral IN vs Peritumoral OUT

Table S4. Biomarkers associations in the validation cohort. Spearman correlation index.

	CD3+			CD4+			CD8+			CD68+		
	Intra	**IN**	**OUT**	**Intra**	**IN**	**OUT**	**Intra**	**IN**	**OUT**	**Intra**	**IN**	**OUT**
CD3+												
Intra	1	**0.80**	0.47	**0.76**	0.59	0.18	**0.79**	0.64	0.35	0.43	0.41	0.40
IN		1	**0.70**	0.58	0.67	0.28	0.60	**0.75**	0.44	0.42	0.53	0.51
OUT			1	0.19	0.34	0.32	0.27	0.47	0.54	0.23	0.31	0.37
CD4+												
Intra				1	**0.80**	0.49	0.69	0.49	0.23	0.43	0.47	0.44
IN					1	**0.67**	0.49	0.63	0.36	0.41	0.55	0.46
OUT						1	0.25	0.37	0.49	0.20	0.34	0.35
CD8+												
Intra							1	**0.72**	0.52	0.27	0.22	0.27
IN								1	0.68	0.33	0.44	0.46
OUT									1	0.19	0.25	0.32
CD68+												
Intra										1	**0.83**	**0.78**
IN											1	**0.88**
OUT												1

Table S5. Associations between biomarkers and clinical characteristics in the validation cohort. Chi-square and Wilcoxon test.

	Stage at diagnosis – n (%)			**Breslow thickness (mm)**		**Ulceration** – n (%)		
	Stage I/II	**Stage III/IV**	**P-value**	**Median (Q1-Q3)**	**P-value**	**Absent**	**Present**	**P-value**
Intratumoral			0.326 [a]		0.002*			0.414
Low CD3+	33 (52.4)	8 (72.7)		4.9 (3.5-8.0)		9 (47.4)	32 (58.2)	
High CD3+	30 (47.6)	3 (27.3)		3.3 (2.6-4.0)		10 (52.6)	23 (41.8)	
Peritumoral IN			1.000[a]		0.018*			0.929
Low CD3+	41 (67.2)	7 (70.0)		4.4 (3.2 -6.0)		13 (68.4)	35 (67.3)	
High CD3+	20 (32.8)	3 (30.0)		3.2 (2.6-4.3)		6 (31.6)	17 (32.7)	
Missing	2	1				0	3	
Peritumoral OUT			1.000 [a]		0.341			1.000 [a]
Low CD3+	60 (98.4)	10 (100.0)		4.0 (3.0-5.9)		19 (100.0)	51 (98.1)	
High CD3+	1 (1.6)	0 (0.0)		2.9 (2.9-2.9)		0 (0.0)	1 (1.9)	
Missing	2	1				0	3	
Intratumoral			0.340 [a]		0.006*			0.101
Low CD4+	35 (55.6)	8 (72.7)		4.7 (3.2-8.0)		8 (42.1)	35 (63.6)	
High CD4+	28 (44.4)	3 (27.3)		3.4 (2.4-4.5)		11 (57.9)	20 (36.4)	
Peritumoral IN			1.000 [a]		0.020*			0.734
Low CD4+	43 (70.5)	7 (77.8)		4.3 (3.2-6.0)		13 (68.4)	37 (72.5)	
High CD4+	18 (29.5)	2 (22.2)		3.3 (2.5-4.1)		6 (31.6)	14 (27.5)	
Missing	2	2				0	4	
Peritumoral OUT			1.000 [a]		0.748			1.000 [a]
Low CD4+	60 (98.4)	9 (100.0)		4.0 (3.0-5.7)		19 (100.0)	50 (98.0)	
High CD4+	1 (1.6)	0 (0.0)		3.4 (3.4-3.4)		0 (0.0)	1 (2.0)	
Missing	2	2				0	4	
Intratumoral			1.000 [a]		0.013*			0.397
Low CD8+	38 (60.3)	7 (63.6)		4.6 (3.2-7.3)		10 (52.6)	35 (63.6)	
High CD8+	25 (39.7)	4 (36.4)		3.3 (2.6-4.5)		9 (47.4)	20 (36.4)	
Peritumoral IN			0.724 [a]		0.001*			0.371
Low CD8+	41 (67.2)	6 (60.0)		4.6 (3.4-7.3)		11 (57.9)	36 (69.2)	
High CD8+	20 (32.8)	4 (40.0)		3.1 (2.4-3.9)		8 (42.1)	16 (30.8)	

