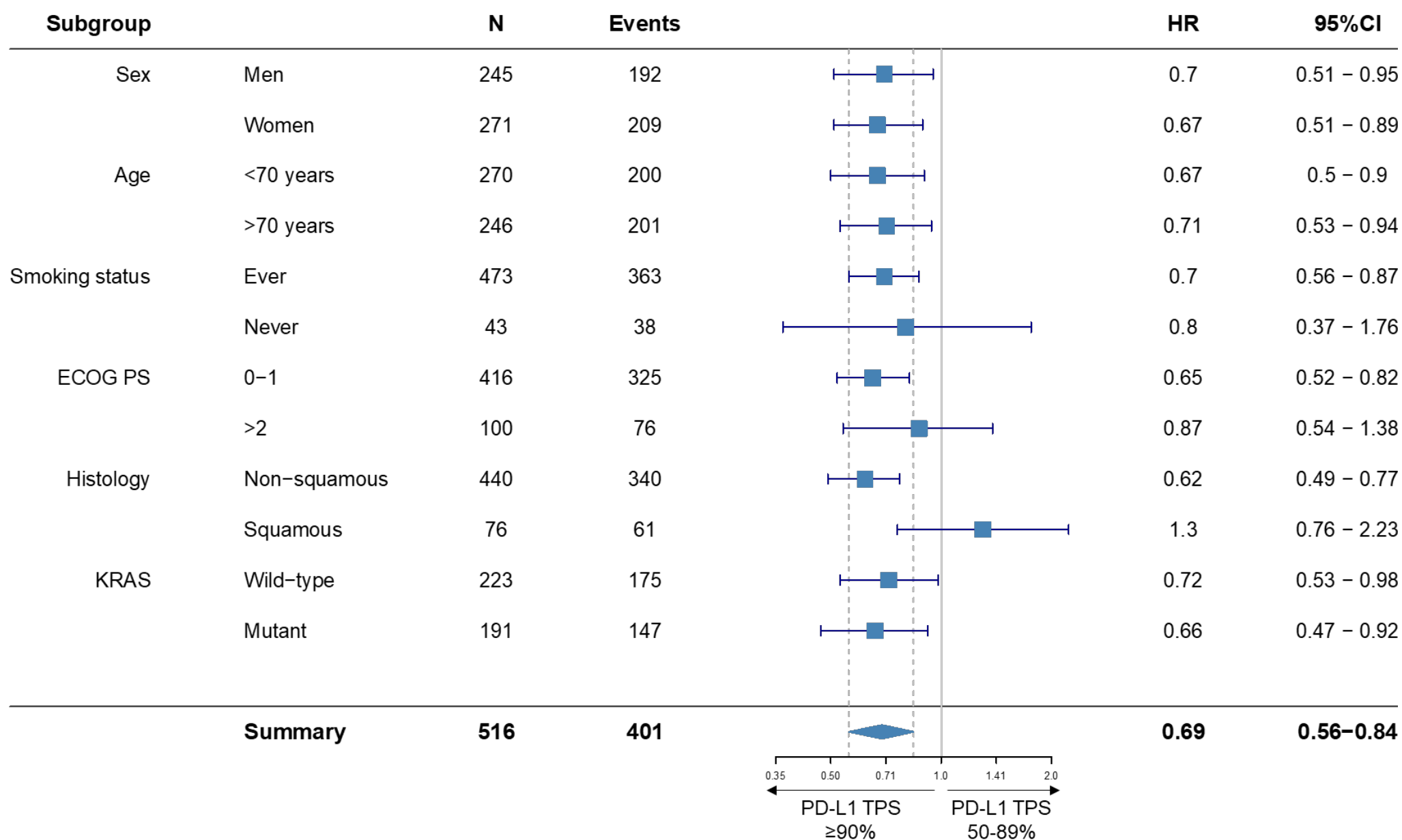
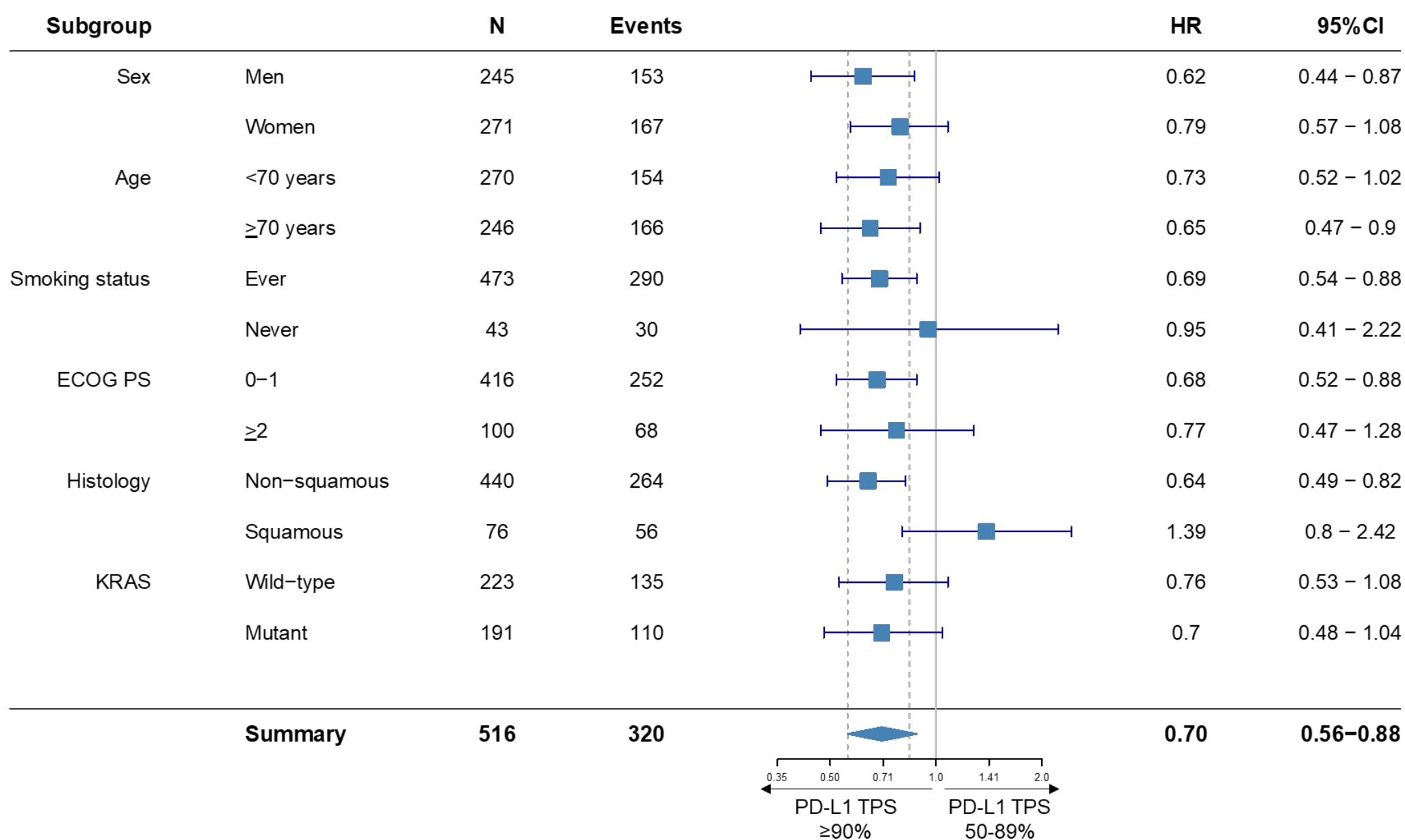


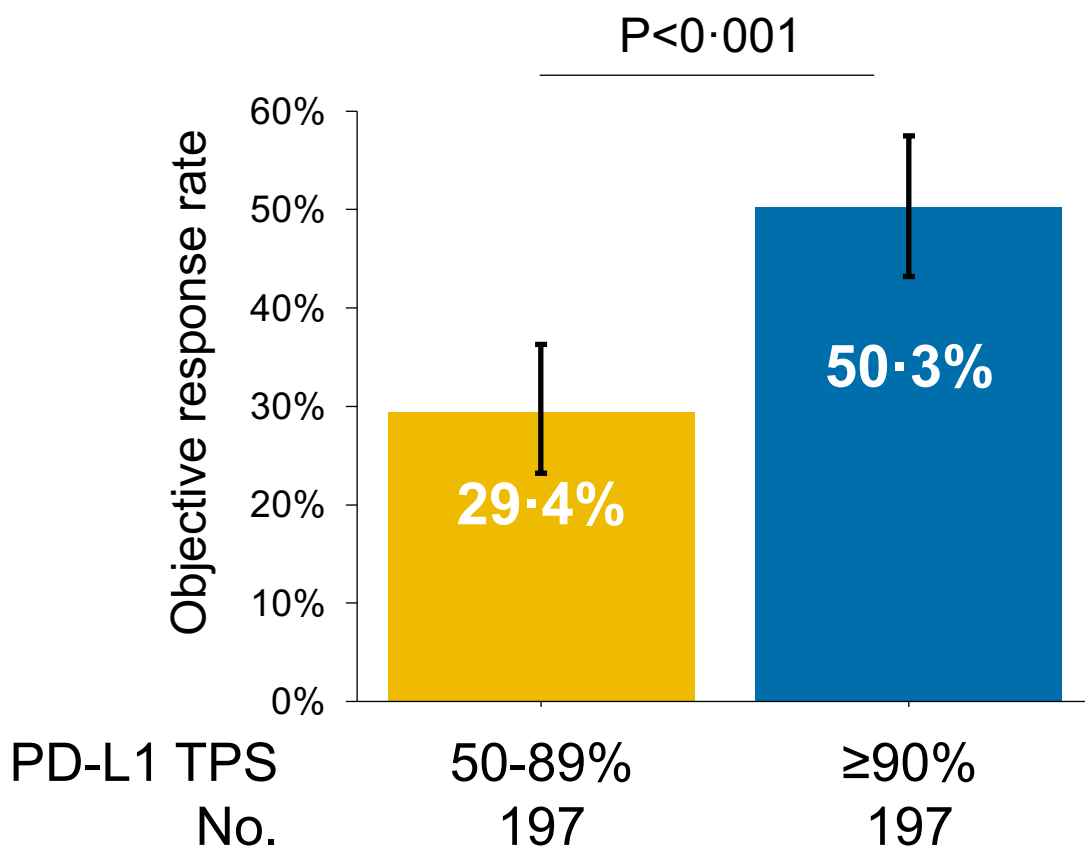
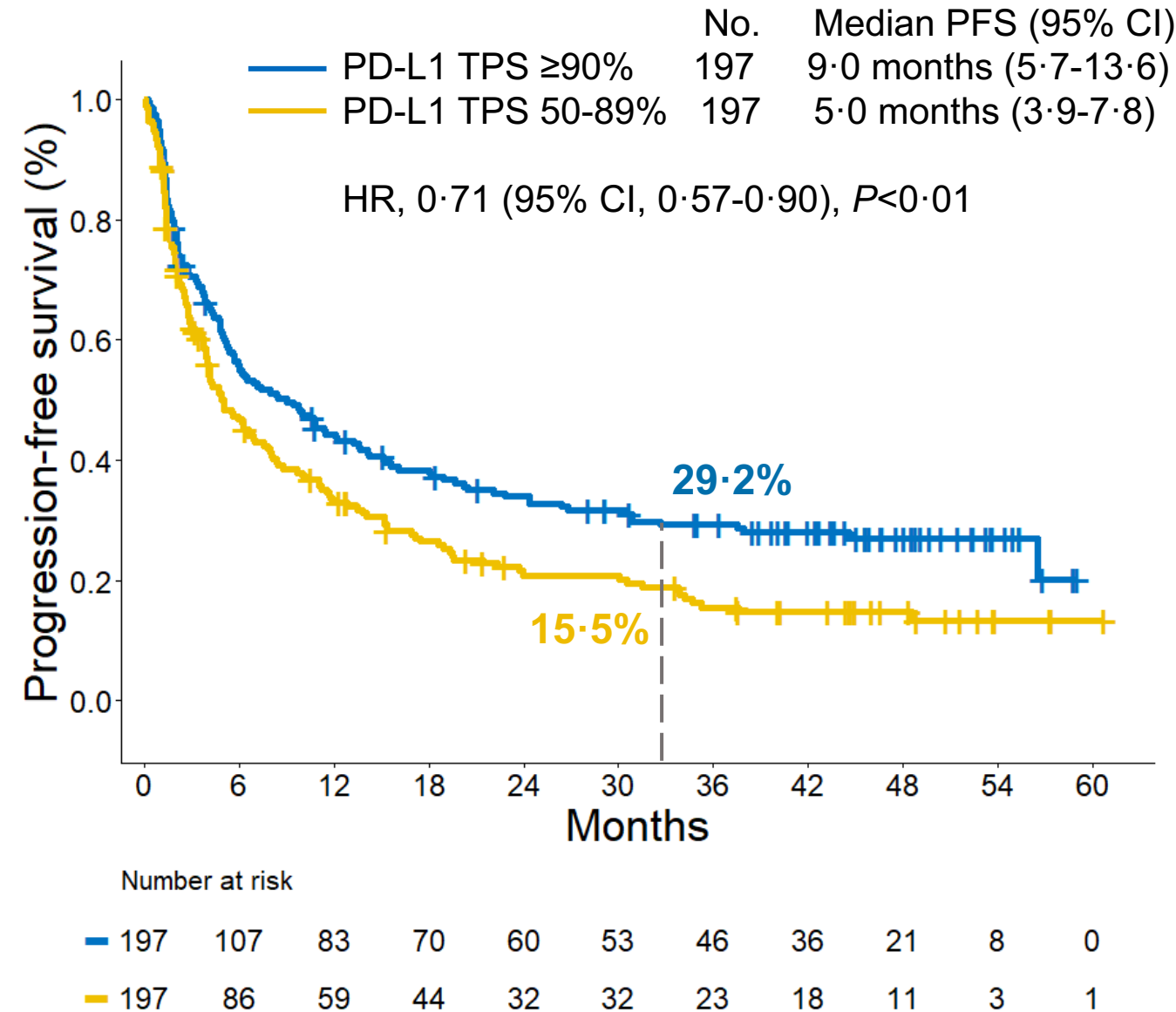
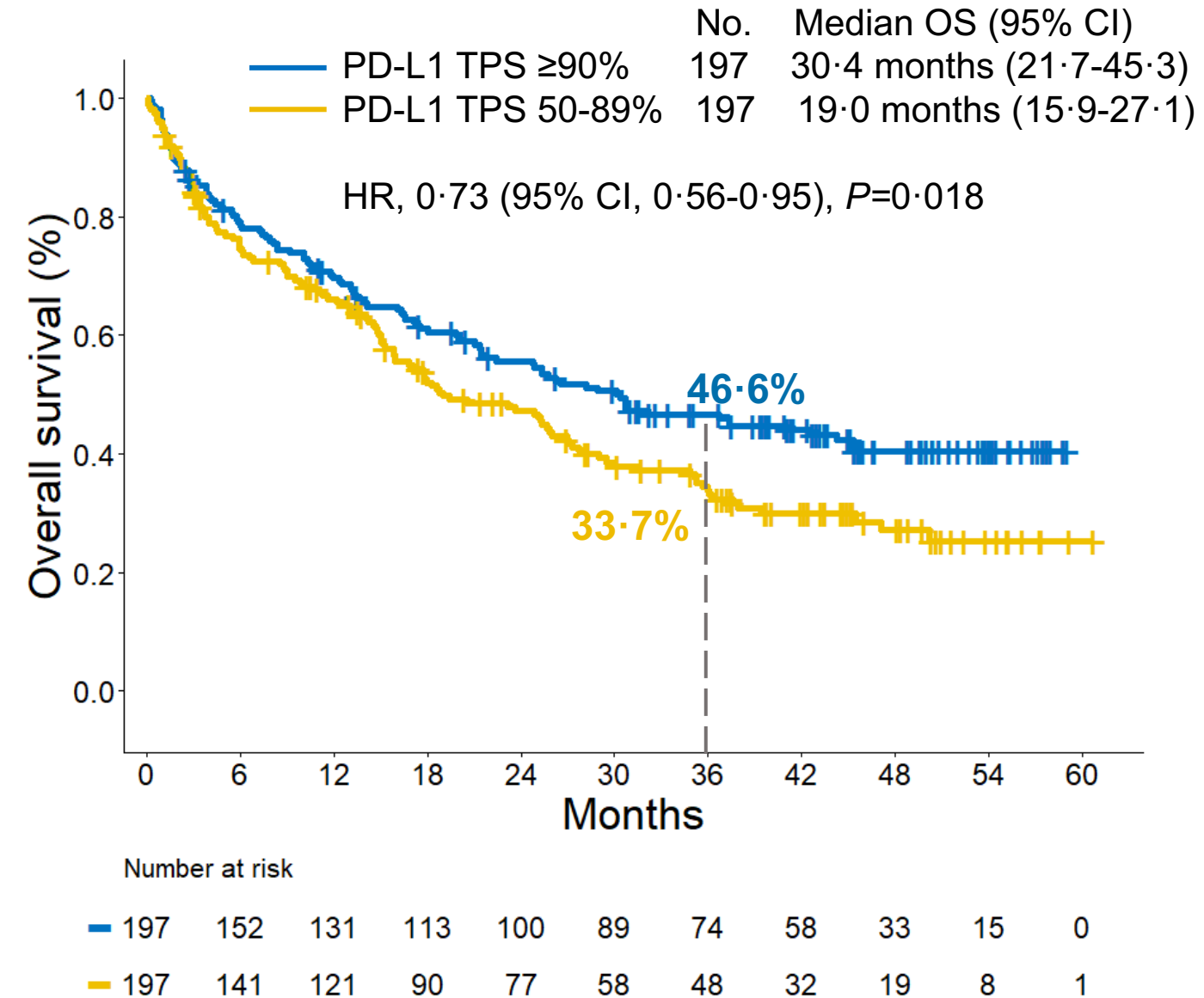
Supplementary Figure 2

