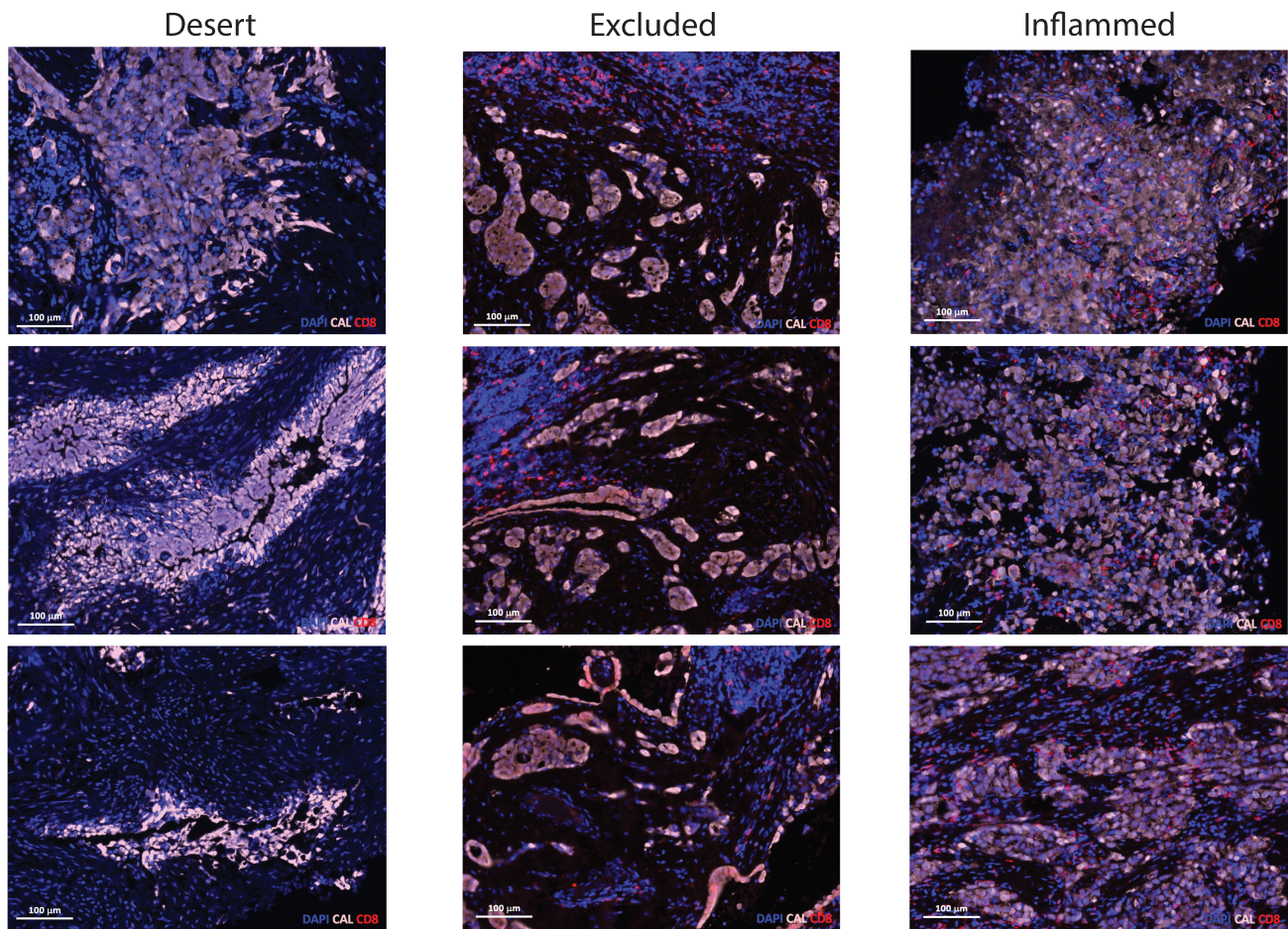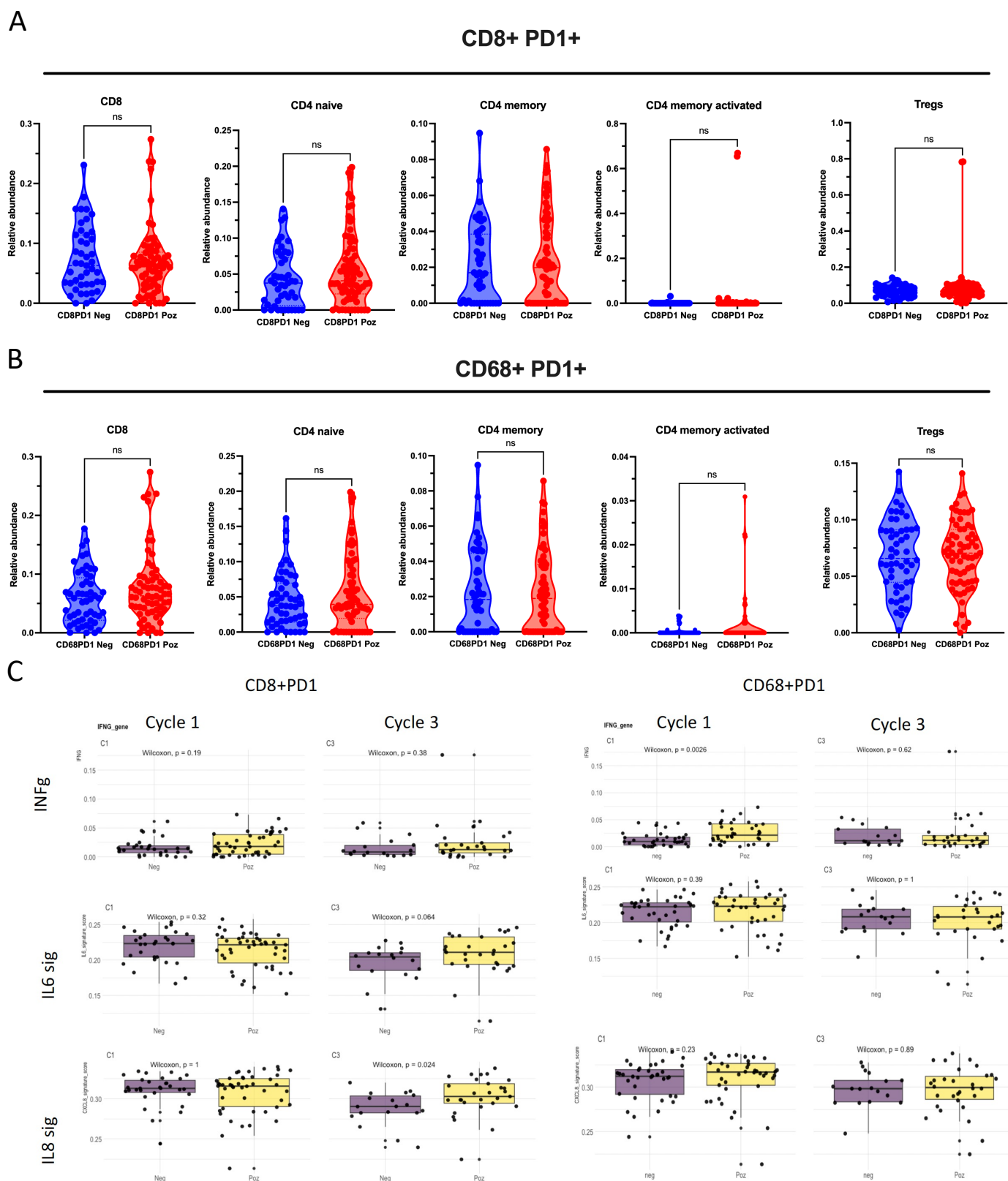**Extended Data Figure 1:** Heatmap for the between-marker Spearman correlations.