	Stage at diagnosis – n (%)			**Breslow thickness (mm)**		**Ulceration** – n (%)		
	Stage I/II	**Stage III/IV**	**P-value**	**Median (Q1-Q3)**	**P-value**	**Absent**	**Present**	**P-value**
Missing	2	1				0	3	
Peritumoral OUT			1.000 [a]		0.295			0.568 [a]
Low CD8+	57 (93.4)	10 (100.0)		4.0 (3.0-6.0)		19 (100.0)	48 (92.3)	
High CD8+	4 (6.6)	0 (0.0)		3.2 (2.8-4.0)		0 (0.0)	4 (7.7)	
Missing	2	1				0	3	
Intratumoral			0.752 [a]		0.440			0.291
Low CD68+	27 (42.8)	4 (36.4)		4.2 (3.2-6.0)		6 (31.6)	25 (45.5)	
High CD68+	36 (57.1)	7 (63.6)		3.9 (2.9-5.7)		13 (68.4)	30 (54.5)	
Peritumoral IN			1.000 [a]		0.149			0.981
Low CD68+	22 (36.1)	4 (40.0)		4.5 (3.2-6.0)		7 (36.8)	19 (36.5)	
High CD68+	39 (63.9)	6 (60.0)		3.5 (2.9-5.3)		12 (63.2)	33 (63.5)	
Missing	2	1				0	3	
Peritumoral OUT			0.093 [a]		0.501			1.000 [a]
Low CD68+	59 (96.7)	8 (80.0)		4.0 (3.0-5.9)		18 (94.7)	49 (94.2)	
High CD68+	2 (3.3)	2 (20.0)		3.1 (2.5-7.8)		1 (5.3)	3 (5.8)	
Missing	2	1				0	3	

[a:] Fisher exact test. * Significant p-value at 0.05 level.

Table S6. Effect of biomarkers density on disease free survival and overall survival in the validation cohort. Univariable and multivariable Cox proportional hazard models.

