





## BRIEF REPORT

# Host immune-inflammatory markers to unravel the heterogeneous outcome and assessment of patients with PD-L1 $\geq 50\%$ metastatic non-small cell lung cancer and poor performance status receiving first-line immunotherapy

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#### Abstract

**Background:** Patients with programmed cell death-ligand 1 (PD-L1)  $\geq 50\%$  metastatic non-small cell lung cancer (mNSCLC) and ECOG performance status (PS) of 2 treated with first-line immunotherapy have heterogeneous clinical assessment and outcomes.

**Methods:** To explore the role of immune-inflammatory surrogates by the validated lung immuno-oncology prognostic score (LIPS) score, including the neutrophil-to-lymphocyte ratio (NLR) and the pretreatment use of steroids, alongside other prognostic variables. A retrospective analysis of 128 patients with PS2 and PD-L1  $\geq 50\%$  mNSCLC treated between April 2018 and September 2019 with first-line pembrolizumab in a real-world setting was performed.

**Results:** With a median follow-up of 15.3 months, the 1-year overall survival (OS) and median progression-free survival (PFS) were 32.3% (95% CI: 30.9–33.9) and 3.3 months (95% CI: 1.8–4.7), respectively. The NLR, lactate dehydrogenase (LDH) and pretreatment steroids results were the only significant prognostic factors on the univariate analysis and independent prognostic factors by the multivariate analysis on both OS and PFS. The LIPS score, including the NLR and pretreatment steroids, identified 29 (23%) favourable-risk patients, with 0 factors, 1-year OS of 67.6% and median PFS of 8.2 months; 57 (45%) intermediate-risk patients, with 1 factor, 1-year OS 32.1% and median PFS 2.7 months; 42 (33%) poor-risk patients, with both factors, 1-year OS of 10.7% and median PFS of 1.2 months.

**Conclusions:** The assessment of pre-existing imbalance of the host immune response by combined blood and clinical immune-inflammatory markers may represent a way to unravel the heterogeneous outcome and assessment of patients with mNSCLC and poor PS in the immune-oncology setting.

#### KEYWORDS

immunotherapy, inflammation, neutrophil-to-lymphocyte ratio (NLR), non-small cell lung cancer, performance status

## INTRODUCTION

Immunotherapy is the standard first-line treatment for patients with metastatic non-small cell lung cancer (mNSCLC) and programmed cell death-ligand 1 (PD-L1) tumour expression  $\geq 50\%$ . It has been challenged by the addition of chemotherapy<sup>1</sup> or a combination of two immune checkpoint inhibitors (ICIs) with chemotherapy,<sup>2</sup> although comparative clinical trials and predictive biomarkers are currently unavailable.

Blood immune-inflammatory indices, such as the neutrophil-to-lymphocyte ratio (NLR), with or without serum lactate dehydrogenase (LDH) and/or PD-L1 tumour expression level,<sup>3</sup> have demonstrated the stratification for prognosis of patients treated with immunotherapy. A

combined prognostic model, namely the lung immuno-oncology prognostic score (LIPS), including validated NLR with a cutoff of 4, Eastern Cooperative Oncology Group Performance Status (ECOG PS) with a threshold of 2 and pretreatment use of steroids, and optional serum LDH with a cutoff of 252 u/l, was built in a large real-world series of patients with mNSCLC and PD-L1 tumour expression  $\geq 50\%$  treated with first-line pembrolizumab.<sup>4</sup>

Most randomised trials have excluded patients with PS 2. The only data available on the safety and/or efficacy with ICIs is from two small sample-sized phase II studies enrolling patients with PS 2 only,<sup>5,6</sup> three subgroup analyses from phase II–III studies on a limited number of patients,<sup>7–9</sup> and some retrospective series.<sup>10–12</sup> They showed limited benefit

from ICIs in patients with PS 2. The different outcomes were probably dependent on the primary condition determining the PS 2, whether tumour burden or comorbidity,<sup>12</sup> and the subjective assessment of the ECOG score.<sup>13</sup>