Extended Data Figure 2: Examples (n=3) for each of the tumor inflammation types

Extended Data Figure 3. CibersortX deconvolution and pathway analysis of peripheral blood whole RNA sequencing, A) Comparison of CibesortX prediction of of cell fractions of CD8 T cells, CD4 T cells and Treg in patients with and without CD8+PD1+ cells. **B)** Comparison of CibesortX prediction of cell fractions of CD8 T cells, CD4 T cells and Treg in patients with and without CD68+PD1+ cells. **C)** Pathway analysis of INFg, IL6 and IL8 signatures comparing CD8+PD1+ or CD68+PD1+ negative and positive patients

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Extended Data Table 1: Baseline characteristics, overall and by treatment arm.

(*) Fisher's exact for categorical, Mann-Whitney U test for continuous variables, (¥) Category "Unknown/Missing" excluded, (§) Categories "Current" & "Former" combined, ($) Categories "1" & "2" combined, (~) 1 case of ECOG PS 2 due to leg braces

Characteristic	Pembrolizumab (n=64)	Chemotherapy (n=61)	All patients (N=125)	p-value*
Sex - n (%)				
Male	51 (79.7)	51 (83.6)	102 (81.6)	0.65
Female	13 (20.3)	10 (16.4)	23 (18.4)	
Age (yrs at randomization)				
Mean (95% CI)	67.6 (65.8 - 69.4)	70.2 (68.5 - 71.9)	68.9 (67.6 - 70.1)	***0.020***
Median (Min-Max)	69 (52 - 83)	72 (53 - 83)	70 (52 - 83)	
Age (category) - n (%)				
<70	36 (56.3)	24 (39.3)	60 (48.0)	0.074
≥70	28 (43.8)	37 (60.7)	65 (52.0)	
Histologic subtype - n (%)				
Epithelioid	59 (92.2)	54 (88.5)	113 (90.4)	0.55
Non-epithelioid	5 (7.8)	7 (11.5)	12 (9.6)	
Smoking history - n (%)				
Current (patient still smokes)	3 (4.7)	3 (4.9)	6 (4.8)	0.60¥
Former (≥ 100 cigarettes in the past during the whole life)	29 (45.3)	23 (37.7)	52 (41.6)	0.38¥,§
Never (0-99 cigarettes during the whole life)	31 (48.4)	35 (57.4)	66 (52.8)	
Unknown/Missing	1 (1.6)	0 (0.0)	1 (0.8)	
ECOG Performance status - n (%)				
0	19 (29.7)	12 (19.7)	31 (24.8)	0.22$
1	44 (68.8)	49 (80.3)	93 (74.4)	
2~	1 (1.6)	0 (0.0)	1 (0.8)	
EORTC Score - n (%)				
Good prognosis	42 (65.6)	47 (77.0)	89 (71.2)	0.17
Poor prognosis	22 (34.4)	14 (23.0)	36 (28.8)	

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Characteristic	Pembrolizumab (n=64)	Chemotherapy (n=61)	All patients (N=125)	p-value*
Prior treatment - n (%)				
Carboplatin/Pemetrexed	23 (35.9)	24 (39.3)	47 (37.6)	0.41
Cisplatin/Pemetrexed	23 (35.9)	18 (29.5)	41 (32.8)	
Platinum+/-Pemetrexed+/-Other	11 (17.2)	15 (24.6)	26 (20.8)	
Cisplatin/Pemetrexed & Carboplatin/Pemetrexed	5 (7.8)	1 (1.6)	6 (4.8)	
Missing	2 (3.1)	3 (4.9)	5 (4.0)	

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Extended Data Table 2: Descriptive statistics of the biomarkers of interest, by treatment arm and overall (N=125)

(§) Mann-Whitney test, (*) Fisher's exact test, (#) without category 'Excluded'

Cut-off	Level	Pembrolizumab (n=64)	Chemotherapy (n=61)	All patients (N=125)	p-value
		CD3			
	n (%)	64 (51.2)	61 (48.8)	125 (100.0)	0.76§
	Mean (95% CI)	670.4 (459.6 - 881.2)	587.0 (403.6 - 770.4)	629.7 (491.3 - 768.2)	
	Median (min-max)	308.9 (25.8 - 3398.3)	272.2 (11.9 - 3924.0)	303.8 (11.9 - 3924.0)	
300	<300	31 (48.4%)	31 (50.8%)	62 (49.6%)	0.86*
	≥300	33 (51.6%)	30 (49.2%)	63 (50.4%)	
		CD8			
	n (%)	64 (51.2)	61 (48.8)	125 (100.0)	0.37§
	Mean (95% CI)	110.1 (49.9 - 170.3)	42.4 (22.4 - 62.4)	77.1 (44.6 - 109.5)	
	Median (min-max)	13.4 (0.0 - 1169.4)	12.6 (0.0 - 378.7)	12.8 (0.0 - 1169.4)	
10	<10	30 (46.9%)	27 (44.3%)	57 (45.6%)	0.86*
	≥10	34 (53.1%)	34 (55.7%)	68 (54.4%)	
		CD68			
	n (%)	64 (51.2)	61 (48.8)	125 (100.0)	0.39§
	Mean (95% CI)	259.3 (195.0 - 323.6)	352.3 (227.8 - 476.9)	304.7 (236.1 - 373.3)	
	Median (min-max)	172.8 (0.2 - 962.2)	162.8 (0.0 - 3095.2)	163.5 (0.0 - 3095.2)	
200	<200	34 (53.1%)	33 (54.1%)	67 (53.6%)	>0.99*
	≥200	30 (46.9%)	28 (45.9%)	58 (46.4%)	
		PD1			
	n (%)	64 (51.2)	61 (48.8)	125 (100.0)	0.058§
	Mean (95% CI)	88.4 (48.5 - 128.2)	122.9 (-3.4 - 249.1)	105.2 (41.2 - 169.2)	
	Median (min-max)	24.5 (0.0 - 774.0)	13.5 (0.0 - 3321.5)	19.1 (0.0 - 3321.5)	
10	<10	20 (31.3%)	24 (39.3%)	44 (35.2%)	0.36*
	≥10	44 (68.8%)	37 (60.7%)	81 (64.8%)	
Median	<19	28 (43.8%)	34 (55.7%)	62 (49.6%)	0.21*
	≥19	36 (56.3%)	27 (44.3%)	63 (50.4%)	