A Progression-free survival to pembrolizumab

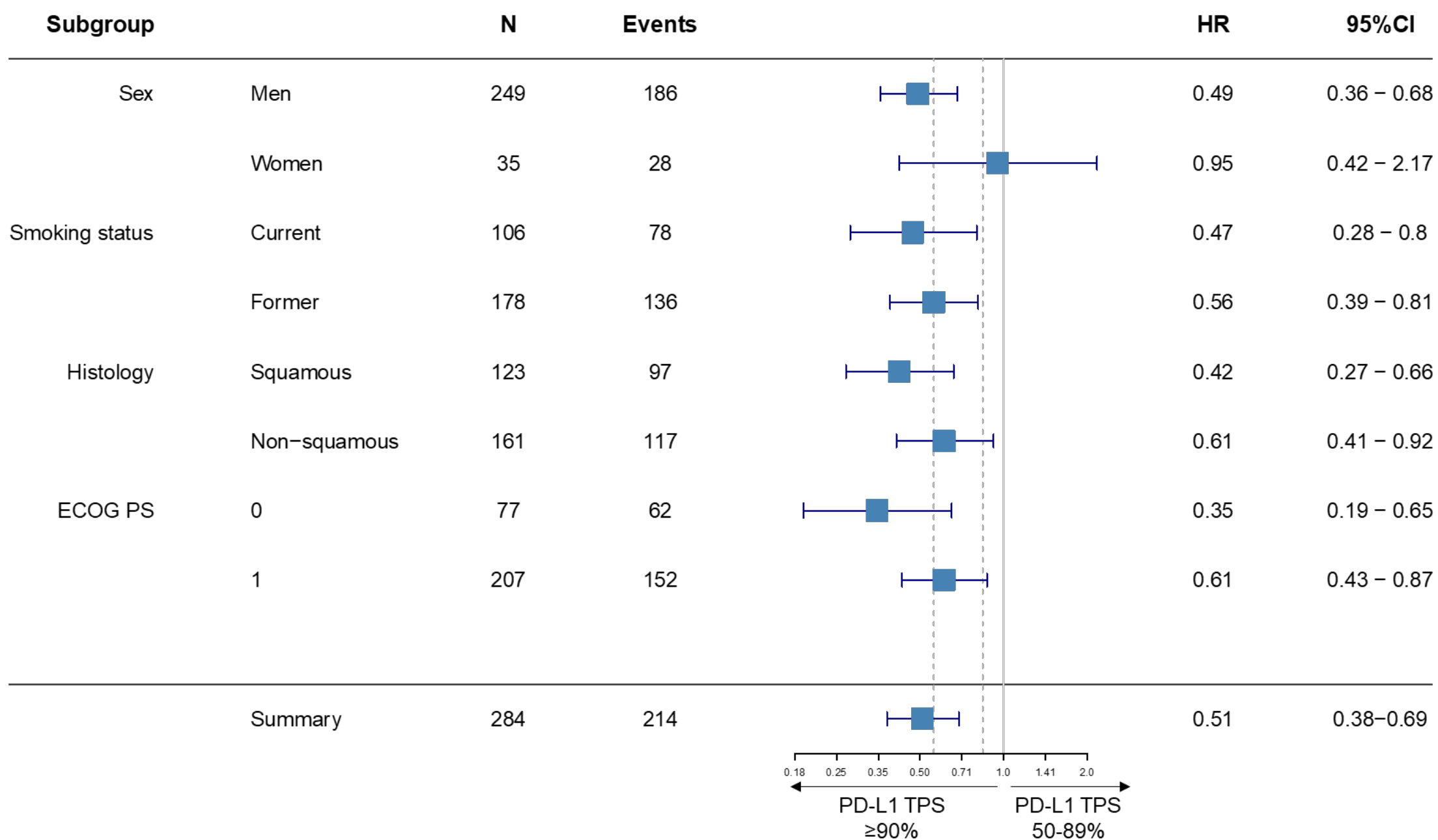


B Overall survival to pembrolizumab

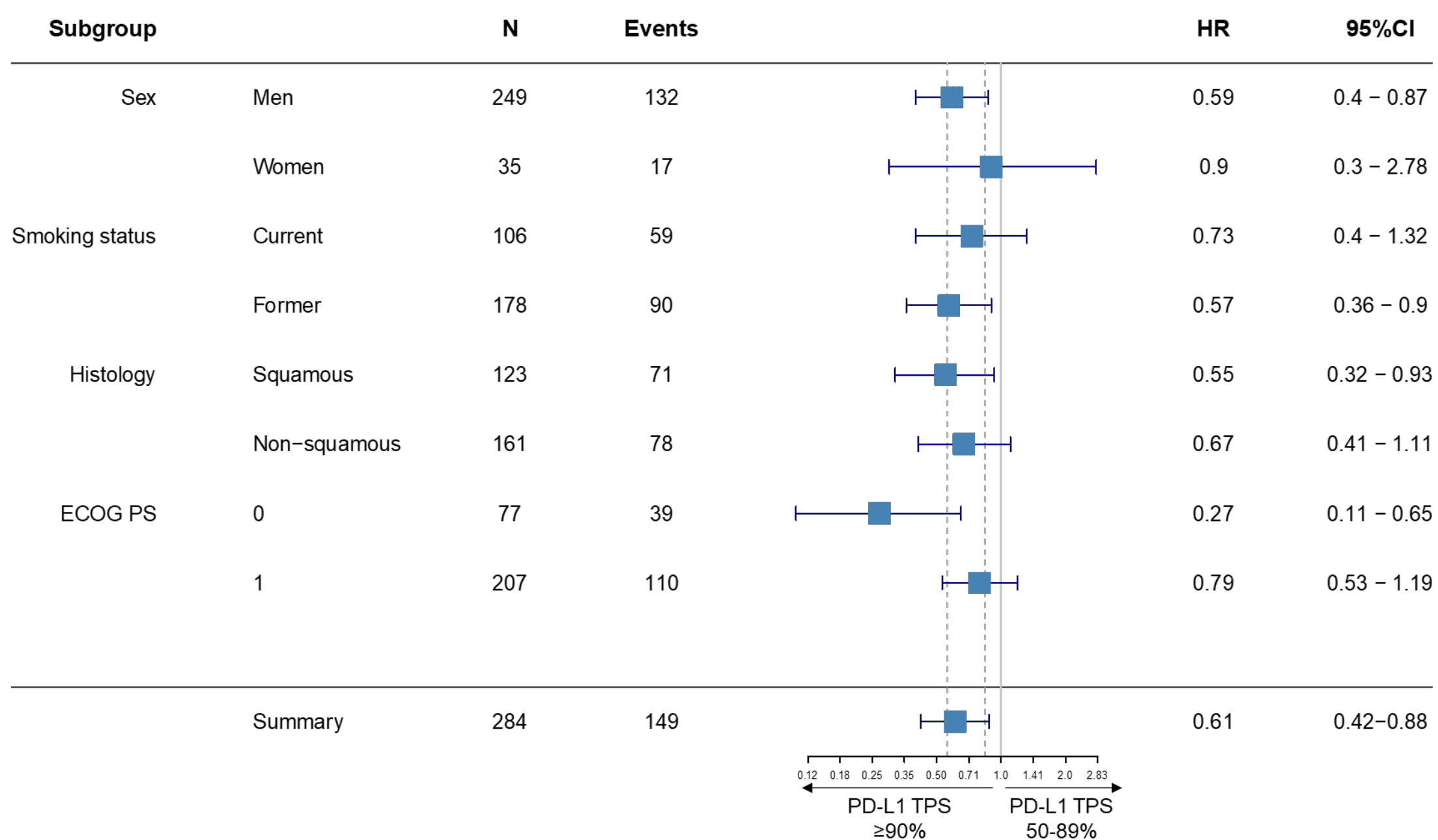


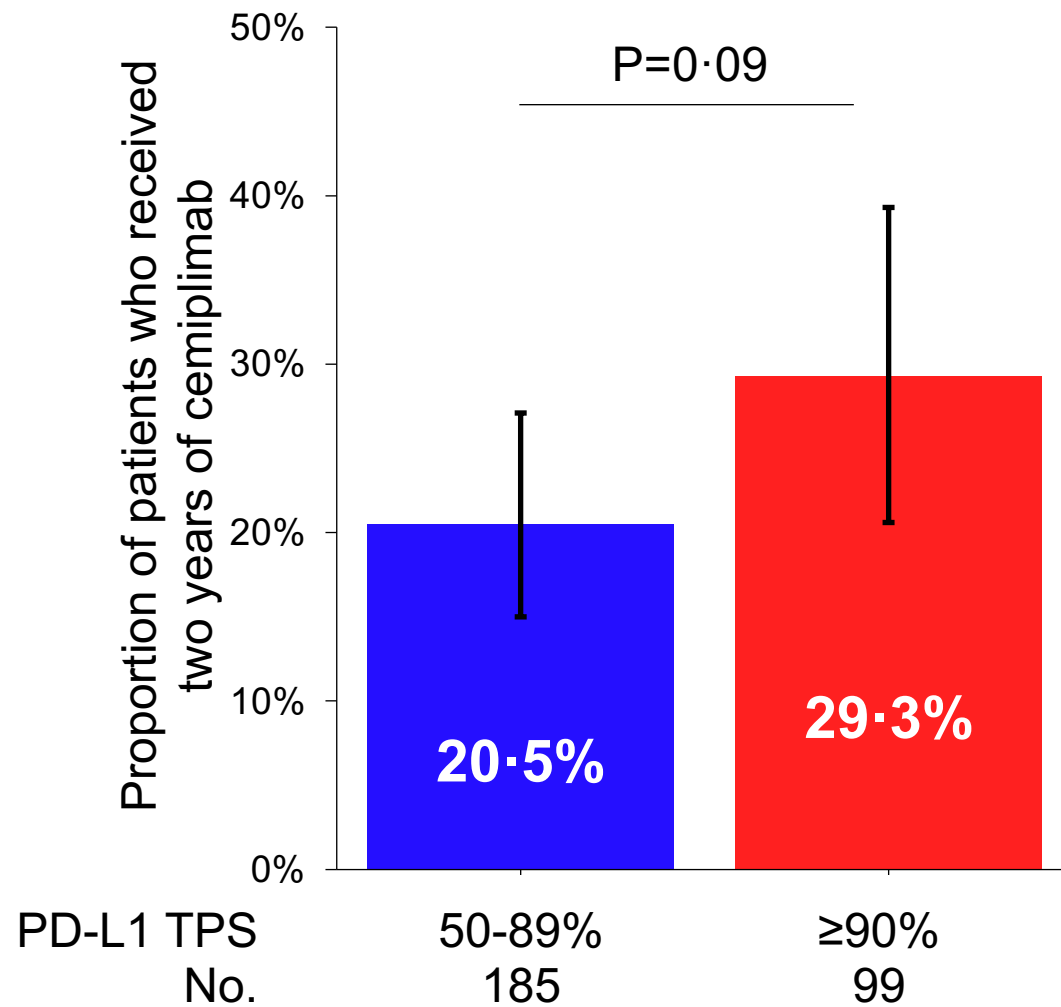
A**B****C**

A Progression-free survival to cemiplimab



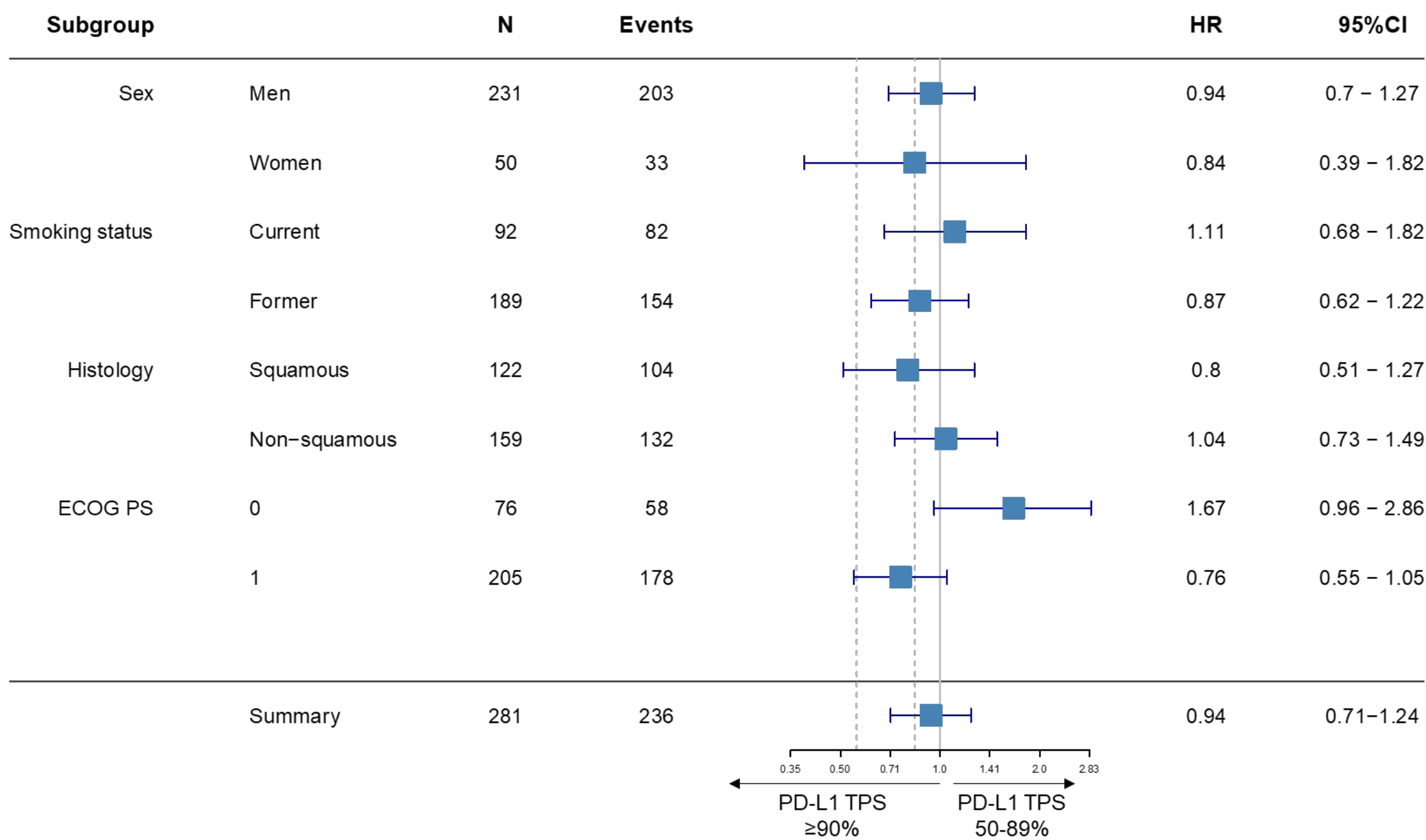
B Overall survival to cemiplimab



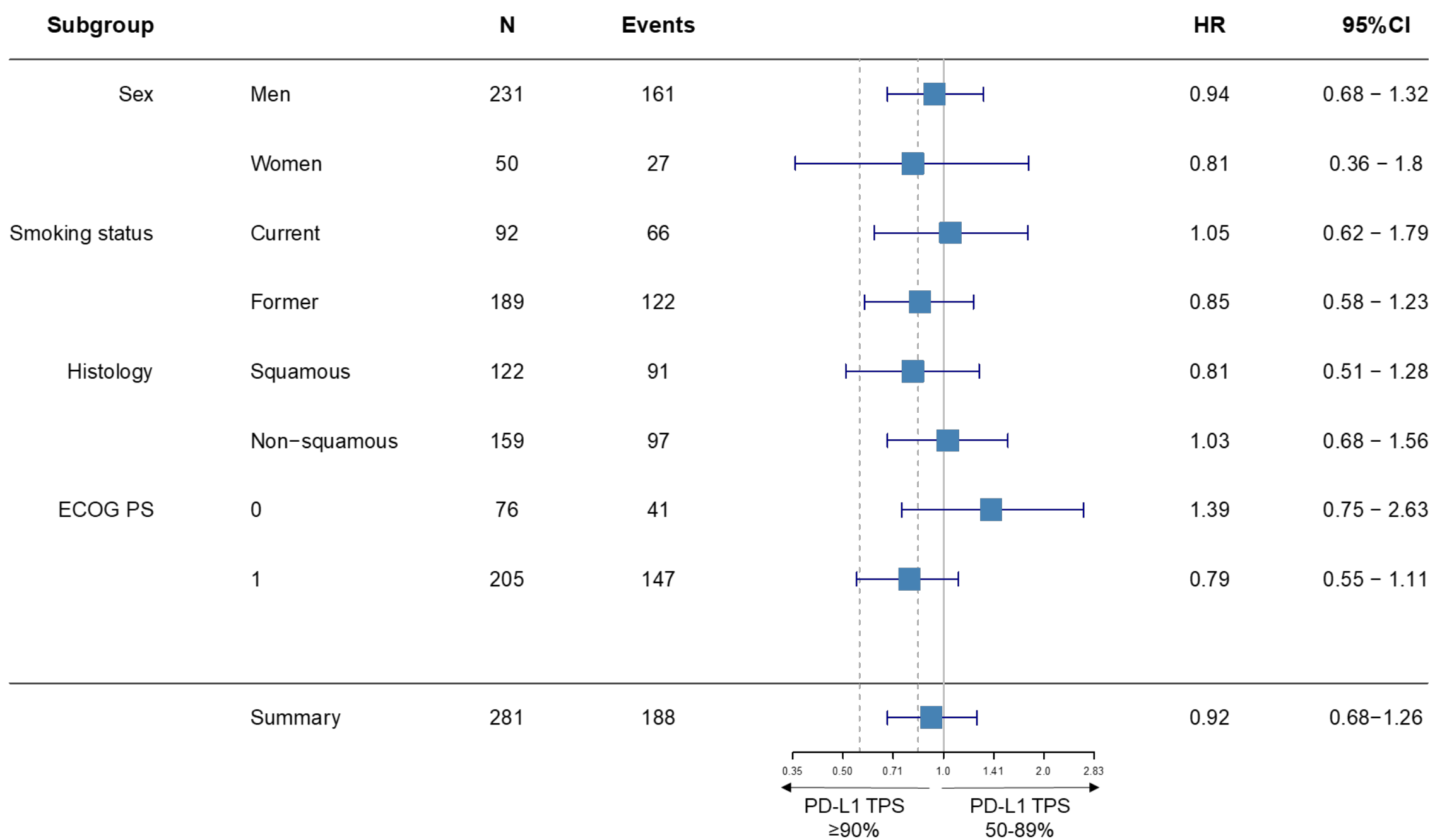


Supplementary Figure 6

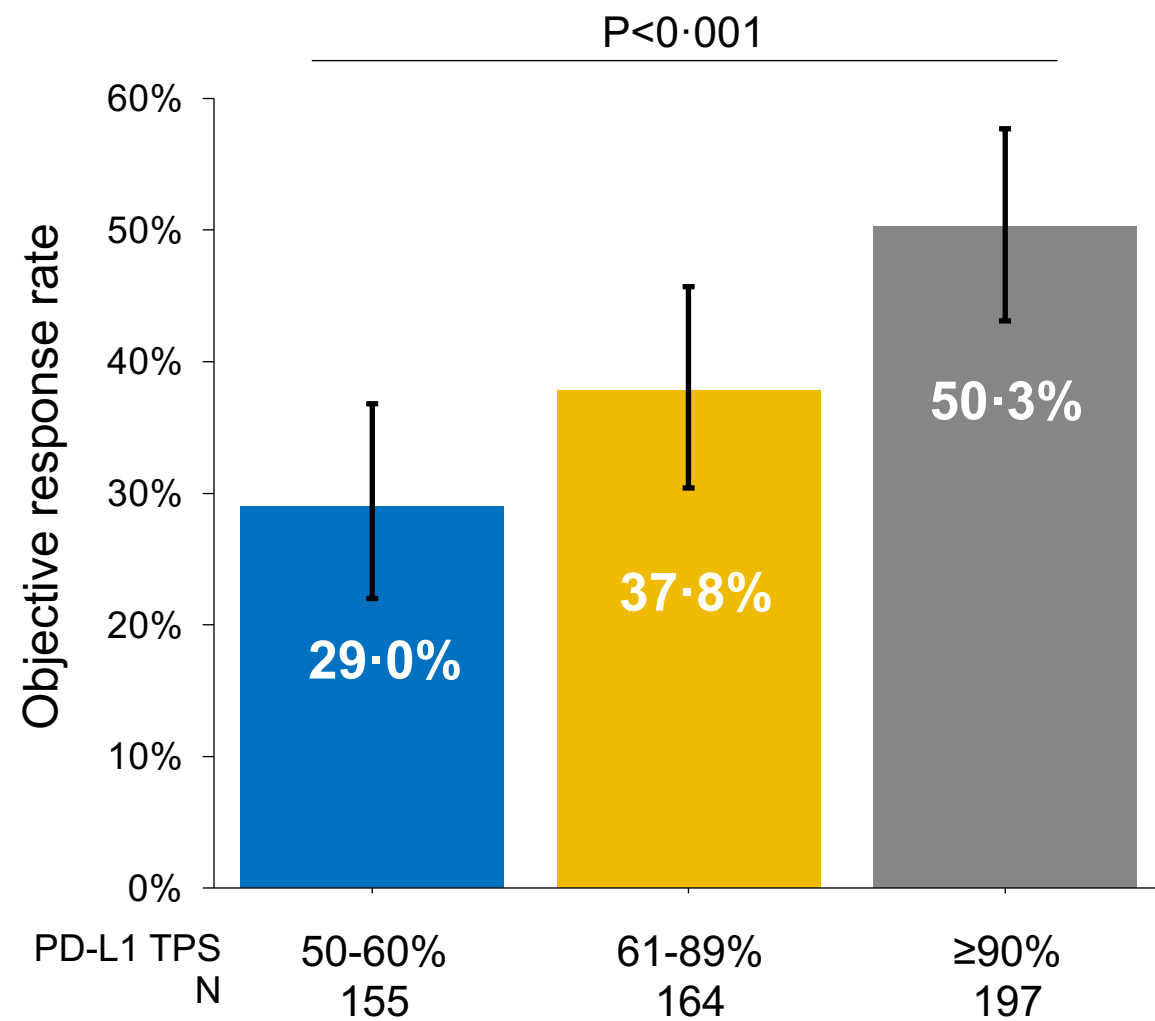
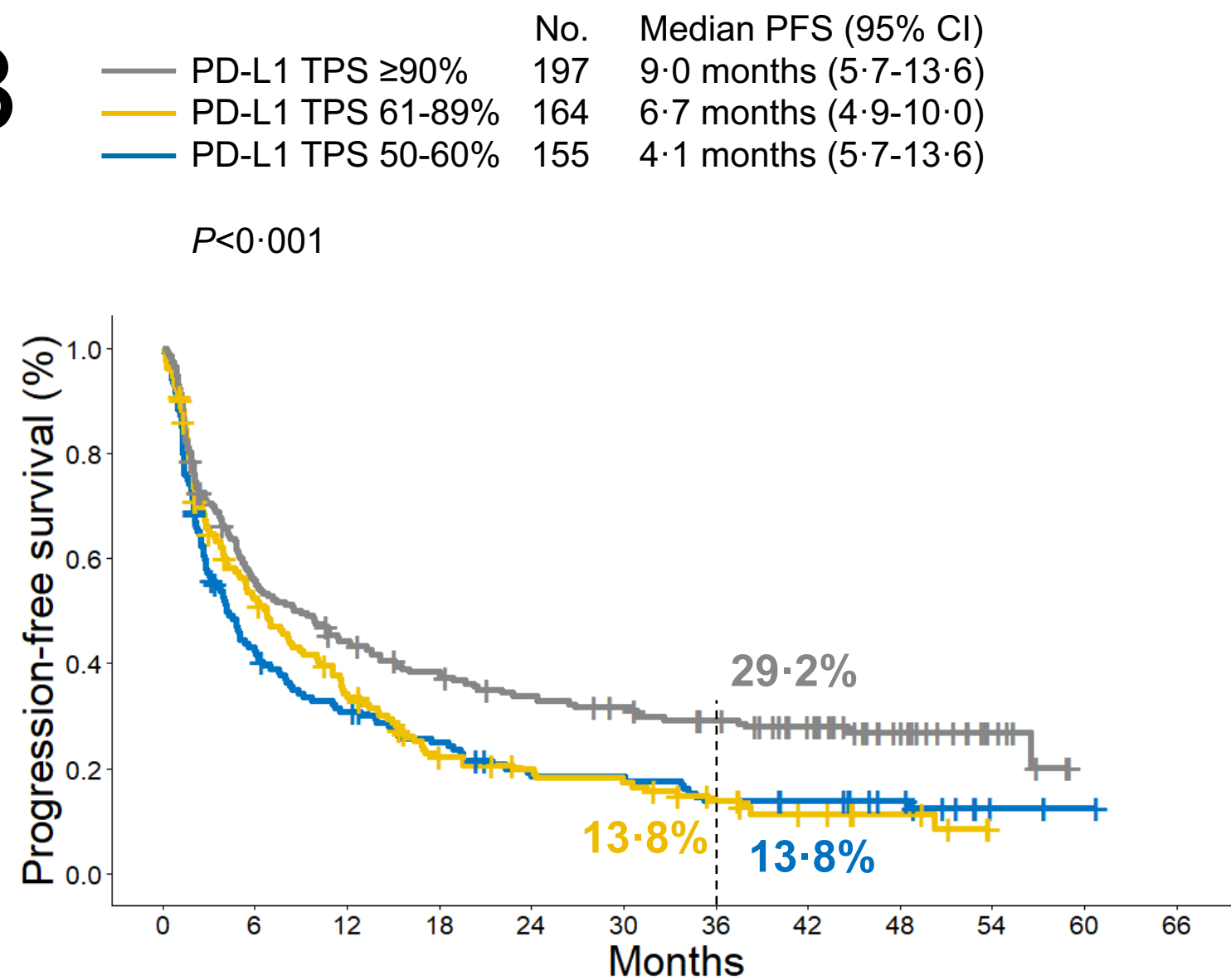
A Progression-free survival to chemotherapy



