iScience, Volume *26*

Supplemental information

Using peripheral immune-inflammatory blood markers in tumors treated with immune checkpoint inhibitors: An INVIDIa-2 study sub-analysis

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Supplementary Data

Supplementary Table 1: Validation of other clinical factors

	All sample (n=1169)	**Lung (n=635)**	**RCC (n=200)**	**Melanoma (n=150)**
	HR (95% CI); p-value	**HR (95% CI); p-value**	**HR (95% CI); p-value**	**HR (95% CI); p-value**
LDH				
<upper limit of normal	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
≥upper limit of normal	1.41 (1.14-1.75); p=0.001	1.39 (1.04-1.87); p=0.027	1.32 (0.79-2.20); p=0.29	1.41 (0.71-2.80); p=0.33
	c-index = 0.533	c-index = 0.523	c-index = 0.542	c-index = 0.544
Gender				
Female	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Male	1.18 (0.97-1.43); p=0.10	1.14 (0.88-1.46); p=0.32	1.35 (0.77-2.37); p=0.29	0.69 (0.37-1.27); p=0.23
ECOG PS				
0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	1.87 (1.56-2.25); p<0.001	1.79 (1.42-2.26); p<0.001	2.28 (1.39-3.76); p=0.001	1.57 (0.78-3.15); p=0.21
2	3.66 (2.52-5.30); p<0.001	3.81 (2.35-6.18); p<0.001	4.34 (1.90-9.89); p<0.001	6.19 (2.10-18.27); p=0.001
3	4.39 (1.41-13.74); p=0.011	3.87 (0.96-15.65); p=0.058	-	-
Smoking status				
Never	1.00 (ref)	1.00(ref)	1.00 (ref)	1.00 (ref)
Former	1.10 (0.89-1.36); p=0.39	0.78 (0.56-1.08); p=0.14	0.61 (0.32-1.17); p=0.14	0.88 (0.42-1.88); p=0.75
Current	1.14 (0.90-1.46); p=0.28	0.74 (0.52-1.06); p=0.10	1.08 (0.59-1.99); p=0.80	0.76 (0.27-2.18); p=0.61
Pre-treatment steroids (Yes vs No)	1.28 (1.06-1.54); p=0.010	1.15 (0.91-1.45); p=0.24	0.85 (0.51-1.44); p=0.55	1.68 (0.86-3.27); p=0.13
Bone metastases (Yes vs No)	1.29 (1.07-1.55); p=0.007	1.34 (1.05-1.71); p=0.020	1.10 (0.68-1.76); p=0.70	1.52 (0.76-3.02); p=0.23
Brain metastases (Yes vs No)	1.18 (0.94-1.49); p=0.15	1.10 (0.82-1.50); p=0.52	1.01 (0.48-2.11); p=0.99	2.00 (1.00-3.97); p=0.049
Liver metastases (Yes vs No)	1.71 (1.35-2.16); p<0.001	2.16 (1.58-2.95); p<0.001	1.75 (0.97-3.15); p=0.063	2.28 (1.19-4.38); p=0.013

Abbreviations: 95% CI, 95% confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; n, number; RCC, renal cell carcinoma

Supplementary Table 2: Validation of original LIPI score

	Whole sample (n=1169)	***Lung cancer (n=635)***	***RCC (n=200)***	***Melanoma (n=150)***
LIPI score	**HR (95% CI); p-value**	**HR (95% CI); p-value**	**HR (95% CI); p-value**	**HR (95% CI); p-value**
0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	1.51 (1.18-1.91); p=0.001	1.54 (1.10-2.16); p=0.011	1.19 (0.69-2.05); p=0.52	1.42 (0.67-3.01); p=0.37
2	2.44 (1.79-3.33); p<0.001	2.29 (1.53-3.43); p<0.001	2.76 (1.21-6.31); p=0.016	6.05 (2.13-17.12); p=0.001
c-index	0.564	0.559	0.563	0.591

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; LIPI score, lung immune prognostic index; n, number; RCC, renal cell carcinoma

Supplementary Table 3: Validation of LIPI score with dNLR replaced by ROC-derived SII value

