Supplementary Materials

Association of the Metabolic Score using Baseline FDG-PET/CT and dNLR with Immunotherapy Outcomes in Advanced NSCLC Patients Treated with First-Line Pembrolizumab.

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Material and Methods

Acquisition parameters for each PET/CT device:

The following four PET/CT scanners were used:

- General Electric Discovery-690 (GE Healthcare, Waukesha, WI) (15 patients) and GE Discovery-710 (7 patients), both with LYSO-based detectors,
- GE Discovery-MI (27 patients) and Philips PET/CT Vereos (14 patients), both combining the small LYSO with the SiPM block design (LightBurst digital detector).

The PET images were reconstructed using the following iterative algorithms:

- GE Discovery-690: Vue Point FX algorithm, time of flight (TOF) reconstruction, matrix 256 × 256, 2 iterations, 24 subsets, post-filter 6.4mm;
- GE Discovery-710: Vue Point HD algorithm, time of flight (TOF) reconstruction, matrix 256 × 256, 2 iterations, 12 subsets, post-filter 6.4mm;
- GE Discovery-MI: Vue Point FX algorithm, time of flight (TOF) reconstruction, matrix 256 × 256, 2 iterations, 17 subsets, post-filter 6.4mm;
- Philips Vereos: OSEM algorithm, time of flight (TOF) reconstruction, matrix 288 × 288, 3 iterations, 5 subsets, post-filter 2mm.

Definition of outcomes:

- Overall Survival (**OS**): defined as the time from the first ICI perfusion to the date of death, due to any cause, or to the date of censoring at the last time the patient was known to be alive.
- Progression-Free Survival (**PFS**): defined as the time from the first pembrolizumab perfusion to disease progression or death from any cause.
- Overall Response Rate (**ORR**): defined as the percentage of patients with a best overall response of complete response (CR) or partial response (PR) at any time during the treatment.
- Disease Control Rate (**DCR**): defined as the percentage of patients with a best overall response of complete response (CR), partial response (PR) or stable disease (SD) at any time during the treatment.
- Length of follow-up: calculated from the date of the initial PET/CT to the date of the last clinical consultation.