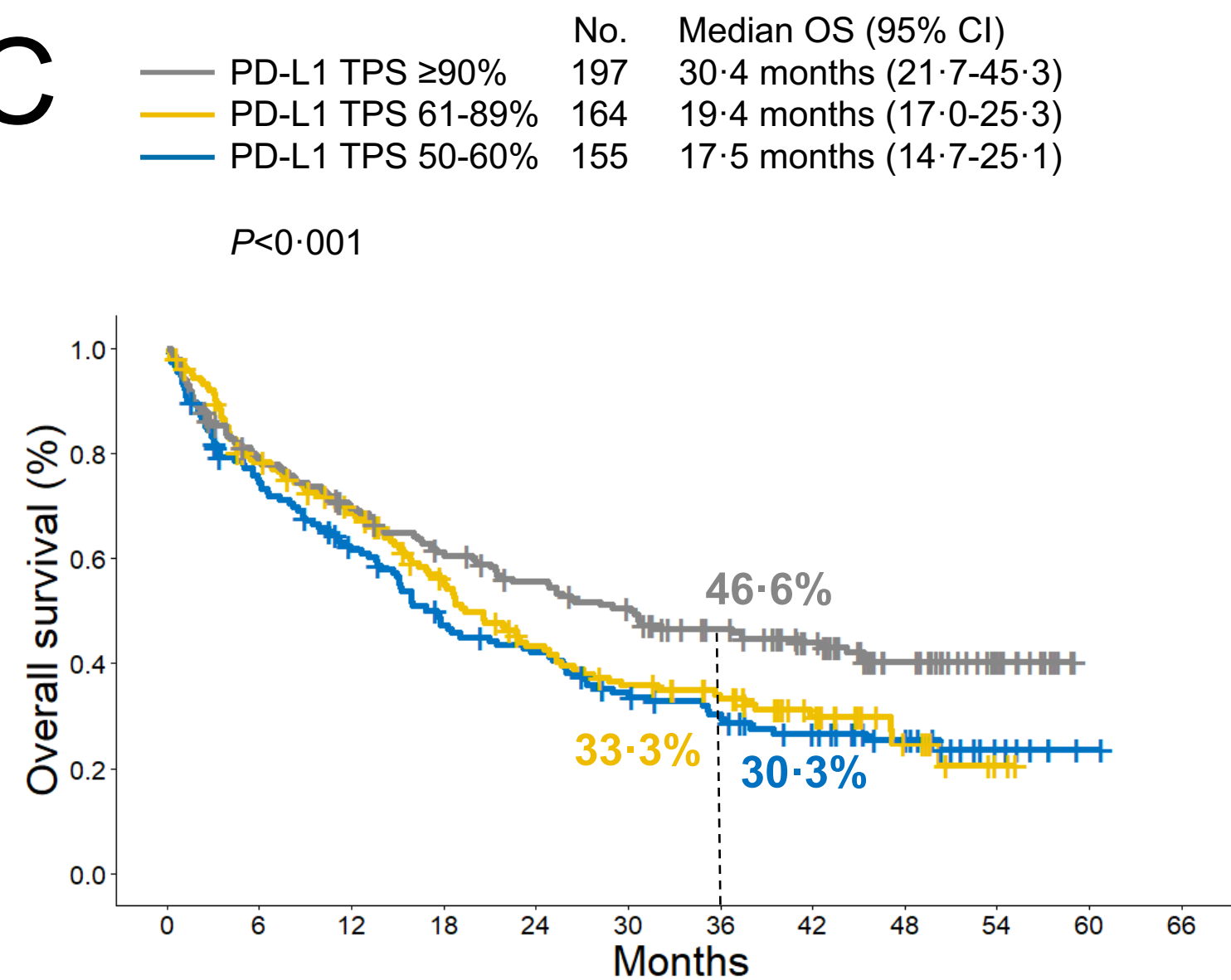
B Overall survival to chemotherapy



Supplementary Figure 7

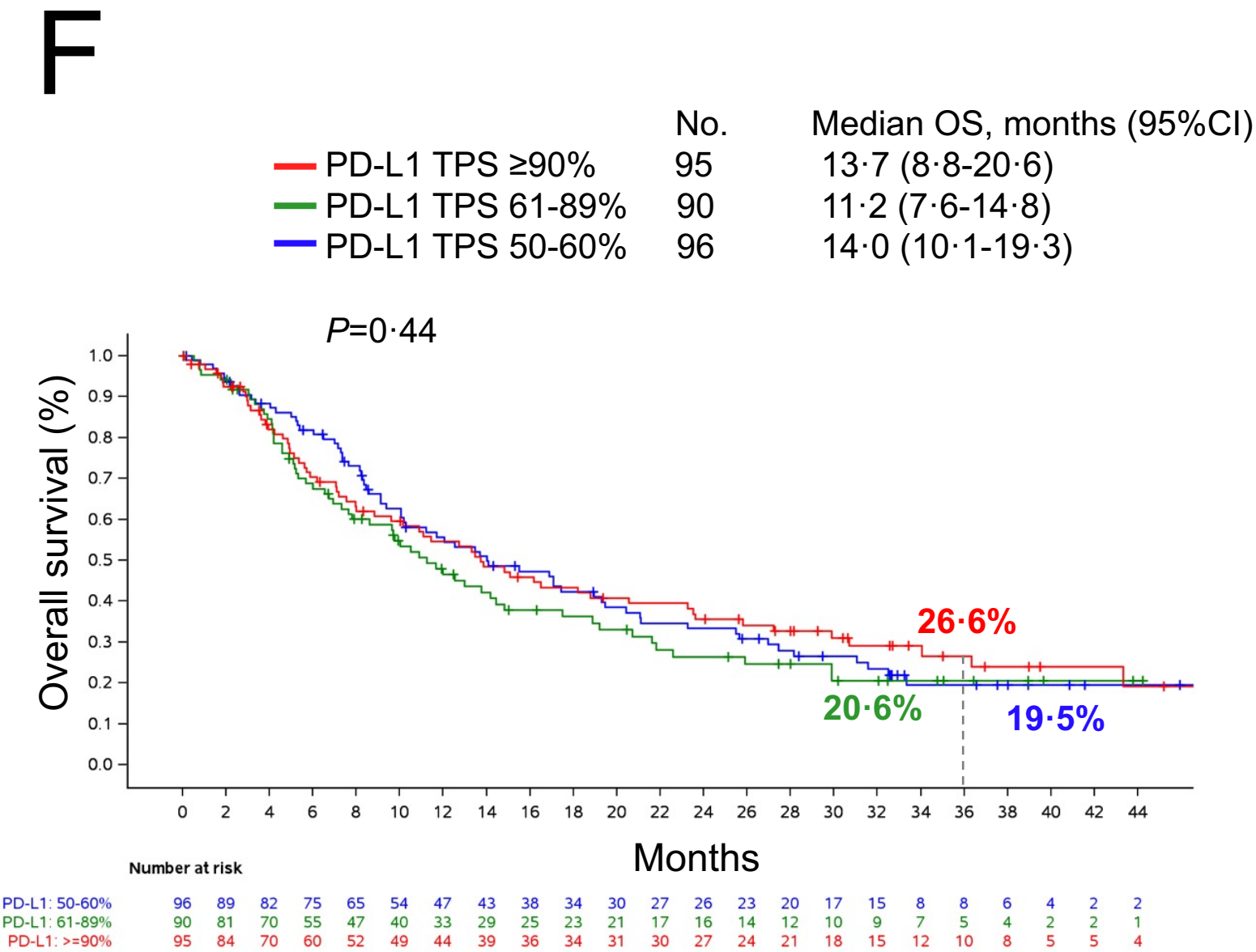
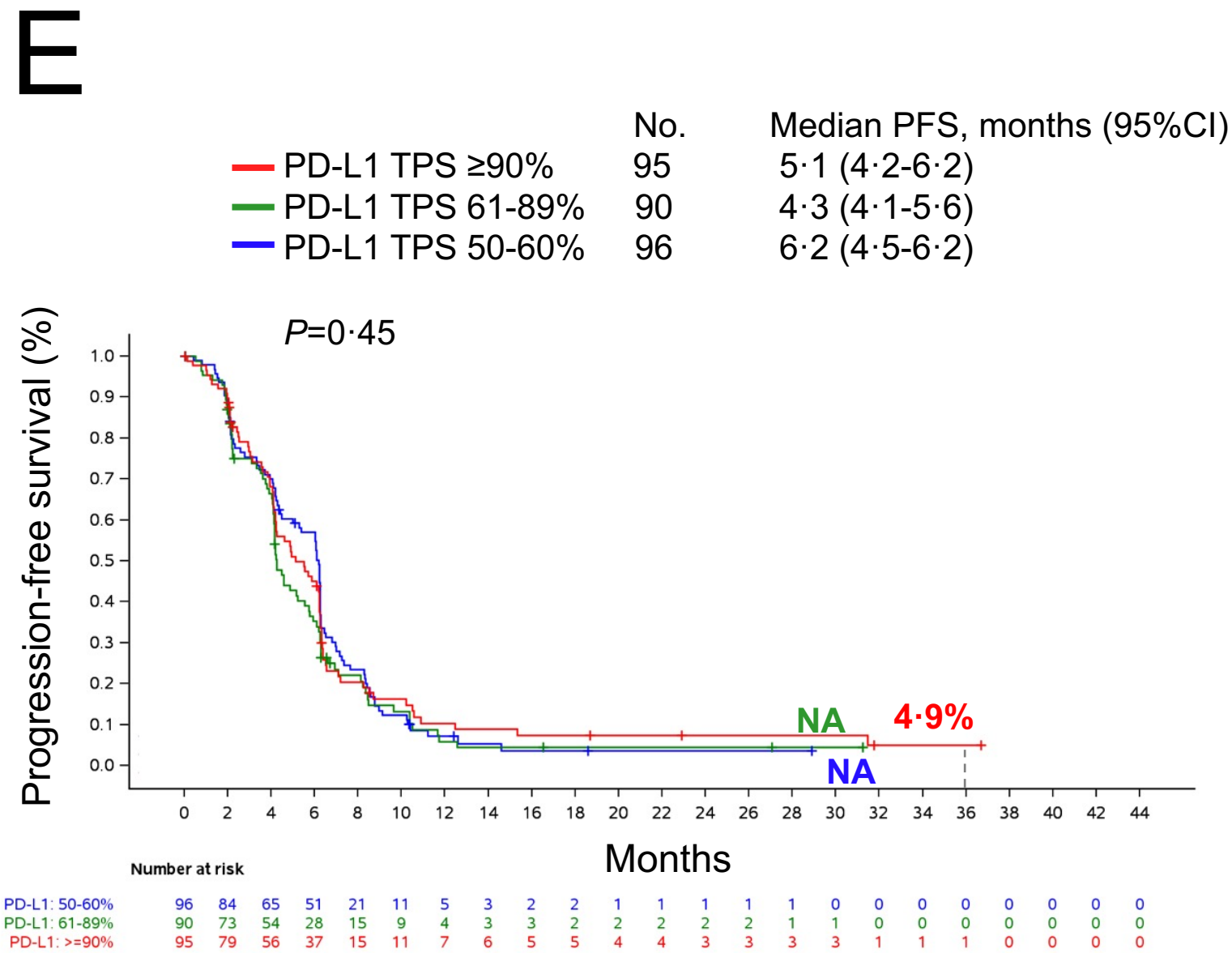