Here, we aimed to explore the prognostic role of the LIPS score<sup>4</sup> in patients with PD-L1 tumour expression  $\geq 50\%$  mNSCLC and ECOG PS 2 treated with first-line pembrolizumab PS 2 in a large real-world series.<sup>4,14</sup>

## METHODS

The study objectives were: (1) to confirm the prognostic role of each pretreatment factor of the LIPS score (excluding the PS) in addition to other prognostic variables and (2) to explore the prognostic stratification by the LIPS score (excluding the PS) in patients with PS 2 and PD-L1 tumour expression  $\geq 50\%$  (assessed by different immunohistochemistry assays depending on local institutional practice) mNSCLC treated with first-line pembrolizumab in a real-world setting.<sup>14</sup>

We performed a logistic regression on OS and PFS of clinical and laboratory variables and related thresholds as previously reported<sup>3,4</sup> (see Table 1), by two-sided log-rank test. No information was available about other potentially

targetable oncogenes beyond *EGFR* and *ALK*, including the tumour mutational burden (TMB), or other molecular alterations known to affect response to ICIs, as they were not routinely tested. The baseline NLR and LDH values were obtained from reports of routine blood samples performed within seven days before treatment initiation and analyzed by local laboratories. A multivariate Cox-regression analysis on OS was performed with significant factors by the univariate analysis. The LIPS score,<sup>4</sup> including the validated NLR and pretreatment steroids, and nonvalidated serum LDH, was assessed by the two-sided log-rank test. A *p*-value  $< 0.05$  was considered statistically significant. Clinical outcome estimation details have already been reported elsewhere.<sup>4</sup>

## RESULTS

A total of 128 patients out of 784 (16%) had PS 2. The clinical characteristics are summarized in Table S1. The baseline NLR was available for all patients; the median value was 5.5 (range, 0.6–47.5), 86 patients (67%) had NLR  $\geq 4.0$ . Fifty-five patients (43%) received pretreatment steroids, mostly (95% of patients) for cancer-related symptoms and with prednisolone  $\geq 10$  mg or equivalent dose (80%) (see Table S1). The

**TABLE 1** Univariate analysis for OS and PFS of baseline NLR, LDH and clinical parameters in ECOG PS 2 mNSCLC patients with PD-L1  $\geq 50\%$

	Values	N	mOS (mo.)	HR (95% CI)	<i>p</i> -value <sup>a</sup>	mPFS (mo.)	HR (95% CI)	<i>p</i> -value <sup>a</sup>
All pts	-	128	4.8	(2.66–6.94)	-	3.3	(1.79–4.72)	-
<b>Biomarker</b>								
NLR	$\geq 4.0$	86	2.9	3.09	<i>&lt;0.001</i>	5.1	1.90	0.005
	<i>&lt; 4.0</i>	42	NR	(1.79–5.34)		1.8	(1.21–3.00)	
LDH	$\geq 252$ u/l	54	3.9	1.96	0.02	2.0	1.81	0.03
	<i>&lt; 252</i> u/l	38	16.9	(1.10–3.47)		5.3	(1.07–3.06)	
PD-L1	$\geq 90\%$	21	3.7	0.81	0.48	2.5	0.81	0.44
	<i>&lt; 90%</i>	76	4.9	(0.46–1.45)		3.7	(0.47–1.39)	
<b>Clinical parameter</b>								
Smoke	Ever	10	4.8	0.99	0.98	3.3	1.18	0.65
	Never	118	4.4	(0.45–2.16)		2.6	(0.57–2.46)	
Histology	Sq	27	3.9	0.65	0.09	2.9	0.76	0.26
	Non-Sq	101	5.9	(0.39–1.07)		3.3	(0.46–1.23)	
Brain	No	93	5.2	1.09	0.74	3.7	1.27	0.30
	Yes	35	4.4	(0.66–1.79)		1.9	(0.81–1.98)	
Liver	No	109	4.8	1.22	0.52	3.3	1.31	0.34
	Yes	19	2.5	(0.67–2.20)		1.8	(0.75–2.28)	
Bone	No	78	5.9	1.41	0.12	4.2	1.48	0.06
	Yes	50	3.7	(0.91–2.18)		1.8	(0.98–2.24)	
BMI	$\geq 24.8$	37	7.7	1.24	0.40	4.0	1.43	0.14
	<i>&lt; 24.8</i>	83	4.4	(0.75–2.03)		2.6	(0.89–2.28)	
Steroids	No	73	8.68	2.58	<i>&lt;0.001</i>	4.6	2.29	<i>&lt;0.001</i>
	Yes	55	1.84	(1.67–4.00)		1.6	(1.53–3.45)	