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Cut-off	Level	Pembrolizumab (n=64)	Chemotherapy (n=61)	All patients (N=125)	p-value
	PDL1				
	n (%)	64 (51.2)	61 (48.8)	125 (100.0)	0.31§
	Mean (95% CI)	465.1 (162.0 - 768.2)	378.4 (213.2 - 543.5)	422.8 (250.1 - 595.4)	
	Median (min-max)	89.0 (0.0 - 8694.7)	146.9 (0.0 - 4110.8)	117.6 (0.0 - 8694.7)	
Median	<118	36 (56.3%)	27 (44.3%)	63 (50.4%)	0.21*
	≥118	28 (43.8%)	34 (55.7%)	62 (49.6%)	
	CD3-PD1				
	n (%)	64 (51.2)	61 (48.8)	125 (100.0)	0.15§
	Mean (95% CI)	62.7 (29.5 - 95.8)	27.6 (14.9 - 40.2)	45.5 (27.4 - 63.6)	
	Median (min-max)	11.8 (0.0 - 619.8)	10.8 (0.0 - 280.6)	11.0 (0.0 - 619.8)	
Median	<11	30 (46.9%)	33 (54.1%)	63 (50.4%)	0.48*
	≥11	34 (53.1%)	28 (45.9%)	62 (49.6%)	
	CD3-PDL1				
	n (%)	64 (51.2)	61 (48.8)	125 (100.0)	0.54§
	Mean (95% CI)	108.5 (30.2 - 186.8)	68.3 (27.4 - 109.2)	88.9 (44.6 - 133.2)	
	Median (min-max)	6.3 (0.0 - 2052.9)	12.9 (0.0 - 1044.1)	9.0 (0.0 - 2052.9)	
Median	<9	33 (51.6%)	30 (49.2%)	63 (50.4%)	0.86*
	≥9	31 (48.4%)	31 (50.8%)	62 (49.6%)	
	CD8-PD1				
	n (%)	64 (51.2)	61 (48.8)	125 (100.0)	0.60§
	Mean (95% CI)	22.7 (6.1 - 39.3)	6.4 (1.6 - 11.3)	14.8 (5.9 - 23.6)	
	Median (min-max)	1.0 (0.0 - 335.8)	1.0 (0.0 - 128.2)	1.0 (0.0 - 335.8)	
1	<1	32 (50.0%)	30 (49.2%)	62 (49.6%)	>0.99*
	≥1	32 (50.0%)	31 (50.8%)	63 (50.4%)	
	CD8-PDL1				
	n (%)	64 (51.2)	61 (48.8)	125 (100.0)	0.53§
	Mean (95% CI)	25.7 (-0.8 - 52.1)	3.8 (2.3 - 5.4)	15.0 (1.5 - 28.5)	
	Median (min-max)	0.7 (0.0 - 807.2)	0.4 (0.0 - 24.4)	0.5 (0.0 - 807.2)	