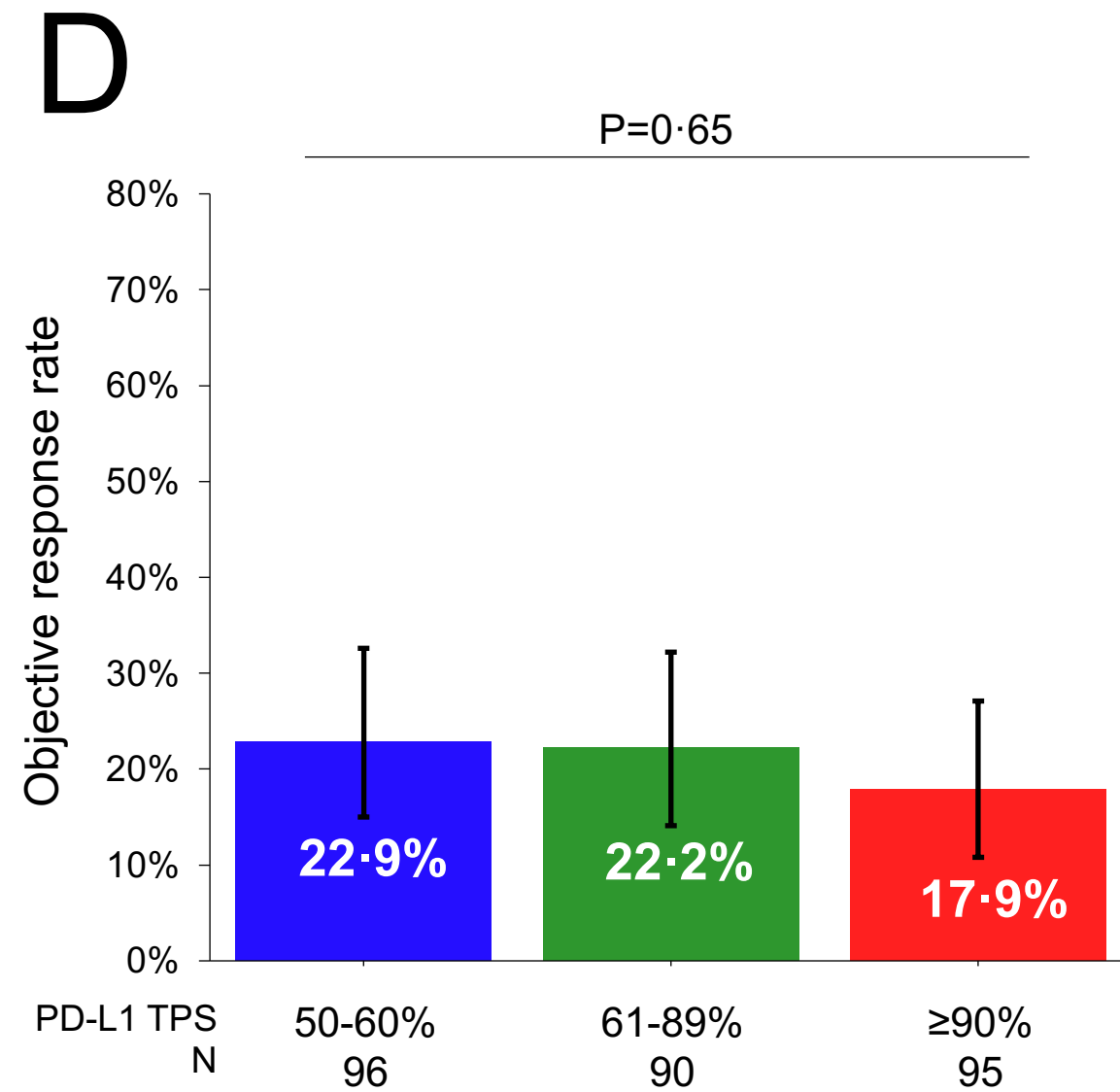
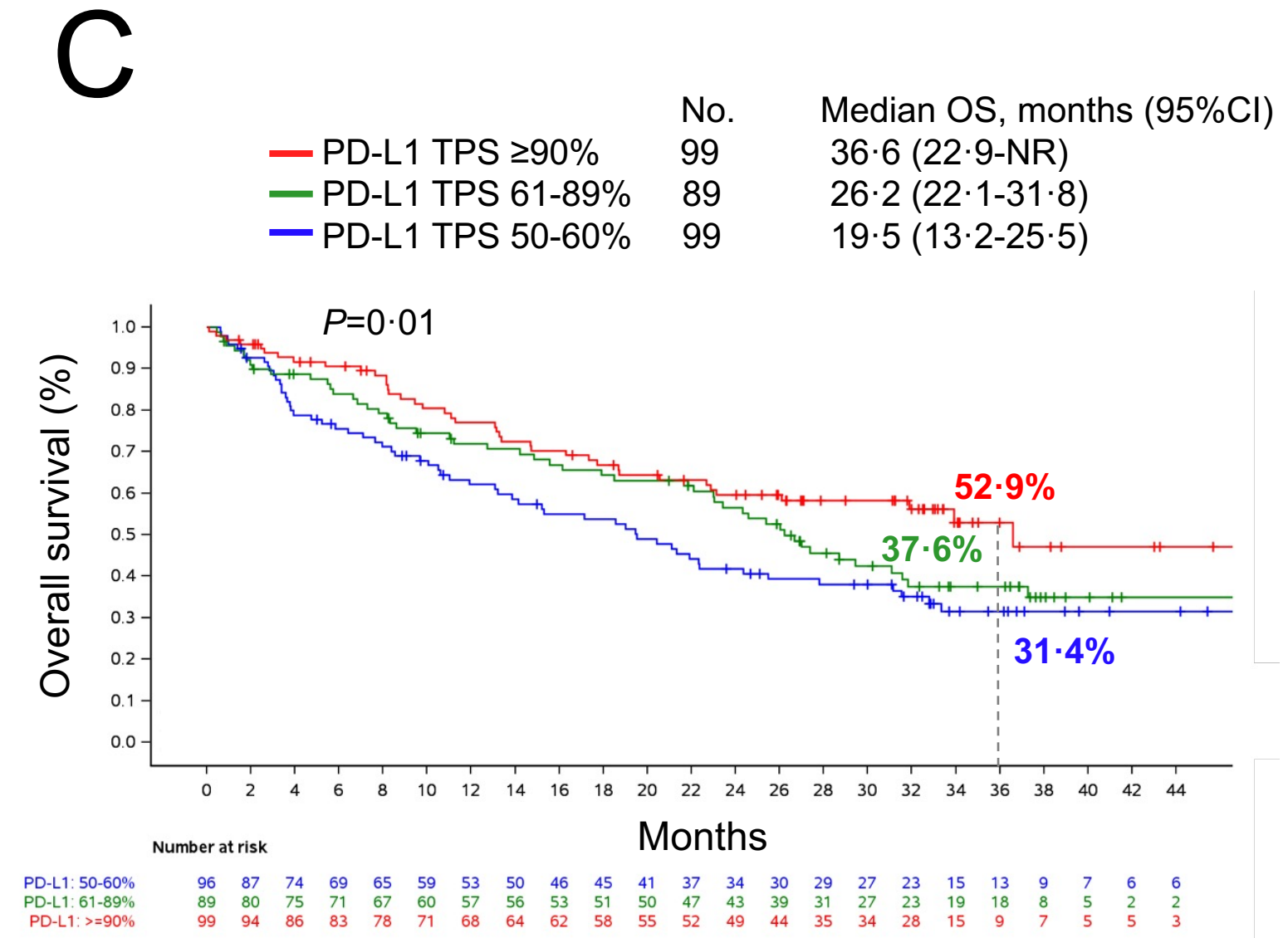
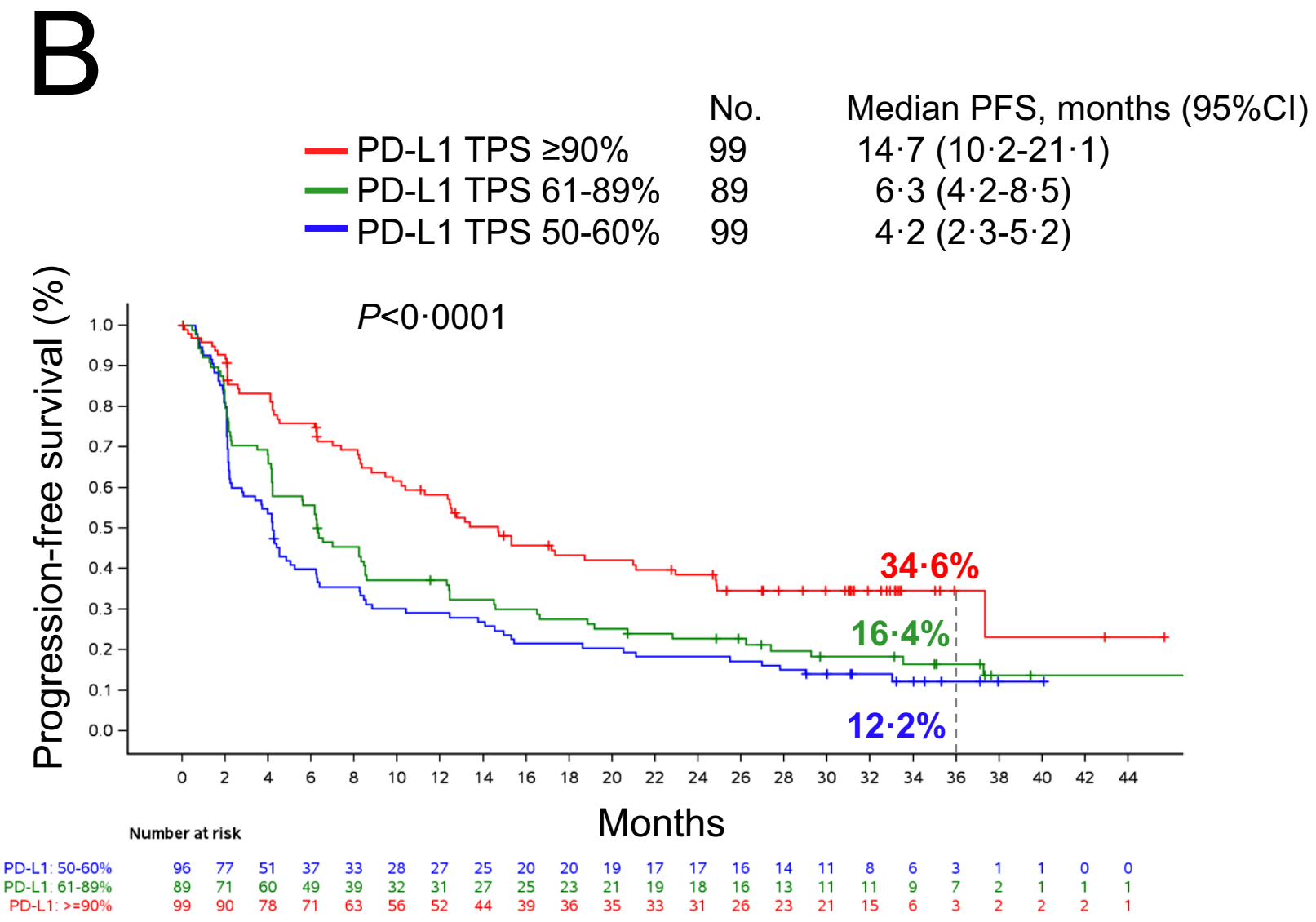
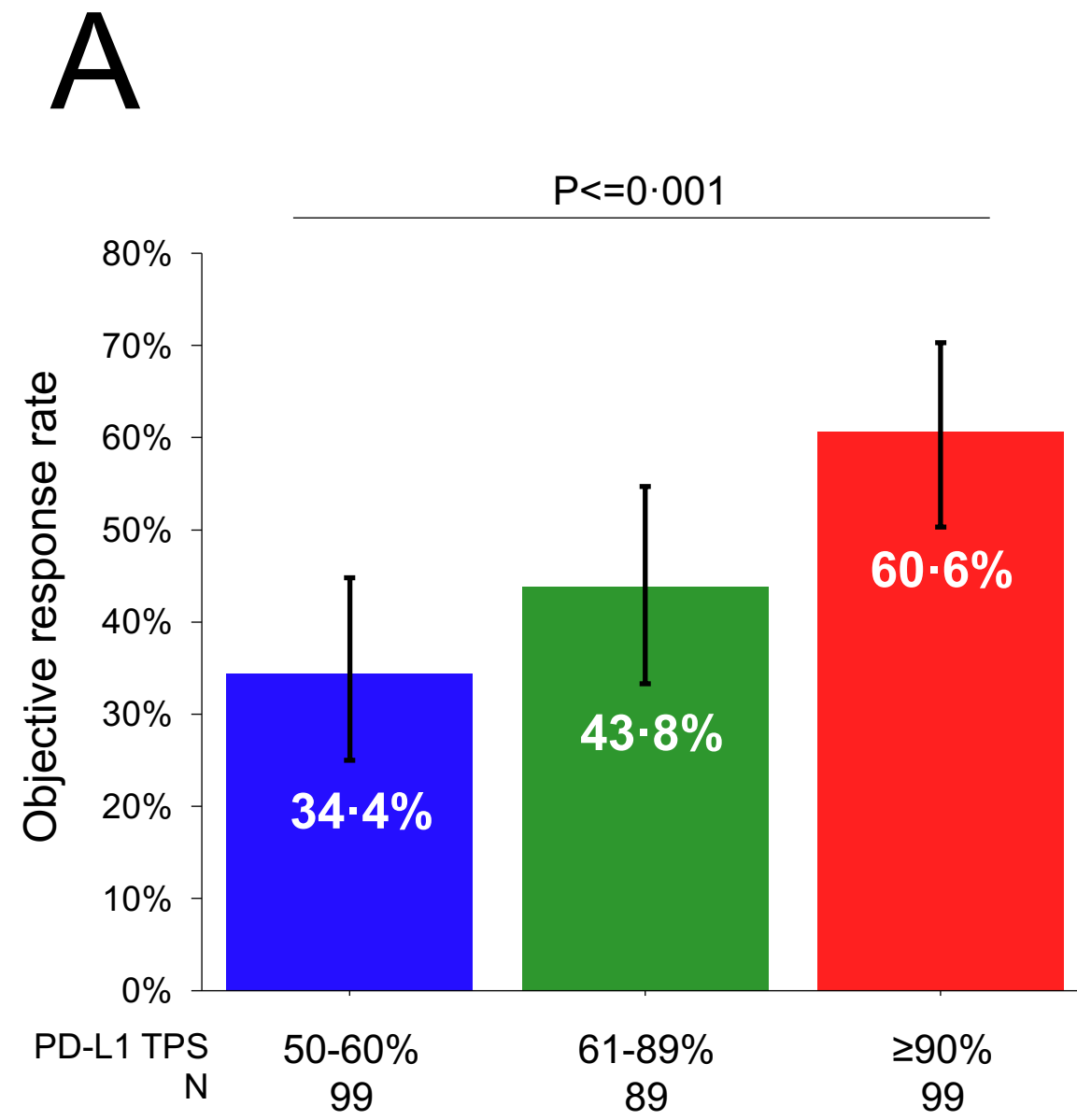
A**Supplementary Figure 8****B**