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; mNSCLC, metastatic non-small cell lung cancer; N number; NA, not assessable; NLR, neutrophil-to-lymphocyte ratio; NR, not reached; OS, overall survival; PD-L1 programmed cell death ligand 1; PFS, progression-free survival; Sq, squamous.

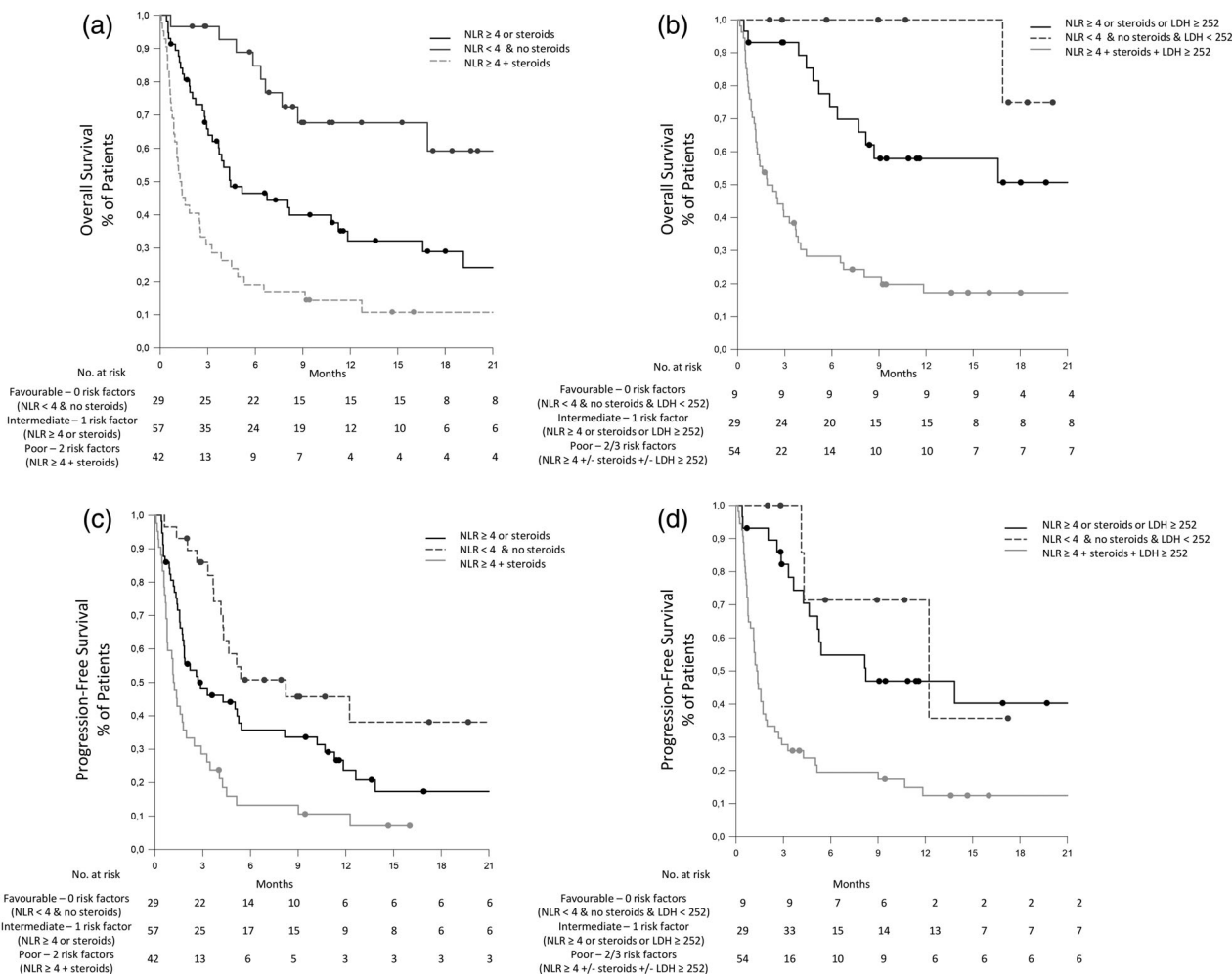
Note: Significant factors are reported in Italics.