	Whole sample (n=1169)	*Lung cancer (n=635)*	*RCC (n=200)*	*Melanoma (n=150)*
LIPI score	**HR (95% CI); p-value**	**HR (95% CI); p-value**	**HR (95% CI); p-value**	**HR (95% CI); p-value**
0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	1.66 (1.21-2.27); p=0.002	1.49 (0.96-2.32); p=0.078	1.02 (0.52-2.01); p=0.96	1.56 (0.66-3.70); p=0.31
2	2.54 (1.79-3.36); p<0.001	2.01 (1.29-3.11); p=0.002	2.03 (1.04-3.97); p=0.038	2.57 (1.05-6.26); p=0.038
c-index	0.578	0.554	0.589	0.605

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; LIPI score, lung immune prognostic index; n, number; RCC, renal cell carcinoma

Supplementary Table 4: Validation of LIPI score with dNLR replaced by ROC-derived NLR value

	Whole sample (n=1169)	*Lung cancer (n=635)*	*RCC (n=200)*	*Melanoma (n=150)*
LIPI score	**HR (95% CI); p-value**	**HR (95% CI); p-value**	**HR (95% CI); p-value**	**HR (95% CI); p-value**
0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	1.54 (1.13-2.09); p=0.006	1.61 (1.04-2.51); p=0.035	0.92 (0.48-1.76); p=0.81	1.54 (0.69-3.44); p=0.29
2	2.33 (1.72-3.16); p<0.001	2.22 (1.44-3.45); p<0.001	1.87 (0.96-3.64); p=0.065	1.59 (0.64-3.97); p=0.32
c-index	0.579	0.566	0.569	0.552

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; LIPI score, lung immune prognostic index; n, number; RCC, renal cell carcinoma

Supplementary Table 5: Validation of original LIPS-3 score

	Whole sample (n=1169)	*Lung cancer (n=635)*	*RCC (n=200)*	*Melanoma (n=150)*
LIPS-3 score	**HR (95% CI); p-value**	**HR (95% CI); p-value**	**HR (95% CI); p-value**	**HR (95% CI); p-value**
0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	1.53 (1.27-1.84); p<0.001	1.34 (1.05-1.70); p=0.017	1.16 (0.72-1.89); p=0.54	1.43 (0.78-2.61); p=0.25
2	8.14 (4.41-15.0); p<0.001	8.89 (4.11-19.23); p<0.001	5.89 (1.40-24.82); p=0.016	21.00 (2.58-171.00); p=0.004
c-index	0.566	0.552	0.535	0.561

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; LIPS-3 score, lung immune-oncology prognostic score; n, number; RCC, renal cell carcinoma

Supplementary Table 6: Validation of LIPS-3 score with literature-reported cut-off NLR value replaced by ROC-derived NLR value

	Whole sample (n=1169)	*Lung cancer (n=635)*	*RCC (n=200)*	*Melanoma (n=150)*
LIPS-3 score	**HR (95% CI); p-value**	**HR (95% CI); p-value**	**HR (95% CI); p-value**	**HR (95% CI); p-value**
0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	1.63 (1.35-1.98); p<0.001	1.48 (1.14-1.92); p=0.003	1.33 (0.80-2.20); p=0.27	1.35 (0.74-2.47); p=0.33
2	9.51 (5.27-17.18); p<0.001	11.14 (5.35-23.21); p<0.001	6.47 (1.52-27.60); p=0.012	20.71 (2.54-168.94); p=0.005
c-index	0.571	0.562	0.546	0.554

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; LIPS-3 score, lung immune-oncology prognostic score; n, number; RCC, renal cell carcinoma

Supplementary Table 7: Validation of LIPS-3 score with literature-reported NLR replaced by ROC-derived SII

	Whole sample (n=1169)	***Lung cancer (n=635)***	***RCC (n=200)***	***Melanoma (n=150)***
LIPS-3 score	**HR (95% CI); p-value**	**HR (95% CI); p-value**	**HR (95% CI); p-value**	**HR (95% CI); p-value**
0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	1.71 (1.40-2.10); p<0.001	1.43 (1.10-1.86); p=0.008	1.76 (1.02-3.05); p=0.043	1.89 (1.02-3.52); p=0.044
2	6.93 (3.74-12.85); p<0.001	10.04 (4.60-21.89); p<0.001	1.76 (0.23-13.26); p=0.58	44.53 (8.73-227.05); p<0.001
c-index	0.571	0.553	0.564	0.609