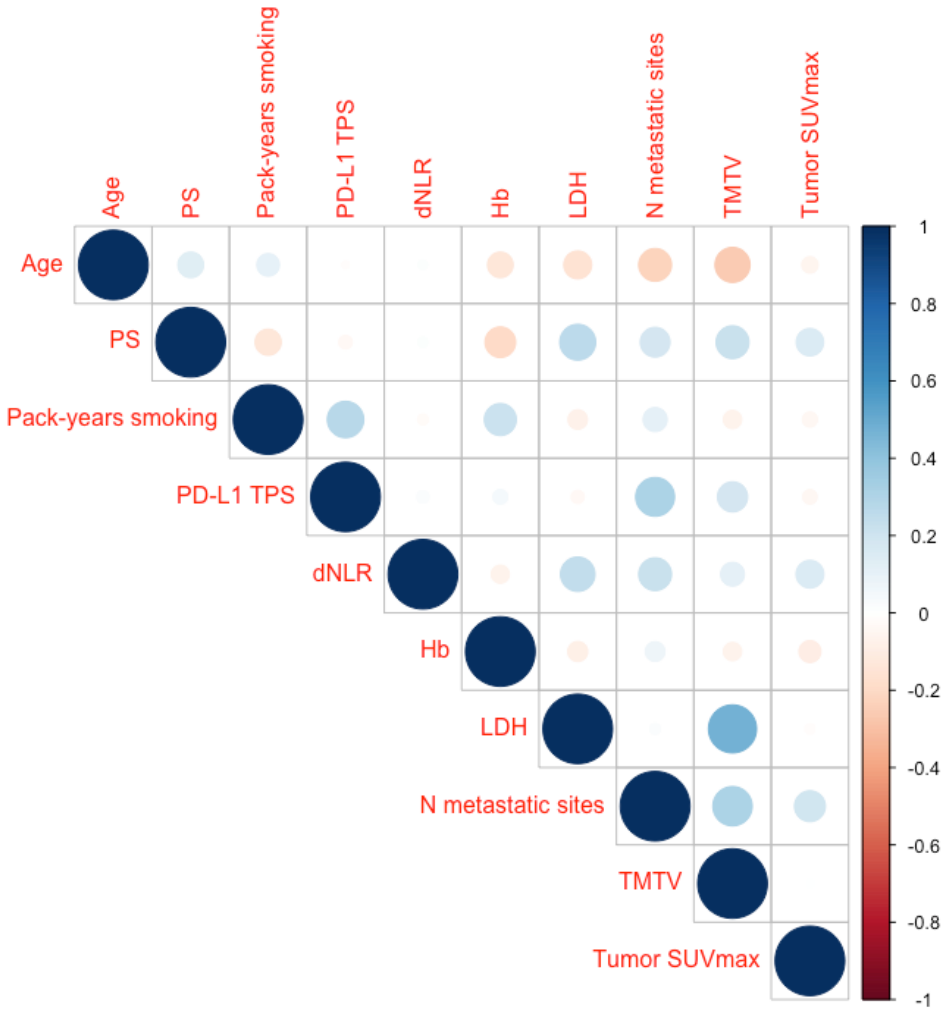

Figure S1. Correlations between tumor SUVmax, TMTV and clinical or biological variables (correlogram).