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Cut-off	Level	Pembrolizumab (n=64)	Chemotherapy (n=61)	All patients (N=125)	p-value
Median	<0.5	31 (48.4%)	31 (50.8%)	62 (49.6%)	0.86[*]
	≥0.5	33 (51.6%)	30 (49.2%)	63 (50.4%)	
CD68-PD1					
	n (%)	64 (51.2)	61 (48.8)	125 (100.0)	0.88[§]
	Mean (95% CI)	6.0 (1.7 - 10.2)	8.1 (-3.0 - 19.1)	7.0 (1.3 - 12.7)	
	Median (min-max)	0.2 (0.0 - 118.9)	0.2 (0.0 - 336.4)	0.2 (0.0 - 336.4)	
0	0	27 (42.2%)	27 (44.3%)	54 (43.2%)	0.86[*]
	>0	37 (57.8%)	34 (55.7%)	71 (56.8%)	
CD68-PDL1					
	n (%)	64 (51.2)	61 (48.8)	125 (100.0)	0.094[§]
	Mean (95% CI)	24.4 (11.2 - 37.7)	32.5 (18.3 - 46.8)	28.4 (18.8 - 38.0)	
	Median (min-max)	3.2 (0.0 - 262.5)	8.4 (0.0 - 361.1)	5.0 (0.0 - 361.1)	
5	<5	36 (56.3%)	26 (42.6%)	62 (49.6%)	0.15[*]
	≥5	28 (43.8%)	35 (57.4%)	63 (50.4%)	
Inflammation type					
Tumor CD8 ≥10/mm^2	Inflamed	34 (53.1%)	34 (55.7%)	68 (54.4%)	>0.99[*,#]
Tumor CD8 <10/mm^2 & Stroma CD8 ≥10/mm^2	Excluded	15 (23.4%)	11 (18.0%)	26 (20.8%)	
Tumor & Stroma CD8 <10/mm^2	Desert	15 (23.4%)	16 (26.2%)	31 (24.8%)	

Extended Data Table 3: Thresholds used for the analyses of 11 biomarkers and co-expressions.

Biomarker	Predefined	Median	Cut-off point
CD3/mm^2	✓		≥300
CD8/mm^2	✓		≥10
CD68/mm^2	✓		≥200
PD-1/mm^2	✓		≥10
		✓	≥19
PD-L1/mm^2		✓	≥118
CD3-PD1/mm^2		✓	≥11
CD3-PDL1/mm^2		✓	≥9
CD8-PD1/mm^2	✓		≥1
CD8-PDL1/mm^2		✓	≥0.5
CD68-PD1/mm^2	✓		>0
CD68-PDL1/mm^2	✓		≥5

Extended Data Table 4: Cox proportional hazards regression for PFS and OS, separately for each biomarker, in the presence of treatment and treatment interaction, adjusted for baseline clinical variables

Categorical Biomarkers	PFS		OS
	HR (95% CI)	interaction p-value*	
CD68	high: 1.56 (0.86 - 2.82) low: 0.63 (0.36 - 1.09)	p = 0.031	No significant effect
PDL1 (high vs low)	1.43 (0.95 - 2.15)	p = 0.083^	
CD3-PD1 (high vs low)	1.57 (1.04 – 2.38)	p = 0.032^	
CD8-PD1	**high: 0.48 (0.27 - 0.84) low: 1.60 (0.88 - 2.89)**	**p = 0.0043**	
CD68-PD1	high: 0.62 (0.36 - 1.06) low: 1.48 (0.79 - 2.75)	p = 0.042	
CD68-PDL1 (high vs low)	1.43 (0.95 - 2.16)	p = 0.087^	
CD3	No significant effect		
CD8			
PD1			
CD3-PDL1			
CD8-PDL1			
Inflammation type			

(*) stratified by histological subtype; (^) not significant interaction

Note 1: *Bold highlighted are the effects significant after FDR adjustment (q=0.0083).*

Note 2: *Each line shows the biomarker effect found significant after backward selection at 10%, accounting also for the interaction with treatment and adjusting for clinical baseline characteristic. In all models, treatment arm is included for adjustment, and the effects of EORTC score and prior treatment were also found significant.*

Note 3: *For all biomarkers with significant interaction by treatment, the presented HR is describing the association of Pembrolizumab vs Chemotherapy, within each biomarker level.*

Extended Data Table 5: BICR ORR by biomarker (N=125; no. of responses=19).