<sup>a</sup>By two-sided log-rank test.

**TABLE 2** Multivariate analysis for OS and PFS of baseline NLR, LDH and pretreatment steroids in ECOG PS 2 mNSCLC patients with PD-L1 ≥ 50%

	Values	N	HR for OS (95% CI)	p-value	HR for PFS (95% CI)	p-value
All pts	-	128	-	-	-	-
<b>Biomarker</b>						
NLR	≥ 4.0	86	2.88	0.001	1.76	0.04
	< 4.0	42	(1.51–5.49)		(1.02–3.03)	
LDH	≥ 252	54	2.03	0.02	1.79	0.03
	< 252	38	(1.14–3.60)		(1.01–3.02)	
<b>Clinical parameter</b>						
Steroids	No	73	2.79	<0.001	2.37	<0.001
	Yes	55	(1.61–4.82)		(1.43–3.93)	

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; LDH lactate dehydrogenase; mNSCLC, metastatic non-small cell lung cancer; N number; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PD-L1 programmed-cell-death ligand 1; PFS, progression-free survival.



**FIGURE 1** OS and PFS by risk categories based on NLR, pretreatment steroids use +/- LDH in patients with mNSCLC, PD-L1 ≥50% and ECOG PS 2

baseline serum LDH was available for 92 (72%) patients; median value was 277 (range 72–2152), 54 patients (59%) had LDH ≥252 u/l. By different combinations of these three factors, there were still 45% to 52% of nonoverlapping patients (see Table S2). The distribution of patients according to NLR, LDH and steroids is shown in Table S2. With a median follow-up of 15.3 months (95% confidence

interval [CI]: 10.5–20.1), 1-year OS was 32.3% (95% CI: 30.9–33.9) and median PFS 3.3 months (95% CI: 1.8–4.7), respectively (see Table S1).

By univariate analysis, the NLR ( $p < 0.001$  and  $p = 0.005$ ), LDH ( $p = 0.02$  and  $0.03$ ) and pretreatment steroids ( $p < 0.001$  for both) were significant prognostic factors for OS and PFS, respectively (see Table 1). The multivariate

analysis confirmed NLR, LDH and pretreatment steroids as independent prognostic factor, with hazard ratio (HR) on OS of 2.88 (95% confidence interval [CI], 1.51–5.49), 2.03 (95% CI: 1.14–3.60) and 2.79 (95% CI, 1.61–4.82) and on PFS of 1.76 (95% CI: 1.02–3.03), 1.79 (95% CI, 1.01–3.02) and 2.37 (95% CI: 1.43–3.93), respectively (see Table 2). According to NLR, LDH and pretreatment steroids, survival curves for OS and PFS with estimates and log-rank *p*-values are shown in Figure S1.