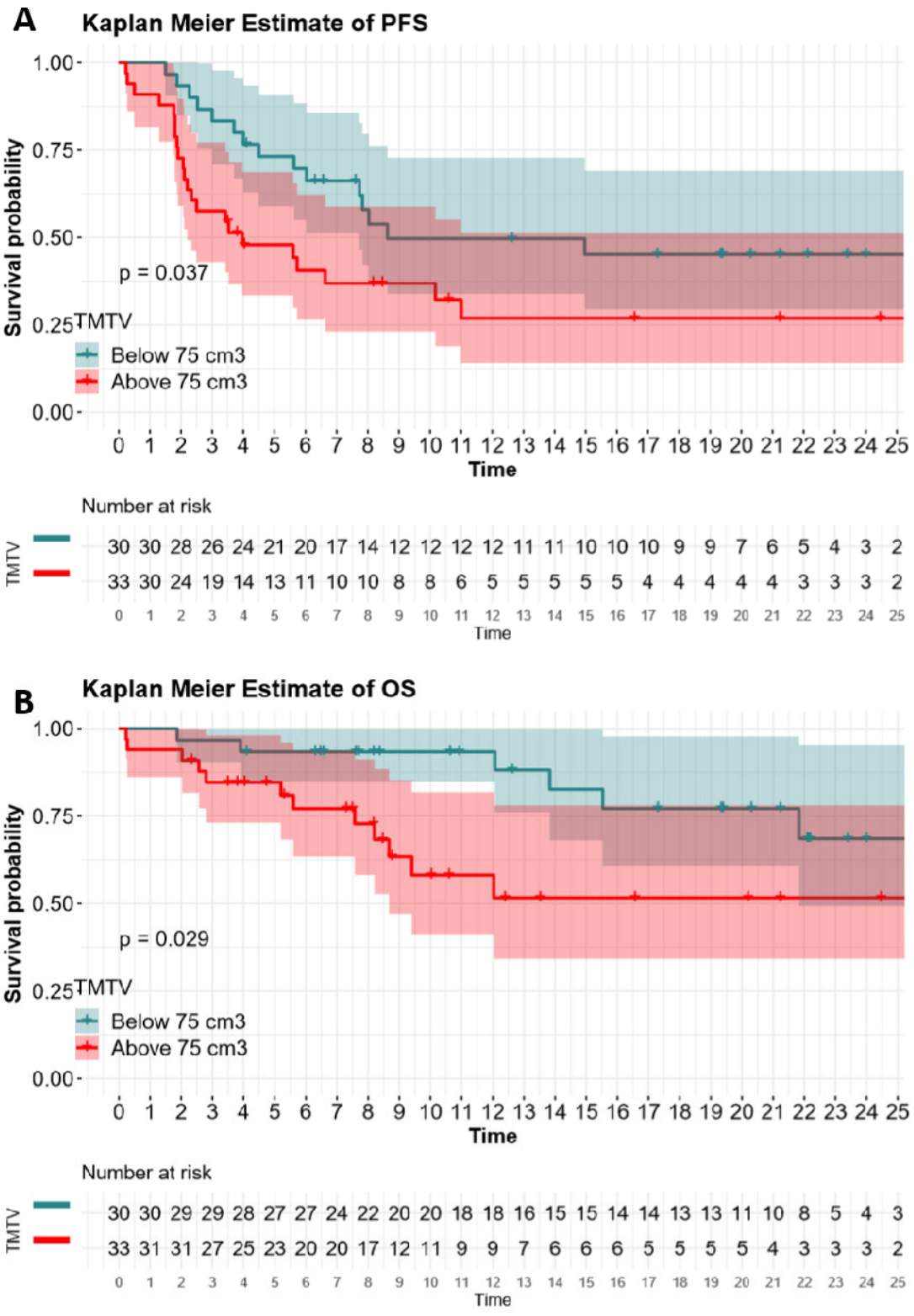

Figure S2. Kaplan-Meier curves for (**A**) Progression-Free Survival (PFS) and (**B**) Overall Survival (OS) stratified according to TMTV in all patients (n = 63).