(*)Fisher's exact test, (§)Breslow test for homogeneity, (£)C-M-H test controlling for treatment, (†)Homogeneity not satisfied, FDR: False Discovery Rate method, NS: Non-significant

	n of patients	N - ORR(%)	95% C.I.	p-value
CD3				
Cut-off 300				
Chemotherapy				
<300	31	3 - 9.7%	2% - 25.8%	0.61*
≥300	30	1 - 3.3%	0.1% - 17.2%	
Pembrolizumab				
<300	31	6 - 19.4%	7.5% - 37.5%	0.56*
≥300	33	9 - 27.3%	13.3% - 45.5%	
Whole cohort				
<300	62	9 - 14.5%	6.9% - 25.8%	0.88£ (0.215§)
≥300	63	10 - 15.9%	7.9% - 27.3%	
CD8				
Cut-off 10				
Chemotherapy				
<10	27	0 - 0.0%	NE - NE	0.12*
≥10	34	4 - 11.8%	3.3% - 27.5%	
Pembrolizumab				
<10	30	5 - 16.7%	5.6% - 34.7%	0.255*
≥10	34	10 - 29.4%	15.1% - 47.5%	
Whole cohort				
<10	57	5 - 8.8%	2.9% - 19.3%	0.052£ (0.215§)
≥10	68	14 - 20.6%	11.7% - 32.1%	
CD68				
Cut-off 200				

	n of patients	N - ORR(%)	95% C.I.	p-value
Chemotherapy				
<200	33	3 - 9.1%	1.9% - 24.3%	0.62*
≥200	28	1 - 3.6%	0.1% - 18.3%	
Pembrolizumab				
<200	34	12 - 35.3%	19.7% - 53.5%	**0.02***
≥200	30	3 - 10%	2.1% - 26.5%	*(NS by FDR, q = 0.004)*
Whole cohort				
<200	67	15 - 22.4%	13.1% - 34.2%	**0.013£**
≥200	58	4 - 6.9%	1.9% - 16.7%	*(NS by FDR, q = 0.004)* (0.663§)
		PD1		
		Cut-off 10		
Chemotherapy				
<10	24	3 - 12.5%	2.7% - 32.4%	0.29*
≥10	37	1 - 2.7%	0.1% - 14.2%	
Pembrolizumab				
<10	20	4 - 20%	5.7% - 43.7%	0.76*
≥10	44	11 - 25%	13.2% - 40.3%	
Whole cohort				
<10	44	7 - 15.9%	6.6% - 30.1%	0.69£ (0.135§)
≥10	81	12 - 14.8%	7.9% - 24.4%	
		Cut-off Median		
Chemotherapy				
<19	34	4 - 11.8%	3.3% - 27.5%	0.12*
≥19	27	0 - 0.0%	NE - NE	
Pembrolizumab				
<19	28	6 - 21.4%	8.3% - 41%	0.775*
≥19	36	9 - 25%	12.1% - 42.2%	
Whole cohort				
<19	62	10 - 16.1%	8% - 27.7%	0.54£ (0.07§)
≥19	63	9 - 14.3%	6.7% - 25.4%	

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	n of patients	N - ORR(%)	95% C.I.	p-value
PDL1				
Cut-off Median				
Chemotherapy				
<118	27	1 - 3.7%	0.1% - 19%	0.62*
≥118	34	3 - 8.8%	1.9% - 23.7%	
Pembrolizumab				
<118	36	7 - 19.4%	8.2% - 36%	0.55*
≥118	28	8 - 28.6%	13.2% - 48.7%	
Whole cohort				
<118	63	8 - 12.7%	5.6% - 23.5%	0.26£ (0.75§)
≥118	62	11 - 17.7%	9.2% - 29.5%	
CD3-PD1				
Cut-off Median				
Chemotherapy				
<11	33	3 - 9.1%	1.9% - 24.3%	0.62*
≥11	28	1 - 3.6%	0.1% - 18.3%	
Pembrolizumab				
<11	30	6 - 20%	7.7% - 38.6%	0.57*
≥11	34	9 - 26.5%	12.9% - 44.4%	
Whole cohort				
<11	63	9 - 14.3%	6.7% - 25.4%	0.92£ (0.29§)
≥11	62	10 - 16.1%	8% - 27.7%	
CD3-PDL1				
Cut-off Median				
Chemotherapy				
<9	30	2 - 6.7%	0.8% - 22.1%	>0.99*
≥9	31	2 - 6.5%	0.8% - 21.4%	
Pembrolizumab				