The LIPS score, including the baseline NLR and pretreatment steroids as risk factors, identified 29 (23%) favourable-risk patients, with 0 factors, 1-year OS of 67.6 and median PFS of 8.2 months; 57 (45%) intermediate-risk patients, with one factor, 1-year OS 32.1% and median PFS 2.7 months; 42 (33%) poor-risk patients, with both factors, 1-year OS of 10.7% and median PFS of 1.2 months (see Figure 1). By the addition of the LDH, nine patients (10%) with 0 factors had 1-year OS of 75% and median PFS of 12.2 months; 29 (32%) with one factor, 1-year OS of 57.9 and median PFS of 8.2 months; and 59 (54%) with  $\geq$  two risk factors, 1-year OS of 17% and median PFS of 1.4 months (see Figure 1).

## DISCUSSION

Historically, the prognosis of patients with mNSCLC and ECOG PS 2, despite treatment with platin-based chemotherapy, has been poor, with a median OS of 3.3 months and a 1-year OS rate  $<$  20%.<sup>15</sup> Conflicting outcome estimates have been observed with ICIs across prospective and retrospective small-sized studies and analyses with a median OS ranging between 3.0 and 10.4 months in untreated patients<sup>5,10</sup> and 4.0 to 9.3 months in pretreated patients.<sup>7,8,12</sup> These data are inferior to those expected for patients with ECOG PS 0–1, although with comparable immune-related toxicity. The heterogeneity of patients defined as ECOG PS 2, due to symptoms from large tumour burden, comorbidity, or both, and interobserver variability of the assessment, underpin these variable results, eventually preventing a relevant proportion of patients from the benefit of ICIs. Better classification of these patients, based on the specific weight of the underlying conditions responsible for the poor PS, would be helpful.<sup>13</sup>

Our study suggests that assessing a pre-existing imbalance of host immune response favouring an inflamed condition may represent a simple tool to unravel these patients' heterogeneous outcome and their evaluation in the immuno-oncology setting. This imbalance might be routinely assessed by either an elevated baseline NLR, which is a surrogate for tumour-associated inflammation and activity of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs), and pretreatment use of steroids.<sup>4</sup> Both these factors resulted as independently prognostic in the present analysis, besides the LDH, which is likely expression of a rapidly growing tumour and large tumour burden.

Prognostic stratification of patients with ECOG PS 2 and high-PD-L1 mNSCLC by the LIPS tool,<sup>4</sup> +/- the serum LDH, could help clinicians in their decision-making by giving valuable information beyond the "solo" ECOG PS

assessment. For instance, according to the LIPS, patients with "favourable" risk (almost one in every 4) should be offered ICIs despite their ECOG PS 2 definition. In contrast, for those with "intermediate" risk (nearly a half), different therapeutic strategies, including the addition of chemotherapy (in Countries where this option is available and reimbursed) and ad hoc clinical trials, should be considered. In this regard, a combination with platinum-based doublets (particularly carboplatin) is the currently recommended option by the European Society for Medical Oncology (ESMO) guidelines.<sup>16</sup> "Poor" risk patients (about one patient every three) are unlikely to benefit from single-agent ICI. For these patients, the best supportive care might be the most reasonable approach. On the other hand, other treatment options, including investigational strategies to reduce the host inflammation, could be considered when clinically feasible.

If available, the information on baseline LDH, in addition to the NLR and pretreatment steroid of the validated LIPS score, might be valuable. It could better identify patients who benefit from immunotherapy through a more accurate definition of those at intermediate-risk. Indeed, patients who fell into the intermediate-risk category according to the LIPS plus the LDH represented 42% of the entire population with a median PFS of  $\geq$ 8.2 months, which was similar to the PFS observed in the LIPS only "favourable-risk" patients accounting for 23% of patients.