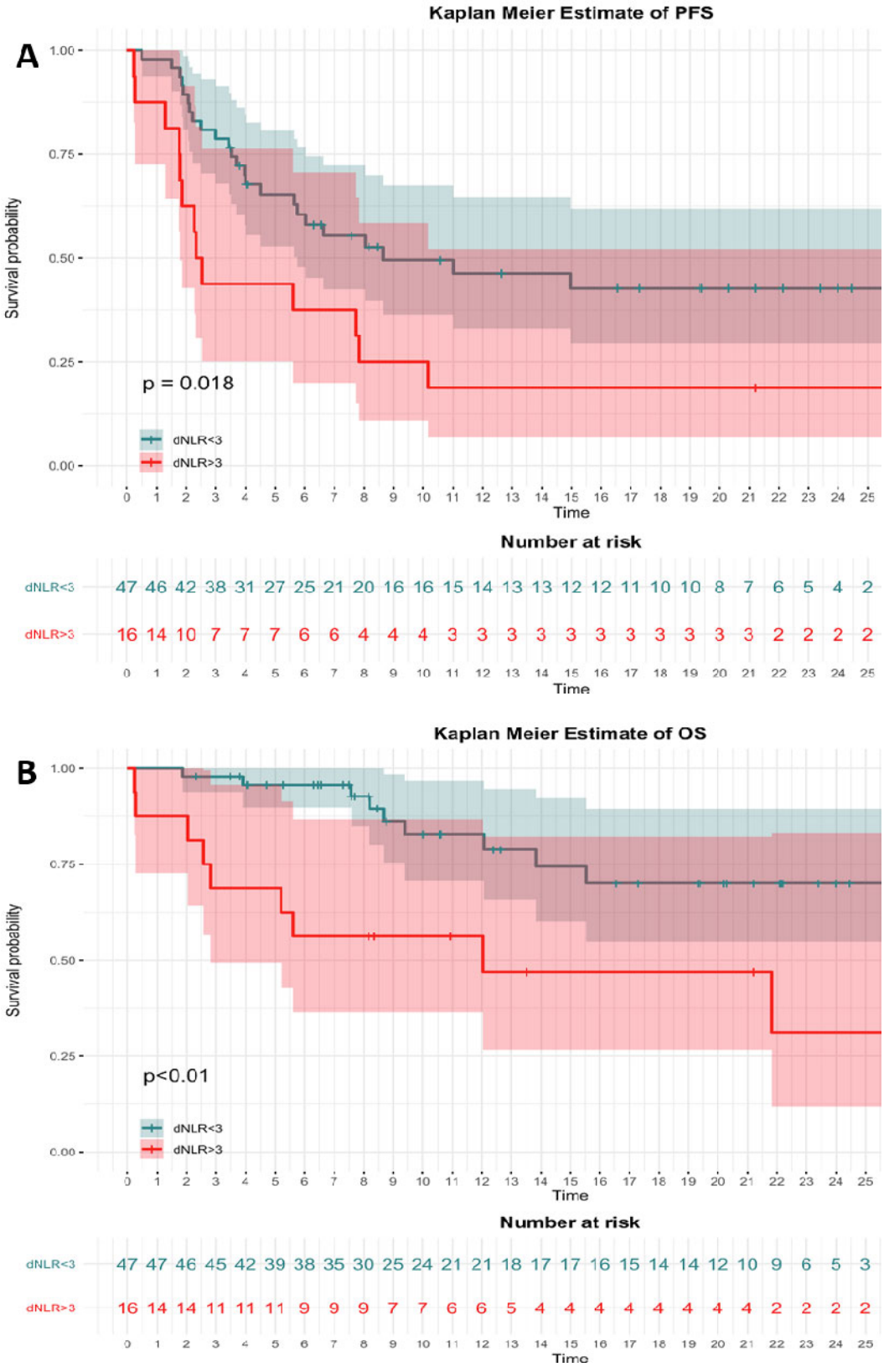

Figure S3. Kaplan-Meier curves for (**A**) Progression-Free Survival (PFS) and (**B**) Overall Survival (OS) stratified according to dNLR in all patients (n = 63).

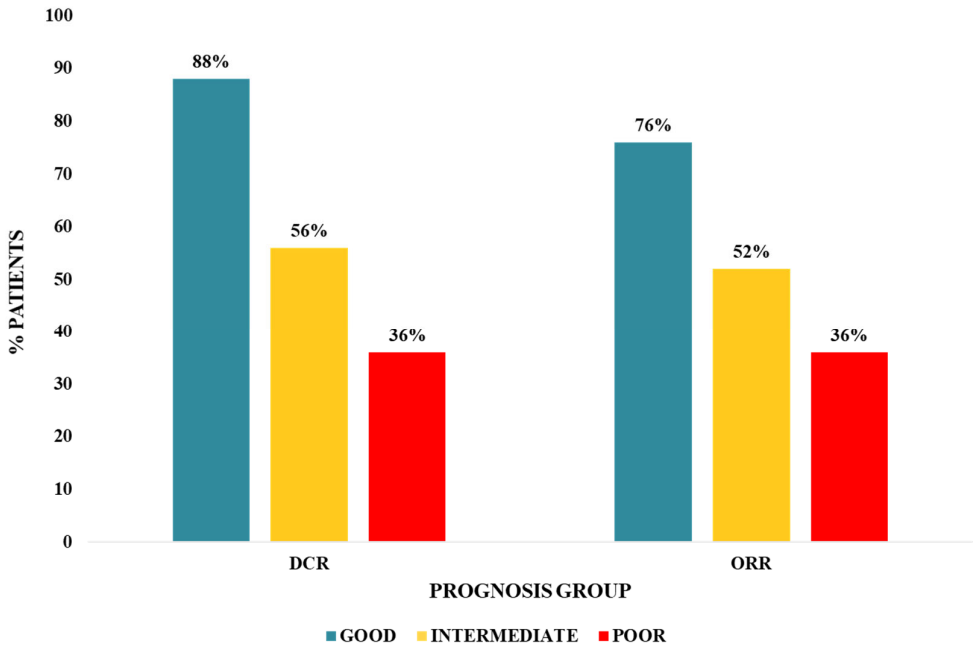

Figure S4. Disease control rate (DCR %) and overall response rate (ORR %) according to the metabolic score.

Table S1. Correlations between TMTV, tumor SUVmax and clinical or biological variables (Spearman's coefficient).

	Correlation with Tumor SUVmax		**Correlation with TMTV**	
	Spearman's coefficient	*p* value	Spearman's coefficient	*p* value
Clinical parameters				
Age	−0.12	0.32	**−0.29**	**0.02**
PS	0.19	0.10	0.23	0.06
Pack-years smoking*	0.01	0.96	−0.20	0.17
PD-L1 expression				
TPS (%)	0.14	0.28	0.22	0.08
Biology				
dNLR	0.18	0.13	0.10	0.46
Hemoglobin	−0.17	0.18	−0.17	0.18
LDH**	−0.01	0.92	**0.41**	**<0.01**
FDG-PET parameters				
Tumor SUVmax	-	-	0.03	0.81
TMTV	0.03	0.81	-	-

Note: * Only smokers (former or current: $n = 60$ pts) were included. ** Available data for a total of 40 patients (63%). Bold values denote statistical significance at the $p < 0.05$ level.

Table S2. Patients treated with corticosteroids at baseline: drug name, doses and indications.