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	n of patients	N - ORR(%)	95% C.I.	p-value
<9	33	6 - 18.2%	7% - 35.5%	0.38*
≥9	31	9 - 29%	14.2% - 48%	
Whole cohort				
<9	63	8 - 12.7%	5.6% - 23.5%	0.39£ (0.59§)
≥9	62	11 - 17.7%	9.2% - 29.5%	
CD8-PD1				
Cut-off 1				
Chemotherapy				
<1	30	3 - 10%	2.1% - 26.5%	0.35*
≥1	31	1 - 3.2%	0.1% - 16.7%	
Pembrolizumab				
<1	32	5 - 15.6%	5.3% - 32.8%	0.24*
≥1	32	10 - 31.3%	16.1% - 50%	
Whole cohort				
<1	62	8 - 12.9%	5.7% - 23.9%	0.46£ (0.093§)
≥1	63	11 - 17.5%	9.1% - 29.1%	
CD8-PDL1				
Cut-off Median				
Chemotherapy				
<0.5	31	1 - 3.2%	0.1% - 16.7%	0.35*
≥0.5	30	3 - 10%	2.1% - 26.5%	
Pembrolizumab				
<0.5	31	4 - 12.9%	3.6% - 29.8%	0.077*
≥0.5	33	11 - 33.3%	18% - 51.8%	
Whole cohort				
<0.5	62	5 - 8.1%	2.7% - 17.8%	**0.029£** *(NS by FDR, q = 0.008)* (0.99§)
≥0.5	63	14 - 22.2%	12.7% - 34.5%	
CD68-PD1				

	n of patients	N - ORR(%)	95% C.I.	p-value
Cut-off 0				
Chemotherapy				
0	27	3 - 11.1%	2.4% - 29.2%	0.31*
>0	34	1 - 2.9%	0.1% - 15.3%	
Pembrolizumab				
0	27	4 - 14.8%	4.2% - 33.7%	0.235*
>0	37	11 - 29.7%	15.9% - 47%	
Whole cohort				
0	54	7 - 13%	5.4% - 24.9%	0.57£ (0.066§)
>0	71	12 - 16.9%	9% - 27.7%	
CD68-PDL1				
Cut-off 5				
Chemotherapy				
<5	26	2 - 7.7%	0.9% - 25.1%	>0.99*
≥5	35	2 - 5.7%	0.7% - 19.2%	
Pembrolizumab				
<5	36	7 - 19.4%	8.2% - 36%	0.55*
≥5	28	8 - 28.6%	13.2% - 48.7%	
Whole cohort				
<5	62	9 - 14.5%	6.9% - 25.8%	0.56£ (0.49§)
≥5	63	10 - 15.9%	7.9% - 27.3%	

Extended Data Table 6: Univariate Cox models for PFS and OS, separately for the <u>continuous</u> biomarker measurements, for the overall cohort (sensitivity analysis).

SI: Significant interaction, SBE: Significant Biomarker Effect (main effect)

Continuous biomarkers	PFS	OS
CD3	-	-
CD8	-	SI, p = 0.060
CD68	-	-
PD1	-	-
PDL1	-	-
CD3-PD1	**SI, p = 0.0014**	SBE, p = 0.096
CD3-PDL1	-	-
CD8-PD1	**SI, p = 0.025**	-
CD8-PDL1	-	-
CD68-PD1	-	SBE, p = 0.055
CD68-PDL1	**SI, p = 0.032**	-

Note 1: Bold highlighted are the effects significant at 5%.
Note 2: In all models, the effect of EORTC score and prior treatment remained significant after backward selection at 10%.

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Extended Data Table 7: Final model for OS after backward multivariable selection at 10%.

	HR (95% C.I.)	interaction p-value*
CD68-PD1 (high vs low)		
Pembrolizumab	0.43 (0.21 - 0.86)	**0.015**
Chemotherapy	1.63 (0.73 - 3.59)	
PDL1 (high vs low)		
Pembrolizumab	0.71 (0.30 - 1.70)	**0.033**
Chemotherapy	2.26 (0.91 - 5.59)	
CD68 (high vs low)		
	1.85 (1.12 - 3.06)	**0.016^**
Sex (female vs male)		
	2.01 (1.02 - 3.95)	**0.043^**
EORTC score (good vs poor prognosis)		
	0.22 (0.12 - 0.41)	**<0.001^**
Prior treatment		
Both/Other/Missing vs. Cisplatin/Pemetrexed	*0.80 (0.46 - 1.39)*	*0.42^*
Carboplatin/Pemetrexed vs. Cisplatin/Pemetrexed	0.41 (0.22 - 0.75)	**0.0041^**
CD3 (high vs low)		
Pembrolizumab	*1.95 (0.81 - 4.69)*	*0.089*
Chemotherapy	*0.83 (0.36 - 1.91)*	
CD3-PDL1 (high vs low)		
	0.48 (0.21 - 1.08)	*0.077^*
Inflammation type		
Excluded vs. Inflamed	*0.50 (0.22 - 1.13)*	*0.094^*
Desert vs. Inflamed	*1.25 (0.64 - 2.43)*	*0.52^*