The proposed stratification for the first time provides useful information for this subgroup of patients that has been a medical challenge since the advent of first-line pembrolizumab for patients with PD-L1 high NSCLC in clinical practice, where the biomarker-driven excitement and the favorable safety profile (as compared to standard chemotherapy) might have occasionally led to desperate approaches.

We acknowledge the retrospective analysis of data from hospital records, and the lack of a control cohort and further molecular characterization as limitations of this study. Furthermore, we tested the LIPS tool in a selected population belonging to a large series we had previously used to validate the NLR and LDH cutoffs we applied and develop that prognostic tool.<sup>4</sup> However, this does not imply their prognostic value would have been confirmed in this already negatively prognostically selected population. Nonetheless, we believe the LIPS score may represent an easy-to-assess, worldwide routinely available and inexpensive prognostic tool that could unravel the heterogeneous clinical behavior and assess patients with PD-L1 tumour expression  $\geq$ 50% mNSCLC and ECOG PS 2. The LIPS score critical prognostic elements may enrich the current treatment decision-making in daily practice and be adopted as stratifying factor in future trials recruiting such patients.

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### CONFLICT OF INTEREST

Dr Marcello Tiseo received speakers' and consultants' fee from Astra-Zeneca, Pfizer, Eli-Lilly, BMS, Novartis, Roche, MSD, Boehringer Ingelheim, Otsuka, Takeda, Pierre Fabre. M.T. received institutional research grants from Astra-Zeneca, Boehringer Ingelheim. Dr Diego Cortinovic received speaker fees/grant consultancies by Astra Zeneca, BMS, MSD, Boehringer Ingelheim, Novartis, Amgen, Roche, Eli Lilly. Dr Francesco Facchinetti has participated to editorial activities sponsored by BMS and Roche. Dr Emilio Bria received speaker and travel fees from MSD, Astra-Zeneca, Pfizer, Helsinn, Eli-Lilly, BMS, Novartis and Roche. Dr Emilio Bria received grant consultancies by Roche and Pfizer. Dr Alessandro Morabito received speaker fees by Astra, Roche, BMS, MSD, Boehringer, Pfizer, Takeda. Dr Francesca Mazzoni received grant consultancies by MSD and Takeda. Dr Raffaele Giusti received speaker fees and grant consultancies by AstraZeneca and Roche. Dr Carlo Genova received speaker fees/grant consultancies by Astrazeneca, BMS, Boehringer-Ingelheim. Dr Alex Friedlaender received grant consultancies by Roche, Pfizer, Astellas and BMS. Dr Rita Chiari received speaker fees by BMS, MSD, Takeda, Pfizer, Roche and AstraZeneca. Dr David J Pinato received lecture fees from ViiV Healthcare, Bayer Healthcare and travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, EISAI, Roche, Astra Zeneca; received research funding (to institution) from MSD, BMS. Dr Alfredo Addeo received grant consultancies by Takeda, MSD, BMJ, AstraZeneca, Roche and Pfizer. Dr Alessio Cortellini received speaker fees and grant consultancies by AstraZeneca, MSD, BMS, Roche, Novartis, and Astellas. All other author declared no interests to disclose.