Patient	**Type of Corticosteroid**	**Daily Dose (mg Prednisone)**	**Reason for Corticosteroid Treatment**
1	prednisolone	80	brain metastasis
2	prednisolone	30	corticotroph deficiency
3	prednisolone	80	brain metastases
4	prednisone	80	brain metastases
5	prednisone	80	colitis
6	prednisolone	60	epiduritis
7	prednisone + fluticasone (inhaled)	40 (oral) + 4 (inhaled)	dyspnea
8	prednisone	80	brain metastases
9	prednisolone	10	epiduritis
10	prednisolone	60	superior vena cava syndrome
11	prednisone	40	brain metastases
12	prednisone	20	brain metastases

Table S3. Comparison of the baseline characteristics of patients with or without corticosteroids at baseline.

	Patients with Corticosteroids (*n* = 13 pts)	**Patients without Corticosteroids (*n* = 50 pts)**	
Variable	median (min–max)	median (min–max)	*p* value
Age	65 (48–86)	65 (37–85)	0.83
Performance status (PS)	1 (0–2)	1 (0–3)	0.84
Pack-years smoking	30 (20–65)	35 (5–100)	0.23
PD-L1 TPS (%)	70 (50–100)	80 (50–100)	0.49
dNLR	2.4 (1.1–14.1)	2.1 (0.9–6.7)	0.16
Hemoglobin (g/dL)	12.8 (9.5–15.4)	12.6 (8.3–16.0)	0.70
LDH* (UI/L)	205 (160–2197)	259 (105–1651)	0.57
N metastatic sites	2 (0–6)	2 (0–5)	0.25
Tumor SUVmax	22.4 (10.4–31.6)	17.7 (5.4–41.4)	0.07
TMTV (cm^3)	94.1 (26.9–209.2)	83.7 (12.4–427.9)	0.94

Table S4. Comparison of the baseline characteristics of high or very-high PD-L1 expressors.

	Patients with very high PD-L1 expression TPS: 90–100 % (*n* = 19 pts)	**Patients with high PD-L1 expression TPS: 50–89 % (*n* = 44 pts)**	
Variable	median (min-max)	median (min–max)	p value
Age	67 (55–85)	63 (37–86)	0.26
Performance status (PS)	1 (0–3)	1 (0–3)	0.55
Pack-years smoking	40 (5–100)	31 (10–75)	0.08
PD-L1 TPS (%)	95 (90–100)	60 (50–80)	<0.01
dNLR	2.1 (0.8–14.1)	2.2 (1.0–8.6)	0.78
Hemoglobin (g/dL)	12.4 (9.3–15.6)	12.8 (8.3–16.0)	0.76
LDH* (UI/L)	254 (141–576)	232 (105–2197)	0.20
N metastatic sites	2 (0–5)	2 (1–6)	0.46
Tumor SUVmax	18.8 (5.9–28.0)	17.6 (5.4–41.4)	0.77
TMTV (cm^3)	96.2 (42.3–269.8)	69.2.7 (12.4–427.9)	0.07

Note: * Available data for a total of 40 patients (63%).

Table S5. Comparison of the baseline characteristics of patients with squamous or non-squamous carcinoma.

	Squamous (*n* = 13 pts)	**Non-squamous (*n* = 50 pts)**	
Variable	median (min–max)	median (min-max)	*p* value
Age	72 (54–86)	64 (37–85)	0.05
Performance status (PS)	1 (0–3)	1 (0–2)	0.08
Pack-years smoking	34 (10–100)	35 (5–90)	0.87
PD-L1 TPS (%)	80 (50–100)	80 (50–100)	0.83
dNLR	2.3 (0.9–6.4)	2.1 (1.0–14.1)	0.77
Hemoglobin (g/dL)	12.1 (8.3–14.7)	12.7 (8.8–16.0)	0.24
LDH* (UI/L)	198 (105–323)	259 (141–2197)	0.21
N metastatic sites	2 (0–4)	2 (0–6)	0.68
Tumor SUVmax	20.6 (5.7–41.4)	16.5 (5.4–31.8)	0.02
TMTV (cm^3)	84.5 (20.2–185.1)	82.7 (12.4–427.9)	0.41

Note: * Available data for a total of 40 patients (63%).

Table S6. Baseline patient characteristics in the three prognostic groups according to the metabolic score.