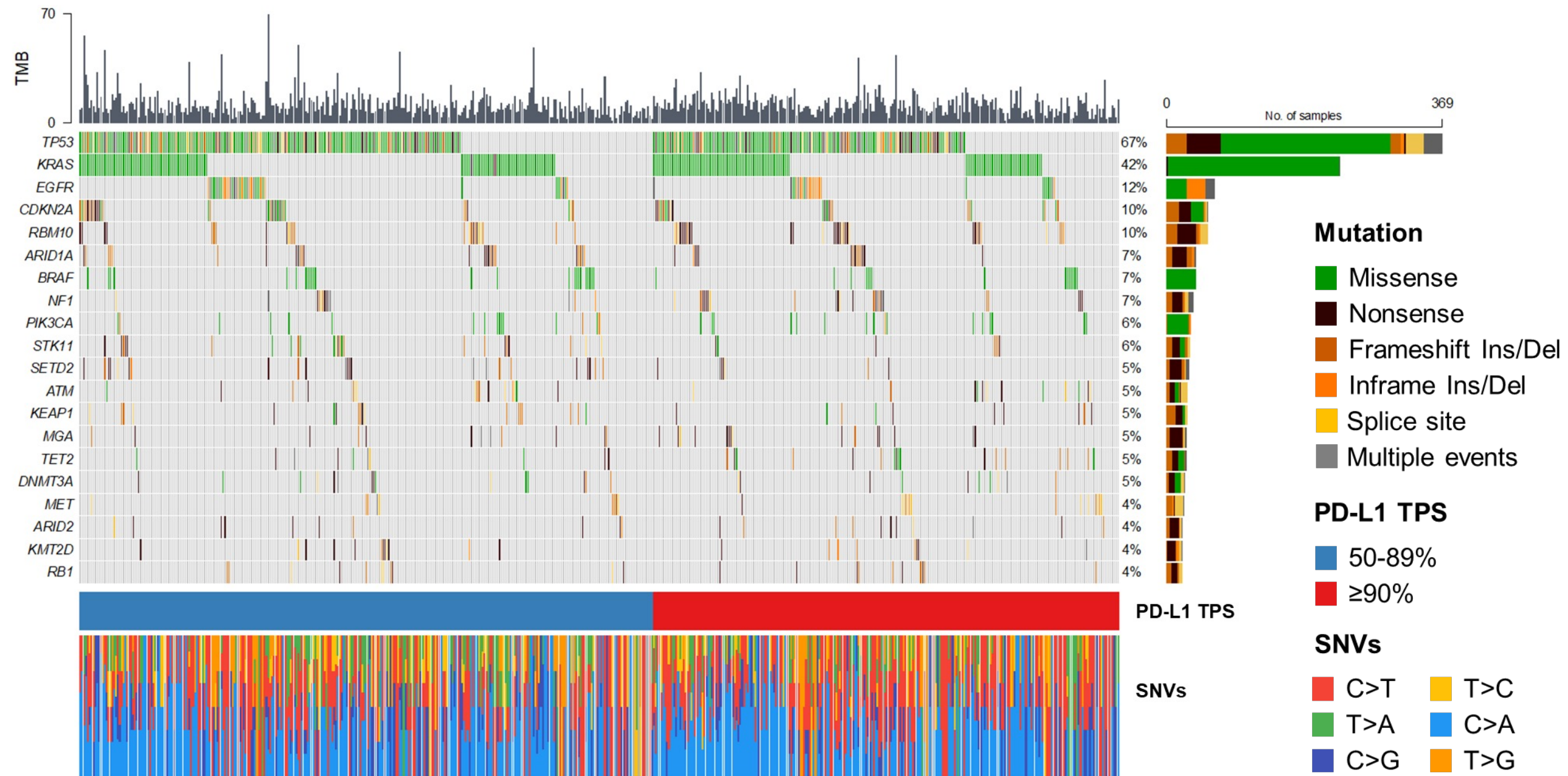
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—	164	164	80	50	29	24	21	14	8	5	0	0	0
—	197	197	107	83	70	60	53	46	36	21	8	0	0

C

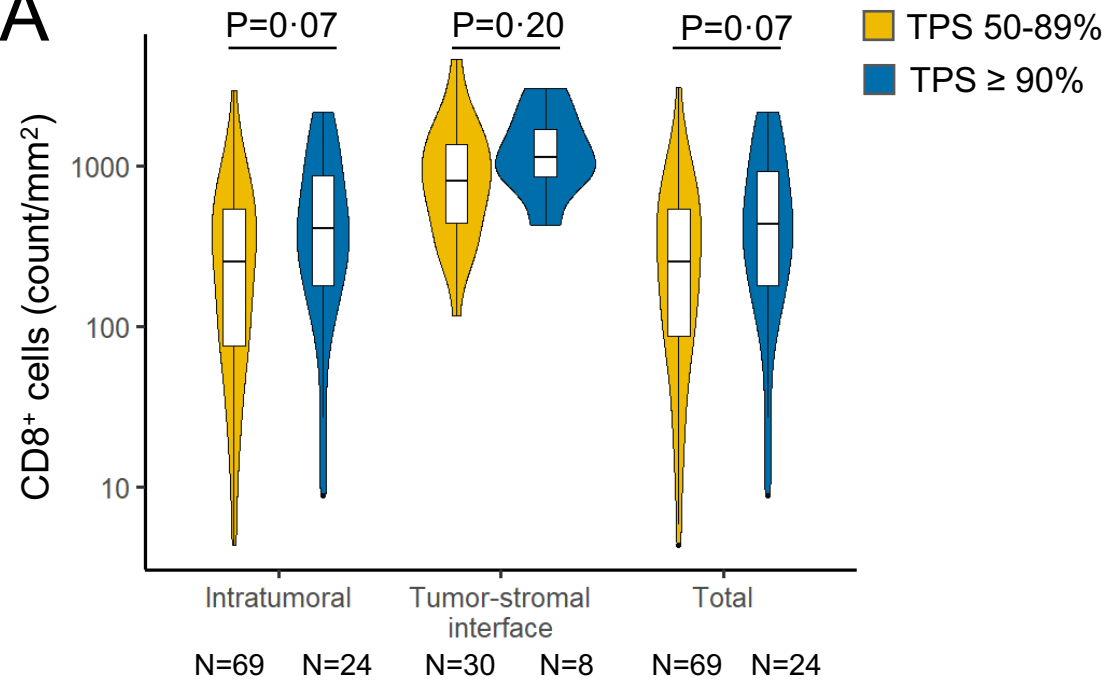
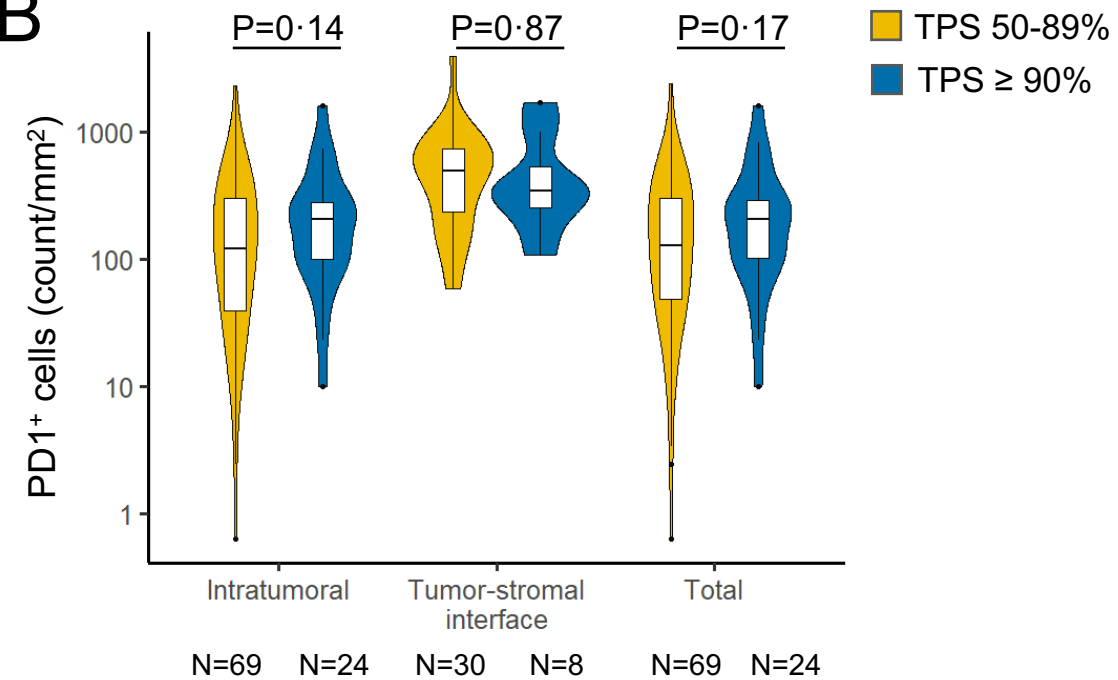
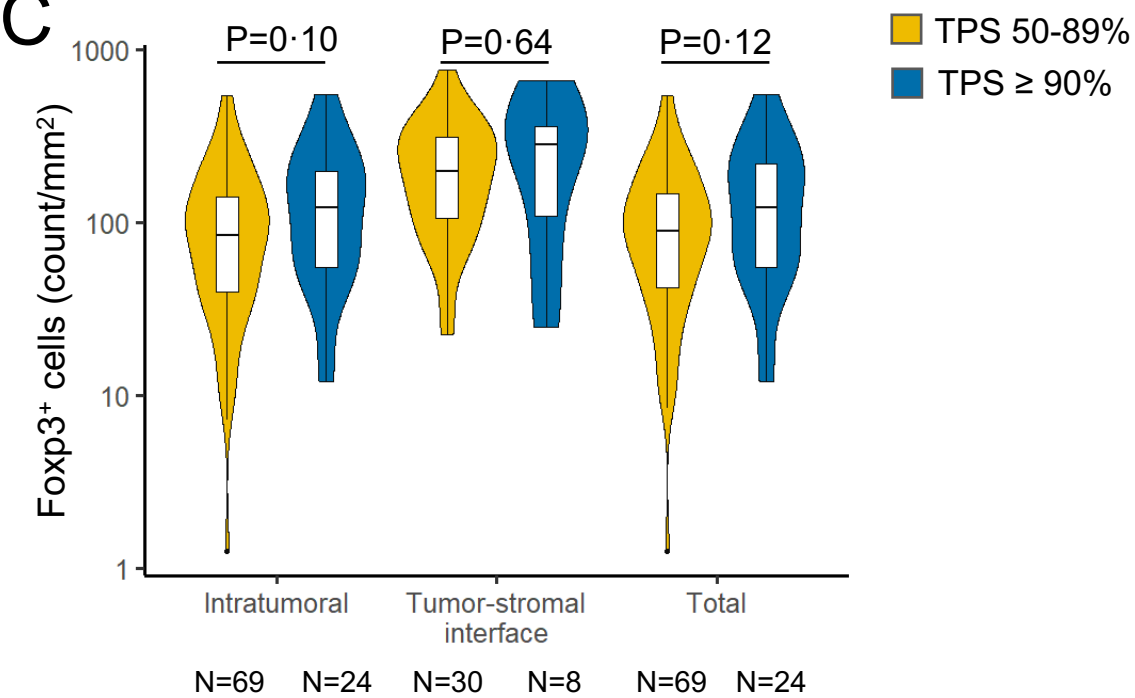
Number at risk		0	6	12	18	24	30	36	42	48	54	60	66
—	155	155	111	87	65	56	42	36	26	18	7	1	0
—	164	164	124	104	78	58	47	38	21	9	2	0	0
—	197	197	152	131	113	100	89	74	58	33	15	0	0