(*) stratified by histologic subtype, (^) no interaction with treatment

Supplemental material

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J Immunother Cancer

	n of patients	n (%) of PFS events	6-m PFS% (95% C.I.)	Median PFS (95% C.I.)	Log-rank p-value
CD3+PD1+CD8-					
Cut-off 6					
Chemotherapy					
<6	34	26 (76.5)	32.2 (16.9 - 48.5)	4.1 (2.1 - 5.4)	
≥6	27	24 (88.9)	19.7 (6.7 - 37.8)	2.3 (2.0 - 3.6)	
All patients	61	50 (82.0)	26.5 (15.6 - 38.7)	2.5 (2.1 - 4.2)	0.16
Pembrolizumab					
<6	28	25 (89.3)	15.4 (4.9 - 31.3)	3.3 (1.9 - 4.2)	
≥6	36	29 (80.6)	30.2 (15.9 - 45.9)	2.4 (2.0 - 4.2)	
All patients	64	54 (84.4)	23.7 (13.9 - 35.0)	2.5 (2.1 - 4.2)	0.35
Whole cohort					
<6	62	51 (82.3)	24.3 (14.2 - 36.0)	4.1 (2.1 - 4.2)	
≥6	63	53 (84.1)	25.8 (15.3 - 37.6)	2.3 (2.1 - 4.1)	
All patients	125	104 (83.2)	25.0 (17.5 - 33.3)	2.5 (2.2 - 4.1)	0.80, 0.77*

(*) Stratified log-rank by histologic subtype

Extended Data Table 8: Analysis of progression-free survival in function of the presence or absence of CD3pPD1pCD8n cells Progression-free survival, within each CD3+PD1+CD8- level, by treatment arm and overall (N=125)
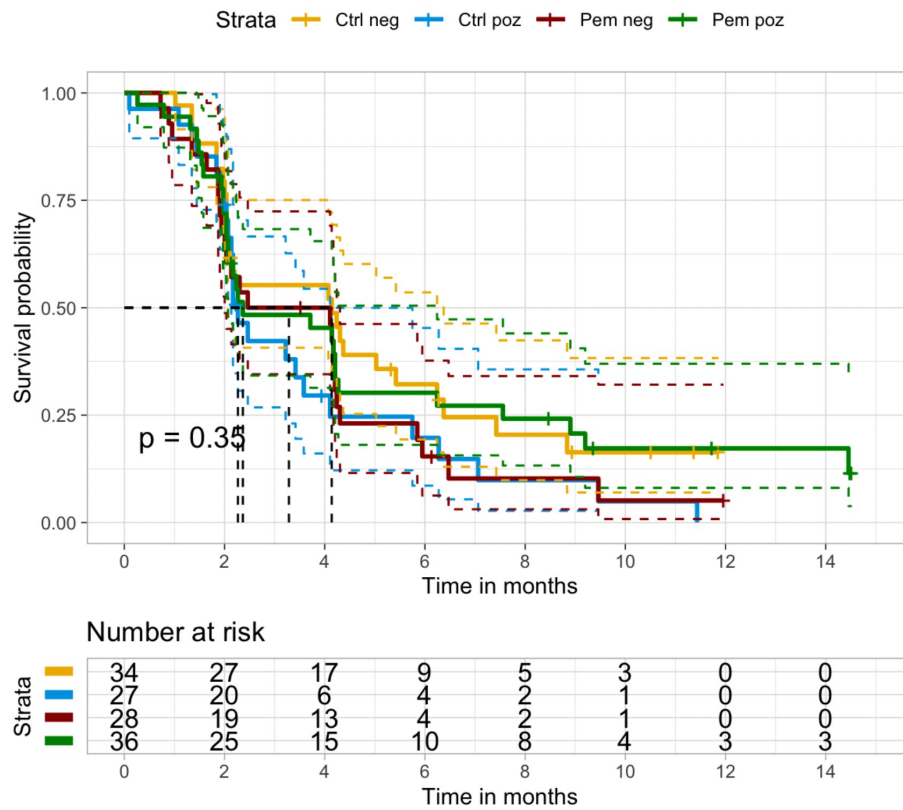
Extended Data Figure 4: Analysis of progression-free survival in function of the presence or absence of CD3pPD1pCD8n cells Kaplan-Meier survival estimates in control and pembrolizumab treated patients with marker (CD3+PD1+CD8-) negative and positive patients