Metabolic Score	Good Prognosis Group	Intermediate Prognosis Group	Poor Prognosis Group
n (%)	25 (40%)	27 (43%)	11 (17%)
ECOG PS			
≥ 2	3 (12%)	5 (19%)	5 (45%)
Histology			
SCC	3 (12%)	8 (30%)	2 (18%)
Smokers			
Always	23 (92%)	26 (96%)	11 (100%)
dNLR			
>3	0 (0%)	5 (19%)	11 (100%)
Hemoglobin			
≤ 12 g/dL	4 (16%)	11 (41%)	7 (64%)
LDH*			
> ULN	6 (24%)	8 (30%)	5 (45%)
N metastatic sites			
> 3	2 (1%)	5 (19%)	4 (36%)
Liver metastasis			
Yes	0 (0%)	5 (19%)	4 (36%)
Tumor SUVmax			
> 16.5	12 (48%)	5 (19%)	7 (64%)
TMTV			
> 75 cm^3	0 (0%)	22 (81%)	11 (100%)

Note: * Available data in a total of 40 patients (63%).

Table S7. Summary of published data for combination of blood inflammatory markers and FDG-PET parameters in advanced NSCLC.

Drug	Line of Therapy	Study	N Patients	Name	Blood Marker (Cut-Off if Categorial Variable)	FDG-PET Marker (Cut-Off if Categorial Variable)	Groups	Outcomes	Significance	Reference
Nivolumab Pembrolizumab Atezolizumab	First-line (16%) Second or further-line (84%)	Retrospective	80	Metabolic Score	dNLR (>3) At baseline	TMTV (>75cm3) At baseline	High risk: 2 factors Intermediate risk: 1 factor Low risk: 0 factor	High risk: poor PFS and OS + no DCB Low risk: good PFS and OS + DCB	**High risk** (p < 0.001): PFS: 1.4 months (95% CI 0.8–2.0) OS: 2.4 months (95% CI 1.9–2.9) **Low risk:** DCB: OR 7.9; p = 0.003	[1]
Nivolumab Pembrolizumab	First-line (24%) Second or further-line (76%)	Prospective	33	IMPI	NLR (>4.9) At first restaging	TLG (>541.5 ml) At first restaging	High risk: 2 factors Intermediate risk: 1 factor Low risk: 0 factor	High risk: poor PFS and OS Low risk: good PFS and OS	**High risk** (p < 0.001): PFS: 1.8 months (95% CI 1.6–2.0) OS: 2.8 months (95% CI 1.4–4.0)	[2]
Nivolumab Pembrolizumab Atezolizumab Nivolumab+Ipililumab	First-line (26%) Second or further-line (74%)	Prospective	46		dNLR (continuous variable) At baseline	TMTV (continuous variable) At baseline		OS Association with HPD	**TMTV** OS: HR, 1.0; p = 0.008 HPD: p = 0.01 **dNLR** OS: HR, 1.2; p = 0.01 HPD: p = 0.04	[3]

Abbreviations

BOR	best overall response
CI	confidence interval
CT	computed tomography
DCB	disease clinical benefit
DCR	disease control rate
dNLR	derived neutrophils-to-lymphocytes ratio
ECOG	eastern cooperative oncology group
FDG	fluoro-deoxy-glucose
HD	high definition
HPD	hyperprogressive disease
HR	hazard ratio
ICIs	immune checkpoint inhibitors
LDH	lactate dehydrogenase
LYSO	lutetium yttrium oxyorthosilicate
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
OSEM	ordered subset expectation maximization
PET	positron emission tomography
PD-L1	programmed cell death ligand-1
PFS	progression-free survival
SCC	squamous cell carcinoma
SiPM	silicon photomultipliers
SUVmax	maximum standard uptake value
TMTV	total metabolic tumor volume
TOF	time of flight
TPS	tumor proportion score

References

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2 Castello, A.; Toschi, L.; Rossi, S.; Mazziotti, E.; Lopci, E. The immune-metabolic-prognostic index and clinical outcomes in patients with non-small cell lung carcinoma under checkpoint inhibitors. *J. Cancer Res. Clin. Oncol.* **2020**, *146*, 1235–1243, doi:10.1007/s00432-020-03150-9.

3 Castello, A.; Rossi, S.; Toschi, L.; Mazziotti, E.; Lopci, E. Hyper-progressive Disease in Patients With Non-Small Cell Lung Cancer Treated With Checkpoint Inhibitors: The Role of 18F-FDG PET/CT. *J. Nucl. Med.* **2019**, doi:10.2967/jnumed.119.237768.