	DISEASE FREE SURVIVAL				OVERALL SURVIVAL			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
CD3+								
Intratumoral *(100 cell/mm2 increase)*	**0.93 (0.89-0.98)**	**0.005***	**0.95 (0.91-0.99)**	**0.027***	**0.94 (0.89-0.98)**	**0.011***	0.96 (0.91-1.01)	0.113
Intratumoral *(high vs low)*	**0.31 (0.16-0.63)**	**0.001***	**0.38 (0.19-0.78)**	**0.008***	**0.36 (0.17-0.75)**	**0.006***	0.53 (0.25-1.13)	0.101
Peritumoral IN *(100 cell/mm2 increase)*	**0.96 (0.93-0.99)**	**0.005***	**0.97 (0.93-1.00)**	**0.030***	**0.96 (0.92-0.99)**	**0.011***	0.97 (0.94-1.00)	0.071
Peritumoral IN *(high vs low)*	0.67 (0.33-1.38)	0.282	0.73 (0.35-1.51)	0.396	0.68 (0.32-1.47)	0.331	0.77 (0.36-1.68)	0.516
Peritumoral OUT *(100 cell/mm2 increase)*	0.90 (0.79-1.02)	0.090	0.89 (0.77-1.02)	0.094	0.92 (0.81-1.04)	0.198	0.91 (0.79-1.04)	0.177
Peritumoral OUT *(high vs low)*	Not estimable (see Table 2)		Not estimable (see Table 2)		Not estimable (see Table 2)		Not estimable (see Table 2)	
CD4+								
Intratumoral *(100 cell/mm2 increase)*	0.99 (0.96-1.01)	0.267	1.00 (0.97-1.02)	0.711	0.99 (0.97-1.02)	0.546	1.01 (0.98-1.03)	0.624
Intratumoral *(high vs low)*	0.73 (0.38-1.38)	0.332	1.14 (0.56-2.31)	0.723	0.84 (0.43-1.64)	0.607	1.43 (0.69-2.97)	0.342
Peritumoral IN *(100 cell/mm2 increase)*	0.98 (0.95-1.01)	0.129	0.99 (0.96-1.02)	0.392	0.98 (0.96-1.01)	0.302	1.00 (0.97-1.03)	0.860
Peritumoral IN *(high vs low)*	0.58 (0.26-1.26)	0.169	0.73 (0.32-1.65)	0.450	0.63 (0.27-1.45)	0.279	0.90 (0.37-2.18)	0.815
Peritumoral OUT *(100 cell/mm2 increase)*	1.04 (0.97-1.12)	0.268	1.05 (0.97-1.14)	0.262	1.07 (1.00-1.16)	0.058	1.08 (1.00-1.18)	0.064
Peritumoral OUT *(high vs low)*	Not estimable (see Table 2)		Not estimable (see Table 2)		Not estimable (see Table 2)		Not estimable (see Table 2)	
CD8+								
Intratumoral *(100 cell/mm2 increase)*	**0.92 (0.87-0.98)**	**0.009***	**0.94 (0.88-0.99)**	**0.030***	**0.93 (0.87-0.99)**	**0.026***	0.95 (0.89-1.01)	0.120
Intratumoral *(high vs low)*	**0.22 (0.10-0.49)**	**<0.001***	**0.23 (0.10-0.50)**	**<0.001***	**0.25 (0.11-0.57)**	**0.001***	**0.30 (0.13-0.70)**	**0.005***
Peritumoral IN *(100 cell/mm2 increase)*	**0.92 (0.88-0.97)**	**0.003***	**0.93 (0.88-0.98)**	**0.006***	**0.93 (0.88-0.98)**	**0.006***	**0.93 (0.88-0.99)**	**0.015***
Peritumoral IN *(high vs low)*	**0.22 (0.09-0.53)**	**<0.001***	**0.21 (0.08-0.52)**	**<0.001***	**0.22 (0.08-0.57)**	**0.002***	**0.23 (0.08-0.61)**	**0.003***
Peritumoral OUT *(100 cell/mm2 increase)*	0.82 (0.66-1.02)	0.073	0.78 (0.61-1.00)	0.052	0.84 (0.68-1.04)	0.118	0.80 (0.62-1.03)	0.078

	DISEASE FREE SURVIVAL				OVERALL SURVIVAL			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Peritumoral OUT *(high vs low)*	Not estimable (see Table 2)		Not estimable (see Table 2)		Not estimable (see Table 2)		Not estimable (see Table 2)	
CD68+								
Intratumoral *(100 cell/mm2 increase)*	1.00 (0.99-1.00)	0.773	1.00 (0.99-1.00)	0.629	1.00 (0.99-1.01)	0.977	1.00 (0.99-1.01)	0.819
Intratumoral *(high vs low)*	0.73 (0.39-1.37)	0.329	0.68 (0.36-1.29)	0.238	0.78 (0.41-1.50)	0.461	0.86 (0.44-1.67)	0.658
Peritumoral IN *(100 cell/mm2 increase)*	1.00 (0.99-1.00)	0.475	1.00 (0.99-1.00)	0.643	1.00 (0.99-1.00)	0.762	1.00 (1.00-1.01)	0.778
Peritumoral IN *(high vs low)*	0.87 (0.45-1.67)	0.672	0.99 (0.51-1.94)	0.984	0.94 (0.47-1.88)	0.861	1.13 (0.56-2.28)	0.735
Peritumoral OUT *(100 cell/mm2 increase)*	1.00 (0.97-1.03)	0.864	0.99 (0.96-1.02)	0.452	1.00 (0.97-1.03)	0.935	1.00 (0.97-1.02)	0.781
Peritumoral OUT *(high vs low)*	0.88 (0.21-3.67)	0.864	0.54 (0.12-2.37)	0.417	0.93 (0.22-3.88)	0.919	0.61 (0.14-2.67)	0.512

Note. Multivariable models adjusted for Breslow thickness, ulceration and stage. * Significant p-value at 0.05 level.