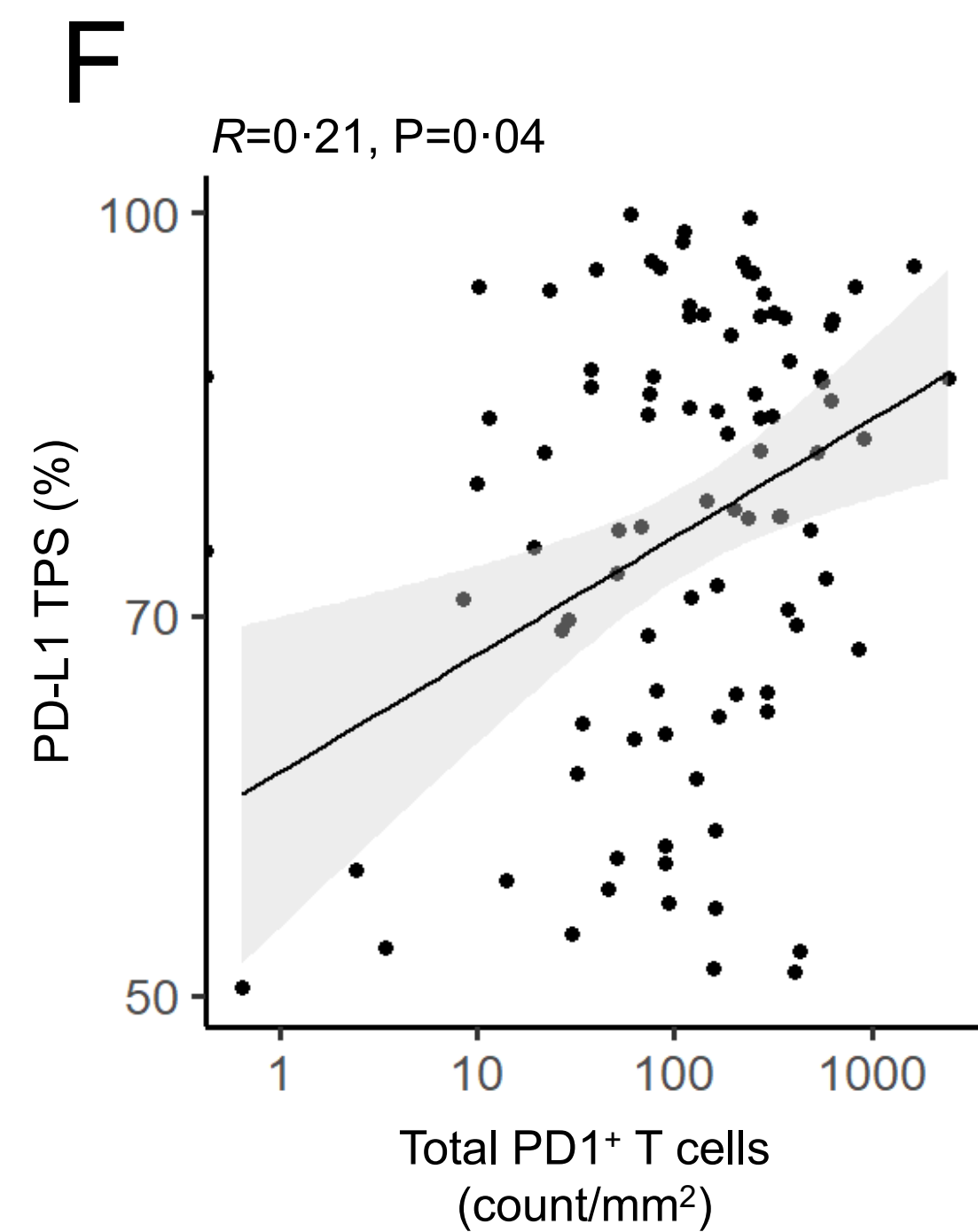
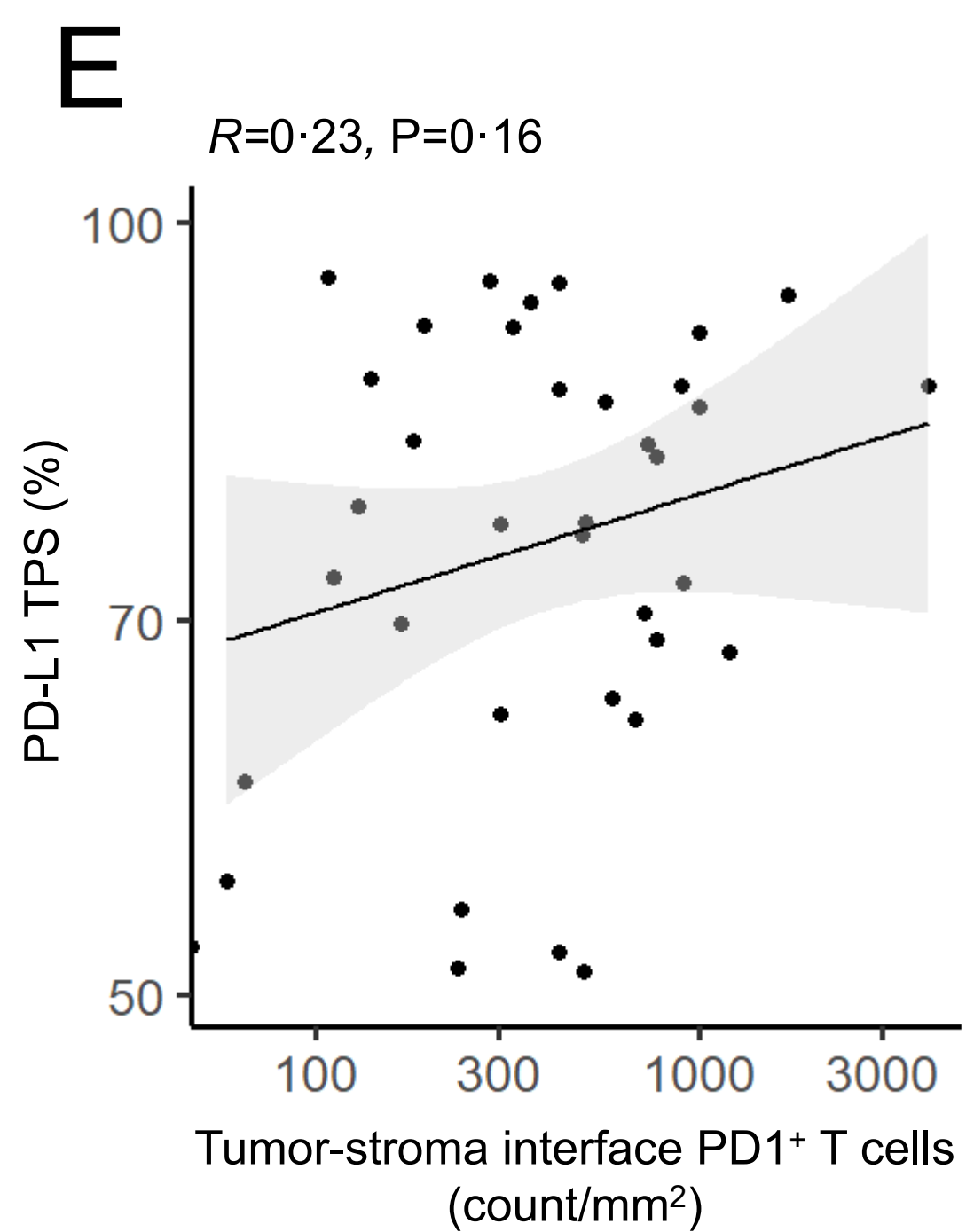
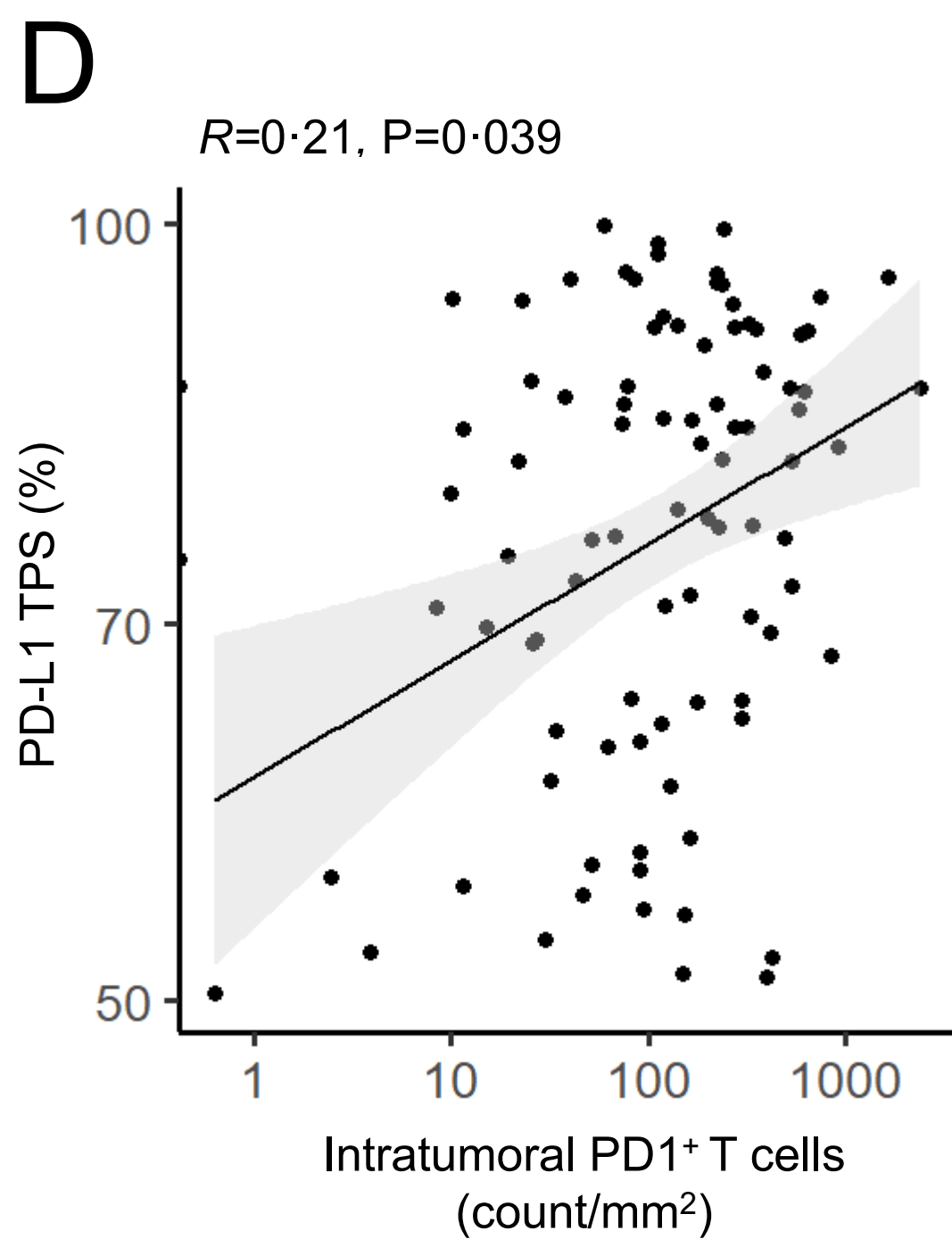
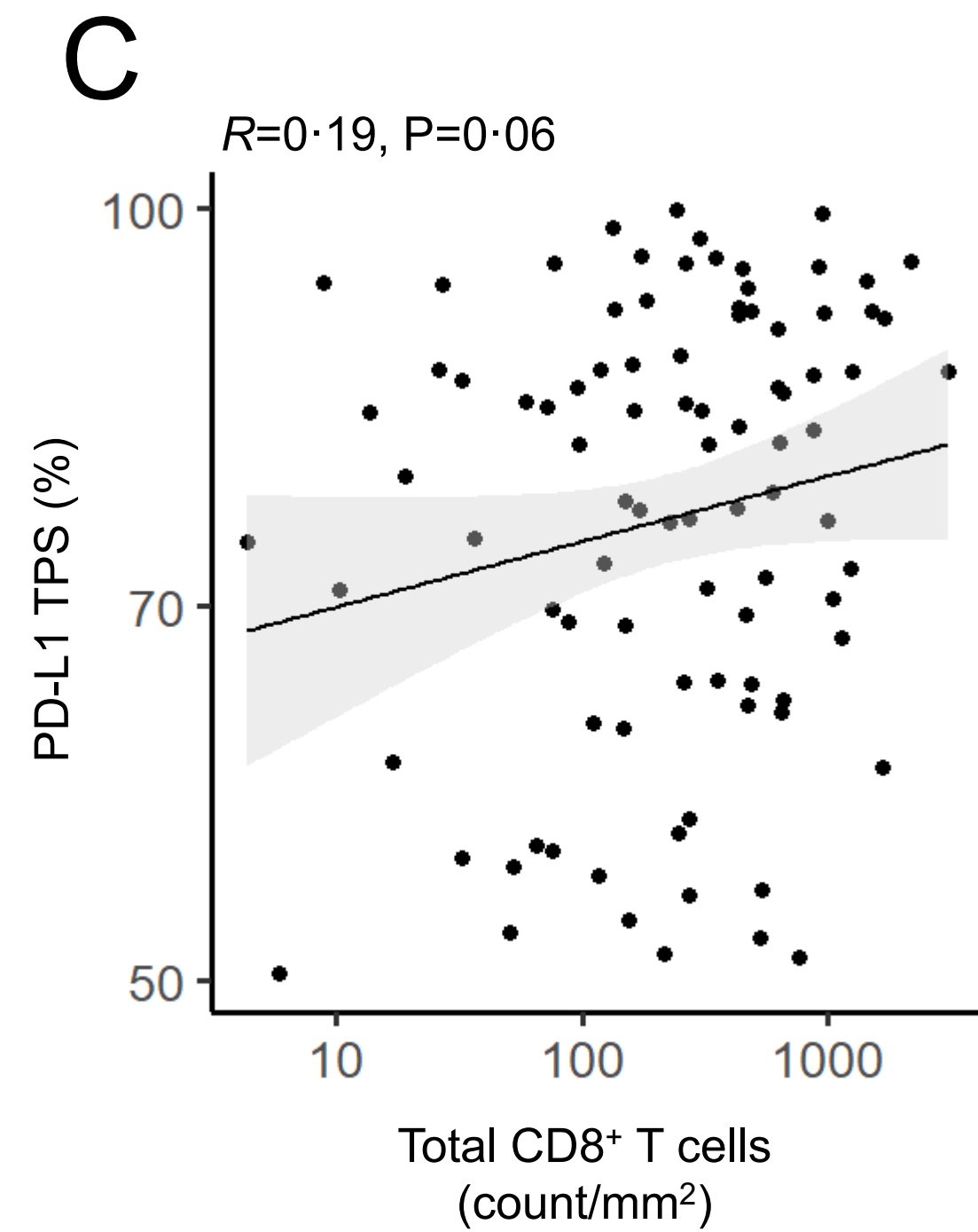
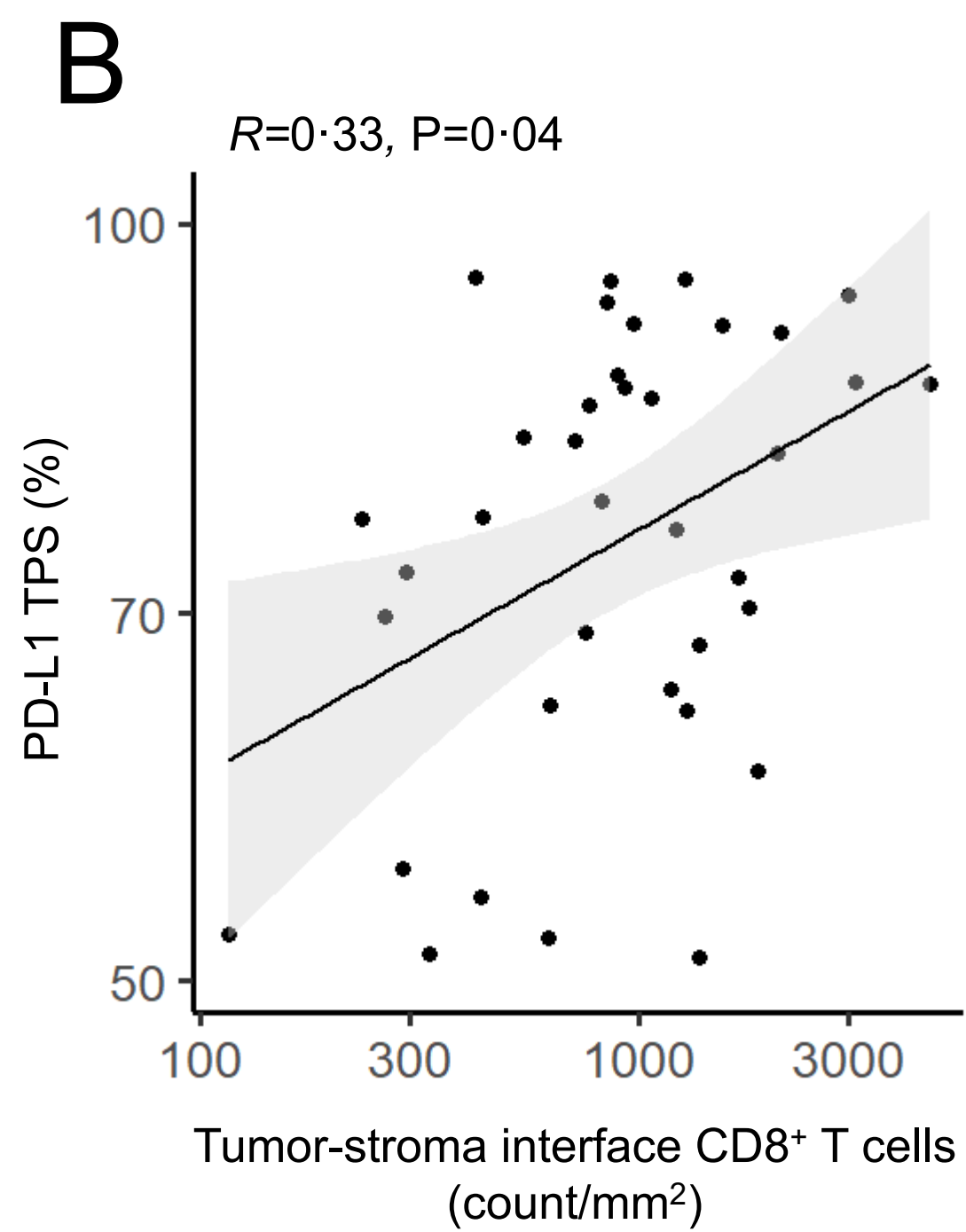
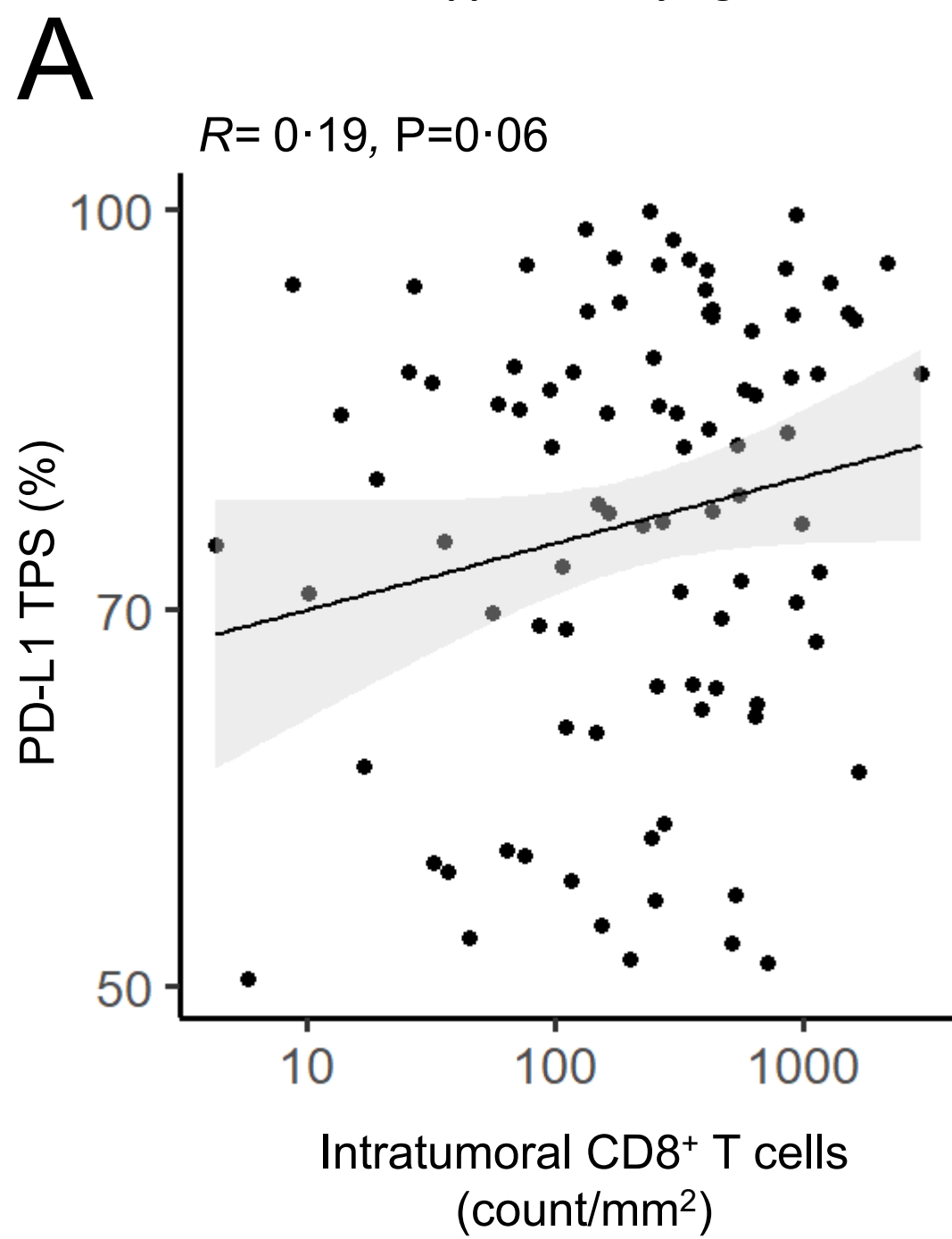
Supplementary Figure 9