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### REFERENCES

- Addeo A, Banna GL, Metro G, Di Maio M. Chemotherapy in combination with immune checkpoint inhibitors for the first-line treatment of patients with advanced non-small cell lung cancer: a systematic review and literature-based meta-analysis. *Front Oncol*. 2019;9:264.
- Paz-Ares L, Ciuleanu TE, Cobo M, Schenker M, Zurawski B, Menezes J, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(2):198–211.
- Banna GL, Signorelli D, Metro G, Galetta D, De Toma A, Cantale O, et al. Neutrophil-to-lymphocyte ratio in combination with PD-L1 or lactate dehydrogenase as biomarkers for high PD-L1 non-small cell lung cancer treated with first-line pembrolizumab. *Transl Lung Cancer Res*. 2020;9(4):1533–42.
- Banna GL, Cortellini A, Cortinovic DL, Tiseo M, Aerts JGJV, Barbieri F, et al. The lung immuno-oncology prognostic score (LIPS-3): a prognostic classification of patients receiving first-line pembrolizumab for PD-L1  $\geq 50\%$  advanced non-small-cell lung cancer. *ESMO Open*. 2021;6:100078.
- Middleton G, Brock K, Savage J, Mant R, Summers Y, Connibear J, et al. Pembrolizumab in patients with non-small-cell lung cancer of performance status 2 (PePS2): a single arm, phase 2 trial. *Lancet Respir Med*. 2020;8:895–904.
- Mark M, Froesch P, Eboulet EI, Addeo A, Pless M, Rothschild SI, et al. SAKK 19/17: safety analysis of first-line durvalumab in patients with PD-L1 positive, advanced nonsmall cell lung cancer and a performance status of 2. *Cancer Immunol Immunother*. 2020;70(5):1255–62.
- Felip E, Ardizzoni A, Ciuleanu T, Cobo M, Laktionov K, Szilasi M, et al. CheckMate 171: A phase 2 trial of nivolumab in patients with previously treated advanced squamous non-small cell lung cancer, including ECOG PS 2 and elderly populations. *Eur J Cancer*. 2020;127:160–72.
- Spigel DR, McCleod M, Jotte RM, Einhorn L, Horn L, Waterhouse DM, et al. Safety, efficacy, and patient-reported health-related quality of life and symptom burden with nivolumab in patients with advanced non-small cell lung cancer, including patients aged 70 years or older or with poor performance status (CheckMate 153). *J Thorac Oncol*. 2019;14:1628–39.
- Barlesi F, Audigier-Valette C, Felip E, Ciuleanu T, Jao K, Rijavec E, et al. OA04.02 CheckMate 817: first-line Nivolumab + Ipilimumab in Patients with ECOG PS 2 and other special populations with advanced NSCLC. *J Thorac Oncol*. 2019;14:S214–5.
- Friedlaender A, Metro G, Signorelli D, Gili A, Economopoulou P, Roila F, et al. Impact of performance status on non-small-cell lung cancer patients with a PD-L1 tumour proportion score  $\geq 50\%$  treated with front-line pembrolizumab. *Acta Oncol*. 2020;59(9):1058–63.
- Lobefaro R, Viscardi G, Di Liello R, Massa G, Lacovino ML, Sparano F, et al. Immunotherapy in advanced Non-Small Cell Lung Cancer patients with poor performance status: the role of clinical-pathological variables and inflammatory biomarkers. *Lung Cancer*. 2021;152:165–73.
- Facchinetti F, Mazzaschi G, Barbieri F, Passiglia F, Mazzoni F, Berardi R, et al. First-line pembrolizumab in advanced non-small cell lung cancer patients with poor performance status. *Eur J Cancer*. 2020;130:155–67.
- Friedlaender A, Banna GL, Buffoni L, Addeo A. Poor-performance status assessment of patients with non-small cell lung cancer remains vague and blurred in the immunotherapy era. *Curr Oncol Rep*. 2019;21:107.
- Cortellini A, Tiseo M, Banna GL, Cappuzzo F, Aerts JGJV, Barbieri F, et al. Clinicopathologic correlates of first-line pembrolizumab effectiveness in patients with advanced NSCLC and a PD-L1 expression of  $\geq 50\%$ . *Cancer Immunol Immunother*. 2020;69(11):2209–21.
- Gridelli C, Ardizzoni A, Le Chevalier T, Manegold C, Perrone F, Thatcher N, et al. Treatment of advanced non-small-cell lung cancer patients with ECOG performance status 2: results of an European experts panel. *Ann Oncol*. 2004;15:419–26.
- Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29:iv192–237.

### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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