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; LIPS-3 score, lung immune-oncology prognostic score; n, number; RCC, renal cell carcinoma

Supplementary Table 8: The REMARK checklist – Data S1

Item to be reported		Reported on Page Number/Line Number	Reported on Section/Paragraph
INTRODUCTION			
1	State the marker examined, the study objectives, and any pre-specified hypotheses.	6/1-4	Background
MATERIALS AND METHODS			
Patients			
2	Describe the characteristics (e.g., disease stage or co-morbidities) of the study patients, including their source and inclusion and exclusion criteria.	6/8-12 9/4-5	Methods Results, Table 1
3	Describe treatments received and how chosen (e.g., randomized or rule-based).	N/A	INVIDIa-2 study
Specimen characteristics			
4	Describe type of biological material used (including control samples) and methods of preservation and storage.	N/A	
Assay methods			
5	Specify the assay method used and provide (or reference) a detailed protocol, including specific reagents or kits used, quality control procedures, reproducibility assessments, quantitation methods, and scoring and reporting protocols. Specify whether and how assays were performed blinded to the study endpoint.	7/13-24 8/1-3	Methods Methods
Study design			
6	State the method of case selection, including whether prospective or retrospective and whether stratification or matching (e.g., by stage of disease or age) was used. Specify the time period from which cases were taken, the end of the follow-up period, and the median follow-up time.	6/8-13	Methods
7	Precisely define all clinical endpoints examined.	6/23-24, 7/1-11	Methods
8	List all candidate variables initially examined or considered for inclusion in models.	8/5-15	Methods
9	Give rationale for sample size; if the study was designed to detect a specified effect size, give the target power and effect size.	N/A	
Statistical analysis methods			
10	Specify all statistical methods, including details of any variable selection procedures and other model-building issues, how model assumptions were verified, and how missing data were handled.	7/23-24 8/1-15	Methods Methods
11	Clarify how marker values were handled in the analyses; if relevant, describe methods used for cutpoint determination.	7/13-21	Methods

RESULTS			
Data			
12	Describe the flow of patients through the study, including the number of patients included in each stage of the analysis (a diagram may be helpful) and reasons for dropout. Specifically, both overall and for each subgroup extensively examined report the numbers of patients and the number of events.	9/1-4	Results
13	Report distributions of basic demographic characteristics (at least age and sex), standard (disease-specific) prognostic variables, and tumor marker, including numbers of missing values.	9/4-5, Table 1	Results, Table 1

Analysis and presentation			
14	Show the relation of the marker to standard prognostic variables.	12/5-23, 13/1-23, 14/1-21	Results
15	Present univariable analyses showing the relation between the marker and outcome, with the estimated effect (e.g., hazard ratio and survival probability). Preferably provide similar analyses for all other variables being analyzed. For the effect of a tumor marker on a time-to-event outcome, a Kaplan-Meier plot is recommended.	11/6-22	Results, Table 2, Table 3, Table 5
16	For key multivariable analyses, report estimated effects (e.g., hazard ratio) with confidence intervals for the marker and, at least for the final model, all other variables in the model.	12/1-3	Results, Table 4
17	Among reported results, provide estimated effects with confidence intervals from an analysis in which the marker and standard prognostic variables are included, regardless of their statistical significance.	9/7-23, 10/1-24, 11/1-4, Table 2, Table 3	Results, Table 2, Table 3
18	If done, report results of further investigations, such as checking assumptions, sensitivity analyses, and internal validation.	Supplementary Table 1	Supplementary Table 1
DISCUSSION			
19	Interpret the results in the context of the pre-specified hypotheses and other relevant studies; include a discussion of limitations of the study.	14/24-25, 15/1-24, 16/1-24, 17/1-24, 18/1-18	Discussion
20	Discuss implications for future research and clinical value.	18/15-23	Discussion, Conclusion

From: McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM: Reporting recommendations for tumor marker prognostic studies (REMARK). J Natl Cancer Inst 2005; 97: 1180-1184.