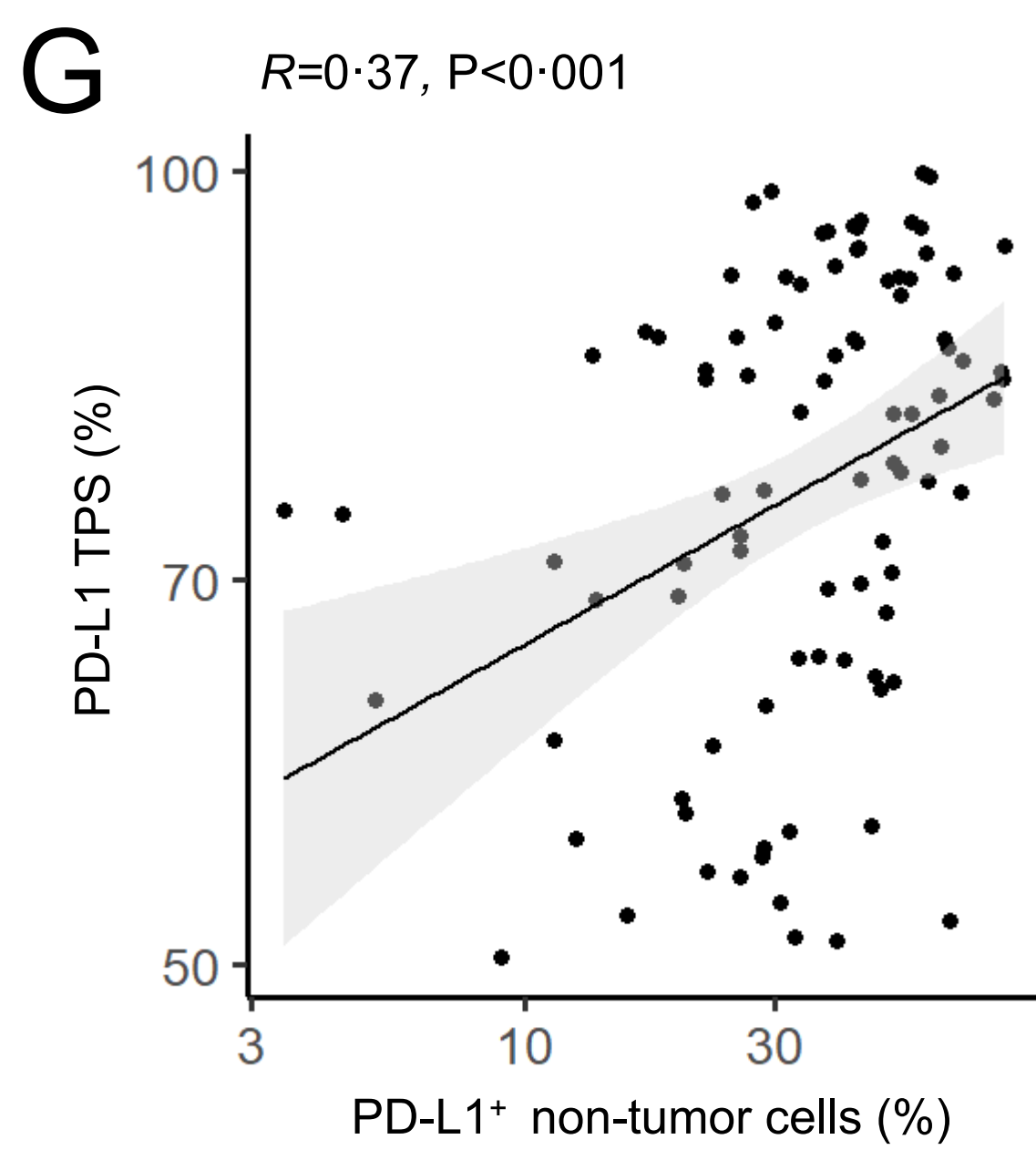
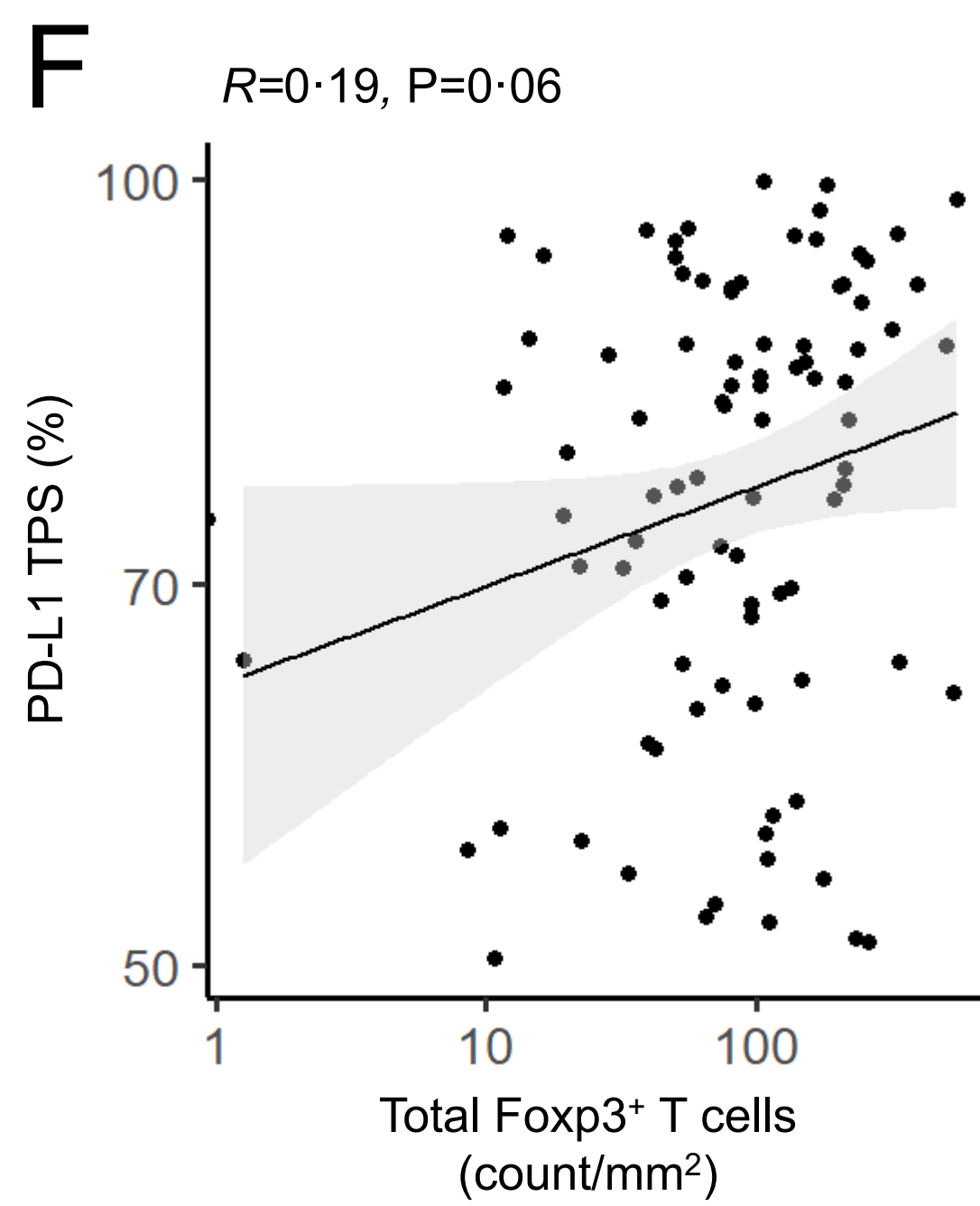
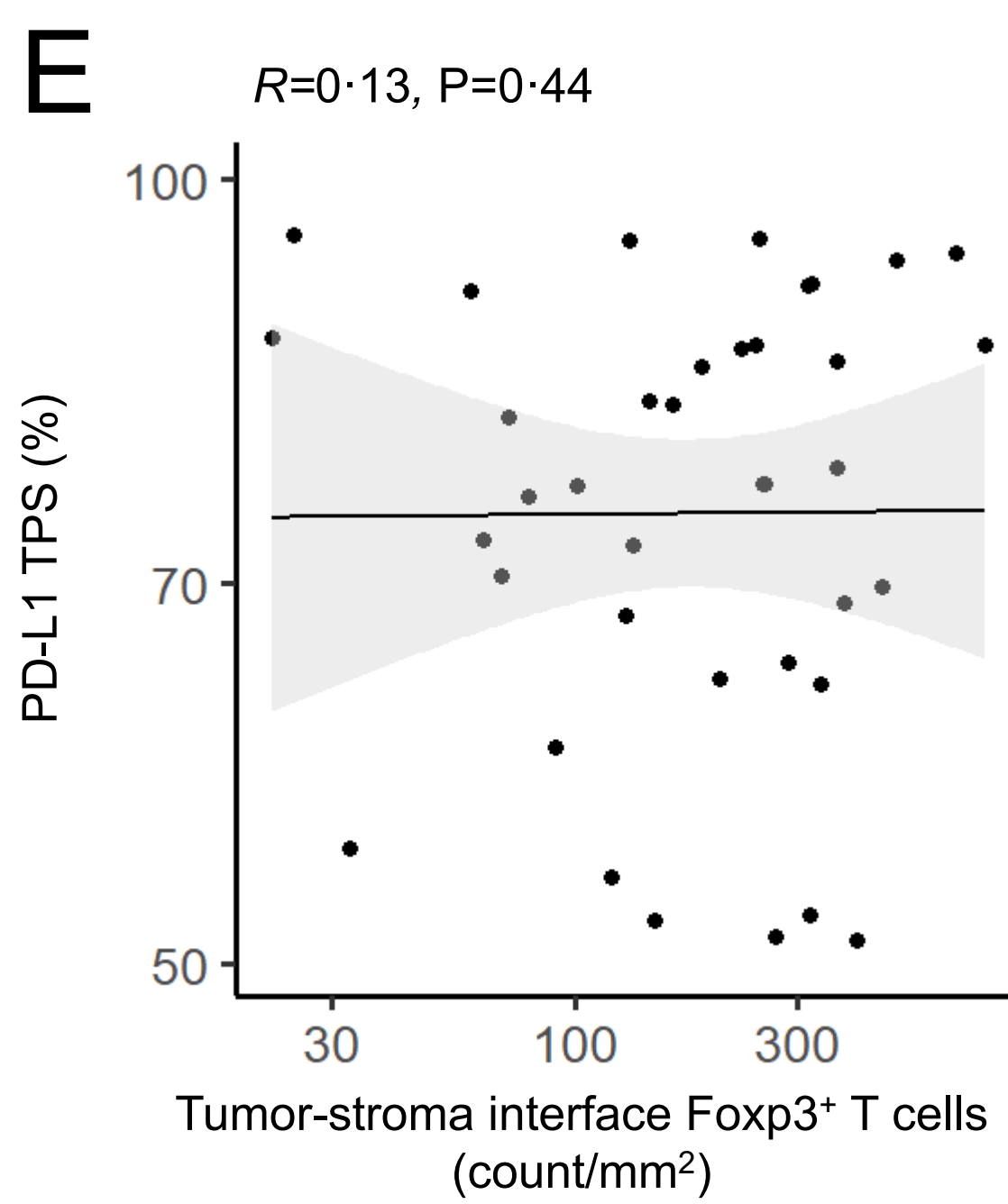
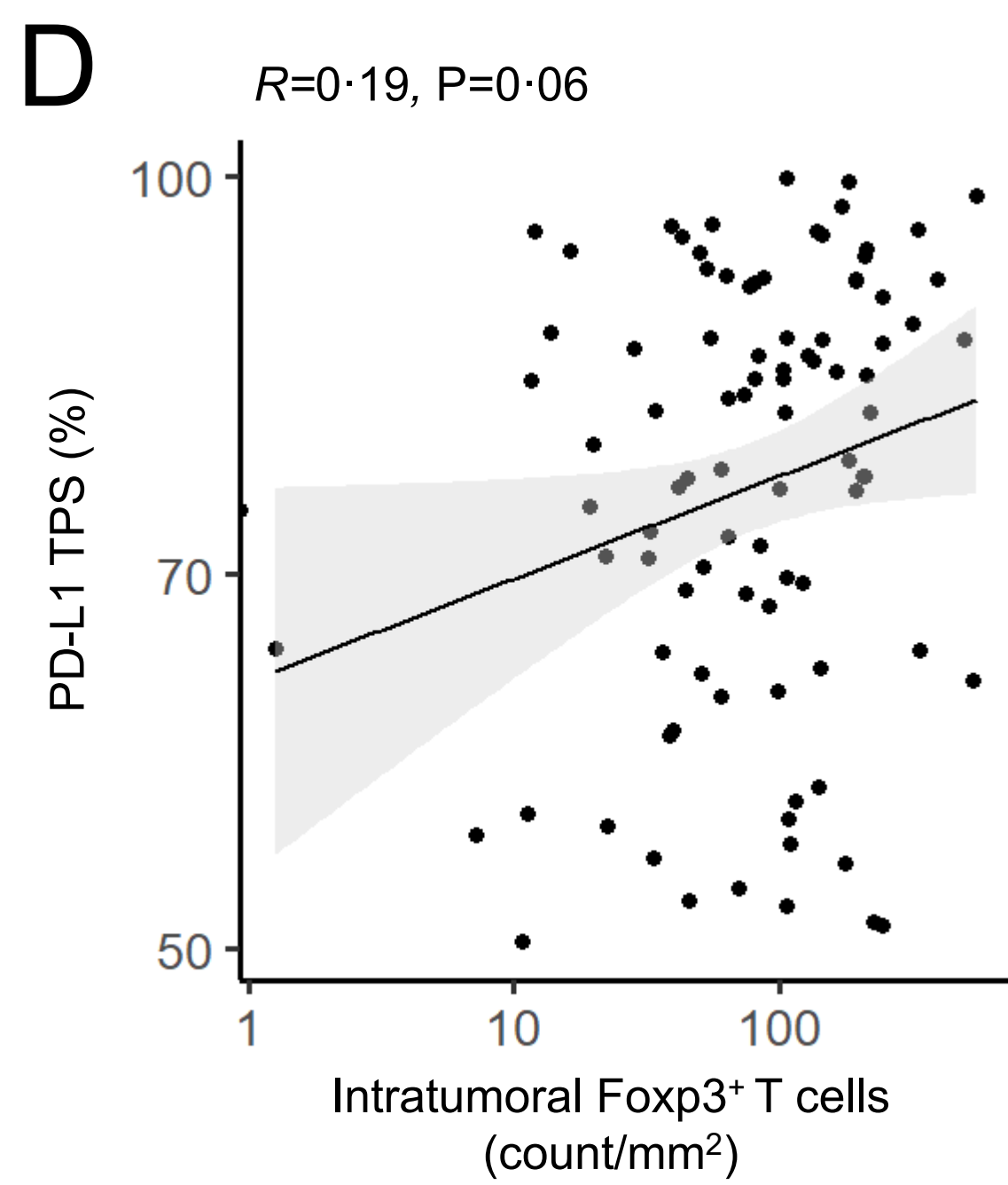
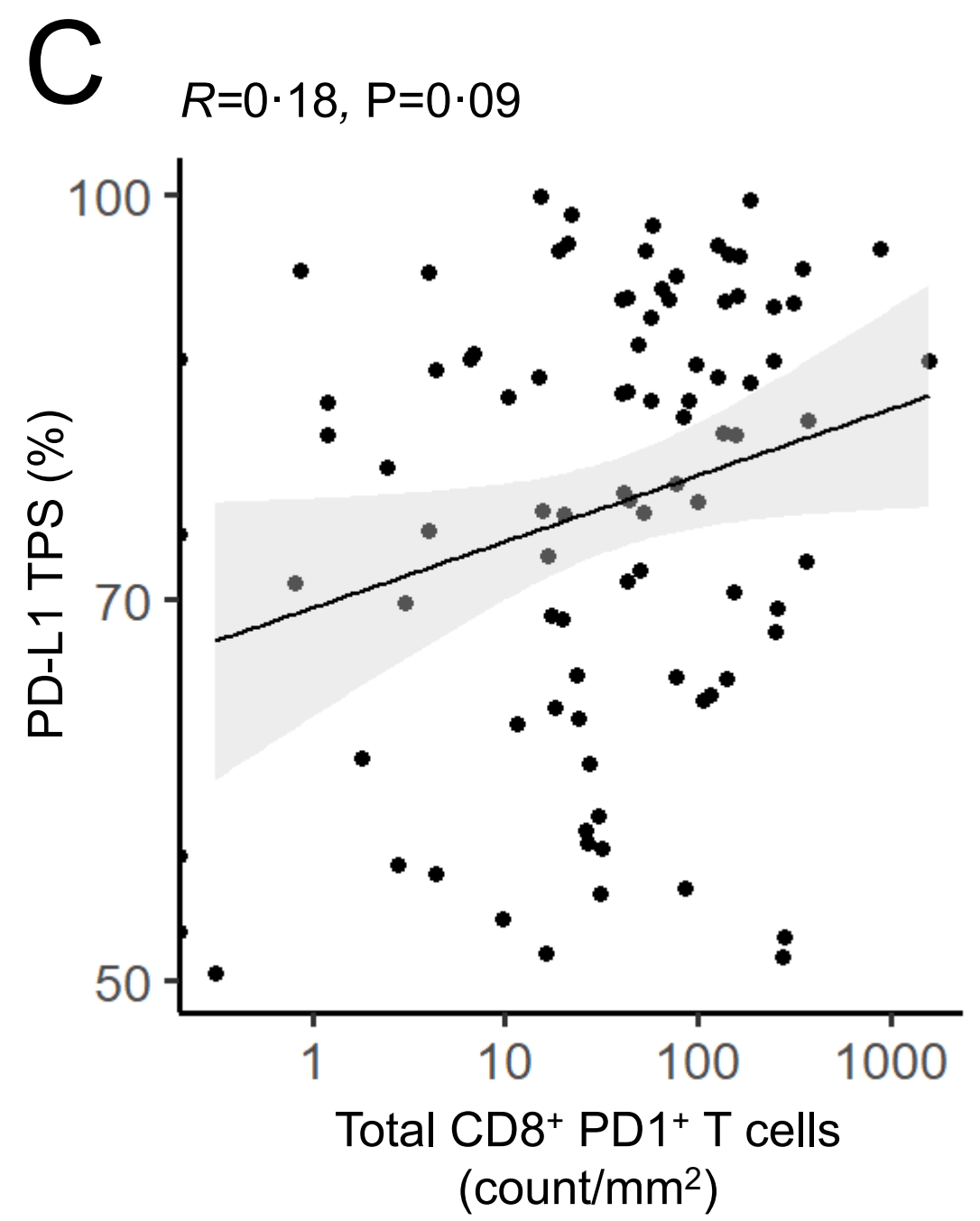
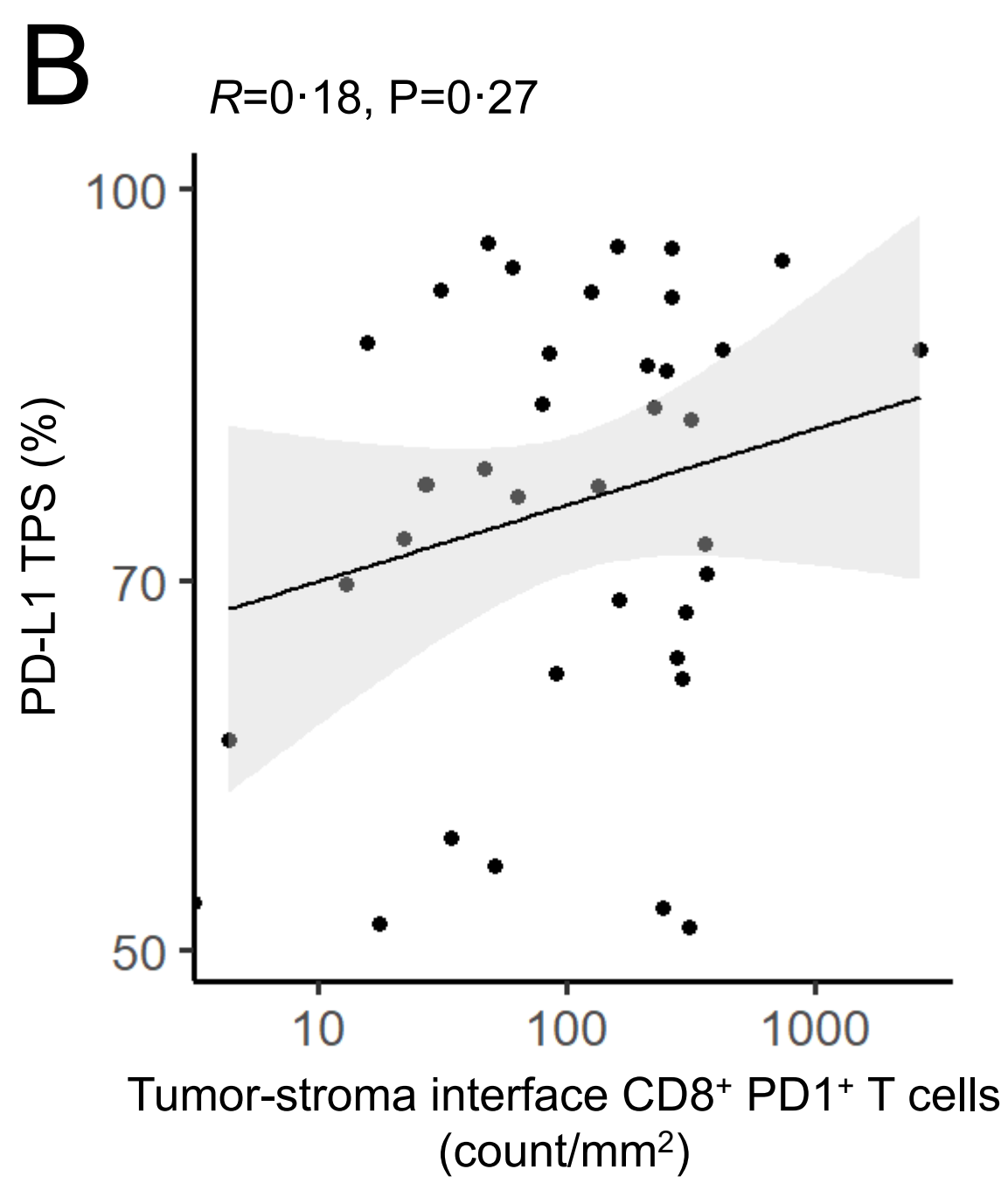
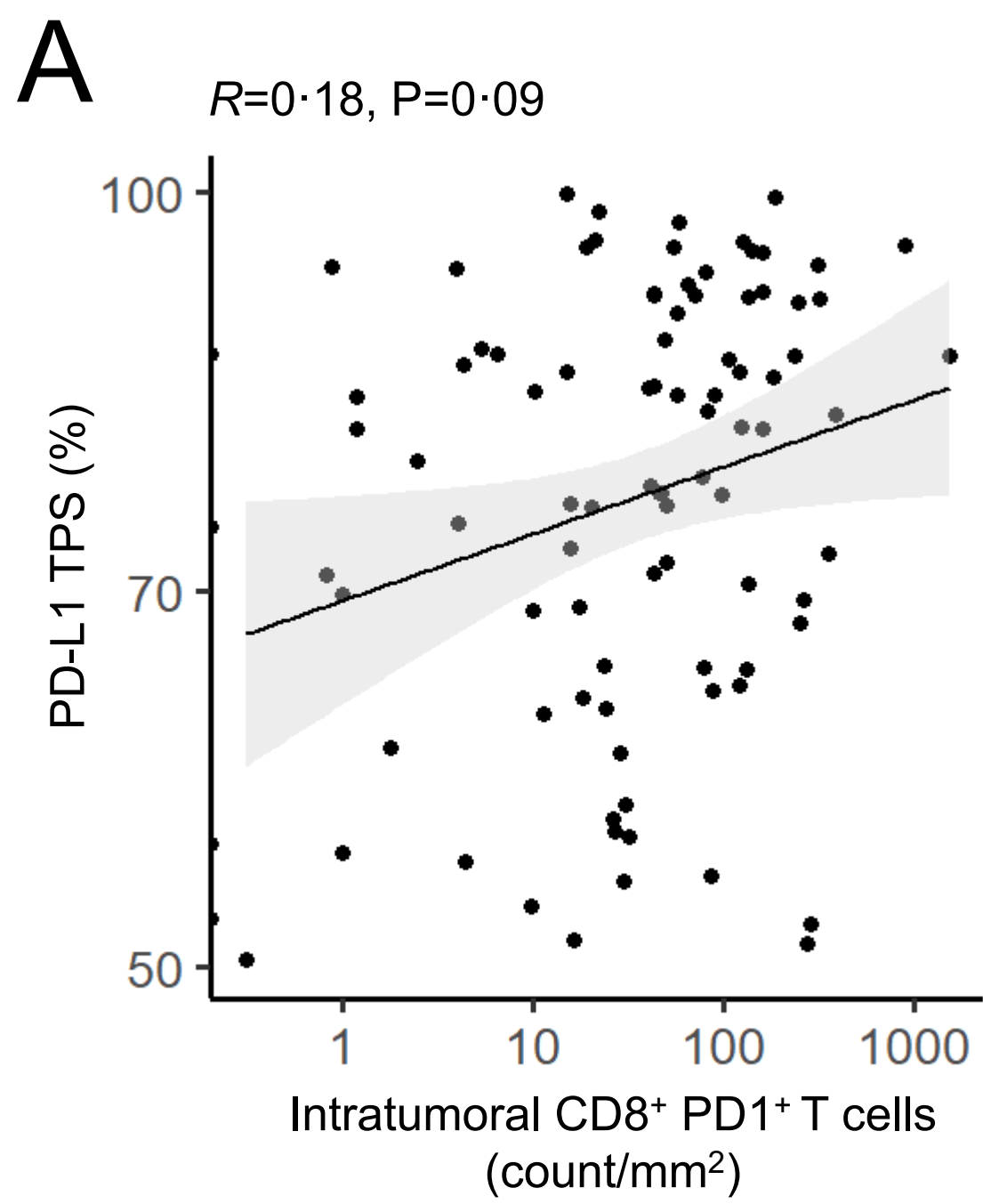




Supplementary Figure 10

A**B****C****Supplementary Figure 11**





Supplementary Figure 13

Supplementary Table 1. Characteristics of 516 patients with advanced NSCLC who received first-line pembrolizumab in the retrospective, multi-center academic cohort.

Characteristic	N=516 (%)
Age , median (range)	69 (30-93)
Sex	
• Men	245 (47.5)
• Women	271 (52.5)
Smoking history	
• Ever	473 (91.7)
• Never	43 (8.3)
Pack/years , median (range)	30 (0-208)
Histology	
• Non-squamous	440 (85.3)
• Squamous	76 (14.7)
ECOG PS	
• 0-1	416 (80.6)
• ≥2	100 (19.4)
Driver	
• KRAS	191 (46.1)
• BRAF	21 (5.1)
• MET	14 (3.4)
• RET	1 (0.2)
• None identified	187 (45.2)
• Not assessed	102
PD-L1 TPS	
• 50-89%	319 (61.8)
• ≥90%	197 (38.2)
Institution	
• MSKCC	225 (43.6)
• DFCI	161 (31.2)
• MGH	67 (13.0)
• MDACC	63 (12.2)

ECOG PS, Eastern Cooperative Oncology Group Performance Status

Supplementary Table 2. Characteristics of 565 patients with advanced NSCLC who received first-line cemiplimab or chemotherapy in the prospective EMPOWER-Lung-01 phase III, randomized clinical trial.

Characteristic	Cemiplimab arm N=284 (%)	Chemotherapy arm N=281 (%)
Age, median (range)	63 (31-79)	64 (40-84)
Sex		
• Men	249 (87.7)	231 (82.2)
• Women	35 (12.3)	50 (17.8)
Histology		
• Non-squamous	161 (56.7)	159 (56.6)
• Squamous	123 (43.3)	122 (43.4)
ECOG PS		
• 0	77 (27.1)	76 (27.0)
• 1	207 (72.9)	205 (73.0)
Region of enrollment		
• Europe	216 (76.1)	217 (77.2)
• Asia	31 (10.9)	29 (10.3)
• Rest of the world	37 (13.0)	35 (12.5)
Smoking status		
• Current	106 (37.3)	92 (32.7)
• Former	178 (62.7)	189 (67.3)
Cancer stage at screening		
• IIIB/C	45 (15.8)	42 (15.0)
• IV	239 (84.2)	239 (85.0)
PD-L1 TPS		
• 50-89%	185 (65.1)	186 (66.2)
• ≥90%	99 (34.9)	95 (33.8)

ECOG PS, Eastern Cooperative Oncology Group Performance Status

Supplementary Table 3. Characteristics of patients with advanced NSCLC who received first-line pembrolizumab according to PD-L1 expression levels (50-89% versus $\geq 90\%$).

Characteristics	PD-L1 TPS 50-89% N=319	PD-L1 TPS $\geq 90\%$ N=197	P
Age , median (range)	69 (35-93)	69 (30-88)	0.71
Sex			
• Male	158 (49.5)	87 (44.2)	0.24
• Female	161 (50.5)	110 (55.8)	
Smoking history			
• Ever	286 (89.7)	187 (94.9)	0.047
• Never	33 (10.3)	10 (5.1)	
Pack/years , median (range)	33.8 (0-200)	30 (0-208)	0.87
Histology			
• Non-squamous	266 (83.4)	174 (88.3)	0.16
• Squamous	53 (16.6)	23 (11.7)	
ECOG PS			
• 0-1	257 (80.6)	159 (80.7)	0.99
• ≥ 2	62 (19.4)	38 (19.3)	
Driver			
• KRAS	110 (44.5)	81 (48.5)	0.34
• BRAF	14 (5.7)	7 (4.2)	
• MET	6 (2.4)	8 (4.8)	
• RET	0 (0.0)	1 (0.6)	
• None identified	117 (47.4)	70 (41.9)	
• Not assessed	72	30	

PS ECOG, Performance Status Eastern Cooperative Oncology Group

Supplementary Table 4. Multivariable Cox regression for progression-free and overall survival in the first-line pembrolizumab cohort.

Variable	Progression-free survival	Overall survival
	Multivariable HR [95% CI], P	Multivariable HR [95% CI], P
Age*	1.00 [0.99-1.01], 0.66	1.01 [1.00-1.02], 0.002
Sex (male versus female)	1.00 [0.81-1.23], 0.98	0.98 [0.78-1.24], 0.89
ECOG PS (≥2 versus 0-1)	1.37 [1.07-1.77], 0.01	1.78 [1.36-2.33], <0.0001
Histology (squamous versus non-squamous)	0.99 [0.75-1.32], 0.99	1.29 [0.95-1.75], 0.09
Smoking history (never versus ever)	1.75 [1.24-2.46], 0.001	1.32 [0.90-1.95], 0.14
PD-L1 TPS (≥90% versus 50-89%)	0.70 [0.57-0.87], 0.001	0.73 [0.58-0.93], 0.01

ECOG PS, Eastern Cooperative Oncology Group Performance Status

*Age is included in the regression model as a continuous variable

Supplementary Table 5. Multivariable Cox regression for progression-free and overall survival to pembrolizumab in the propensity-score matched cohort.

Variable	Progression-free survival	Overall survival
	Multivariable HR [95% CI], P	Multivariable HR [95% CI], P
Age*	1.00 [0.99-1.01], 0.32	1.01 [1.00-1.03], 0.007
Sex (male versus female)	1.02 [0.80-1.29], 0.86	0.95 [0.73-1.25], 0.75
ECOG PS (≥ 2 versus 0-1)	1.44 [1.08-1.90], 0.01	1.76 [1.30-2.39], <0.001
Histology (squamous versus non-squamous)	1.05 [0.72-1.53], 0.79	1.38 [0.92-2.05], 0.11
Smoking history (never versus ever)	1.99 [1.21-3.29], 0.006	1.44 [0.83-2.50], 0.19
PD-L1 TPS ($\geq 90\%$ versus 50-89%)	0.72 [0.58-0.91], 0.007	0.75 [0.58-0.97], 0.03

ECOG PS, Eastern Cooperative Oncology Group Performance Status

*Age is included in the regression model as a continuous variable

Supplementary Table 6. Characteristics of 284 patients with advanced NSCLC who received first-line cemiplimab in the EMPOWER-Lung 1 trial by PD-L1 expression levels.

Characteristic*	PD-L1 TPS 50-89% N=185 (%)	PD-L1 TPS ≥90% N=99 (%)	P
Age , median (range)	63 (31-79)	64 (43-79)	0·55
Sex			
• Male	160 (86·5)	89 (89·9)	0·45
• Female	25 (13·5)	10 (10·1)	
Histology			
• Non-squamous	105 (56·8)	56 (56·6)	0·95
• Squamous	80 (43·2)	43 (43·4)	
ECOG PS			
• 0	52 (28·1)	25 (25·2)	0·68
• 1	133 (71·9)	74 (74·7)	
Smoking status			
• Current	73 (39·5)	33 (33·3)	0·37
• Former	112 (60·5)	66 (66·7)	

*Driver mutation status was not available for this cohort.

ECOG PS, Eastern Cooperative Oncology Group Performance Status

Supplementary Table 7. Characteristics of 281 patients with advanced NSCLC who received first-line platinum-based chemotherapy in the EMPOWER-Lung 1 phase III, randomized clinical trial by PD-L1 expression levels.

Characteristic*	PD-L1 TPS 50-89% N=186 (%)	PD-L1 TPS ≥90% N=95 (%)	P
Age, median (range)	64 (40-81)	35 (46-84)	0·26
Sex			
• Male	153 (82·3)	78 (82·1)	0·95
• Female	33 (17·7)	17 (17·9)	
Histology			
• Non-squamous	102 (54·8)	57 (60·0)	0·45
• Squamous	84 (45·2)	38 (40·0)	
ECOG PS			
• 0	48 (25·8)	28 (29·5)	0·57
• 1	138 (74·2)	67 (70·5)	
Smoking status			
• Current	65 (34·9)	27 (28·4)	0·29
• Former	121 (65·1)	68 (71·6)	

*Driver mutation status was not available for this cohort.

ECOG PS, Eastern Cooperative Oncology Group Performance Status

Supplementary Table 8. Baseline clinicopathologic characteristics of patients with non-small cell lung cancer with PD-L1 TPS 50-89% versus those with PD-L1 TPS \geq 90% whose tumors underwent comprehensive tumor genomic profiling at DFCI.

Clinical Characteristic, n (%)	PD-L1 TPS 50-89% N=305	PD-L1 TPS \geq 90% N=248	P-value
Age, median (range)	67 (29-98)	67 (27-90)	0.90
Sex			0.79
• Male	118 (38.7%)	99 (39.9%)	
• Female	187 (61.3%)	149 (60.1%)	
Smoking status			0.03
• Current/Former	243 (79.7%)	215 (86.7%)	
• Never	62 (20.3%)	33 (13.3%)	
Pack/Years, median (range)	23 (0-200)	25 (0-120)	0.16
Histology			1.0
• Non-squamous	283 (92.8%)	230 (92.7%)	
• Squamous	22 (7.2%)	18 (7.6%)	
TMB, mut/Mb	9.9 (0-70.2)	10.9 (1.5-43.3)	0.22
Stage at time of sequencing			0.96
• I	19 (6.23%)	16 (6.45%)	
• II	11 (3.61%)	7 (2.82%)	
• III	32 (10.5%)	26 (10.5%)	
• IV	243 (79.7%)	199 (80.2%)	

Supplementary Table 9. Baseline clinicopathologic characteristics of patients with non-small cell lung cancer with PD-L1 TPS 50-89% vs ≥90% whose tumors underwent multiplexed immunofluorescence at DFCI.

Clinical Characteristic, n (%)	PD-L1 TPS 50-89% N=69	PD-L1 TPS ≥90% N=24	P-value
Age, median (range)	68 (29-85)	71 (28-85)	0.33
Sex			0.63
• Male	44 (63.8%)	14 (58.3%)	
• Female	25 (36.2%)	10 (41.7%)	
Smoking status			1
• Current/Former	57 (82.6%)	21 (87.5%)	
• Never	11 (15.9%)	3 (12.5%)	
• Not available	1		
Pack-years, median (range)	32.5 (3-90)	40 (15-122)	0.31
Histology			0.55
• Nonsquamous	58 (84.1%)	19 (79.2%)	
• Squamous	11 (15.9%)	5 (20.8%)	
Stage at ImmunoProfile			0.43
• I	17 (24.6%)	3 (12.5%)	
• II	8 (11.6%)	3 (12.5%)	
• III	10 (14.5%)	2 (8.3%)	
• IV	34 (49.3%)	16 (66.7%)	
Site of biopsy			0.80
• Primary lung tissue	46 (66.7%)	15 (62.5%)	
• Metastatic tissue	23 (33.3%)	9 (37.5%)	