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Efficacy outcomes and prognostic factors from real-world patients with advanced non-small-cell lung cancer treated with first-line chemoimmunotherapy: The Spinnaker retrospective study

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ABSTRACT

Background: Efficacy outcomes and prognostic factors of real-world patients with advanced non-small cell lung cancer (aNSCLC) treated with first-line chemoimmunotherapy are still limited.
Patients and Methods: In the retrospective Spinnaker study, data was collected from patients in six United Kingdom and one Swiss oncology centres with first-line pembrolizumab plus platinum-based chemotherapy. Efficacy outcomes and potential prognostic factors were estimated aiming at developing a prognostic model.
Results: Three-hundred-eight patients were included, 32% ≥ 70 years, with ≥ 3 metastatic sites in 33%, brain or liver metastases in 10% and 12%, respectively. With a median follow-up of 18.0 months (mo.) (range, 15.9–20.1), median overall survival (OS) and progression-free survival (PFS) were 12.7 mo. (range, 10.2–15.2), and 8.0 mo. (range, 7.1–8.8), respectively. The neutrophils-to-lymphocytes ratio (NLR) and systemic immune-inflammatory index (SII) (i.e., NLR × platelet count) were both significantly higher in ECOG PS 1 ($p = 0.0147$ and $p = 0.0018$, respectively), underweight or normal body mass index ($p = 0.0456$ and $p = 0.0062$, respectively), ≥3 metastatic sites ($p = 0.0069$ and $p = 0.112$), pretreatment steroids ($p = 0.0019$ and $p = 0.0017$). By MVA, the number of metastatic sites ≥ 3 ($p < 0.001$ and $p = 0.002$), squamous histology ($p = 0.033$ and $p = 0.013$) and SII ≥ 1444 ($p = 0.031$ and $p = 0.009$, respectively) were associated with both worse OS and PFS and led to a highly discriminating three-class risk prognostic model.
Conclusion: Real-world PFS with chemoimmunotherapy in aNSCLC patients is similar to that reported in clinical trials. A high number of metastatic sites, squamous histology and high SII are adverse prognostic factors that might contribute to a clinically useful prognostic model.

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1. Introduction

Treatment of advanced non-small cell lung cancer (aNSCLC) has moved into an entirely new era thanks to the targeted and immunological therapies [1,2]. The benefit of patients with untreated, EGFR/ALK/ROS1 wild-type NSCLC from anti-programmed death-1 (PD-1)/anti-programmed death ligand-1 (PD-L1) immune checkpoint inhibitors (ICIs), has been demonstrated in several randomised phase III clinical trials [3–6].

ICIs can be offered either as a monotherapy or combination regimens with platinum-based chemotherapy [1,2,7]. The KEYNOTE-024 study was the pivotal trial leading to the approval of monotherapy with the anti-PD-1 agent pembrolizumab by proving its overall survival (OS) benefit over platinum-based chemotherapy in aNSCLC patients with PD-L1 tumour proportion score (TPS) 50% or greater [8]. Subsequently, the KEYNOTE-042 trial confirmed the OS benefit of pembrolizumab over platinum-based chemotherapy in patients with lower thresholds of PD-L1 tumour expression (i.e., ≥1%, ≥20%, and ≥ 50%), albeit a direct relationship between the OS benefit and the level of PD-L1 expression was observed [9,10]. The anti-PD-L1 atezolizumab and the anti-PD-1 agent cemiplimab have been recently offered as alternative options to pembrolizumab for high PD-L1 aNSCLC based on the results of the IMpower110 [11] and EMPOWER-Lung 1 [12] studies, respectively.

On the other hand, the combination of immunotherapy plus chemotherapy has been approved based on the results of the KEYNOTE-189 study, which additionally challenged chemotherapy in patients with nonsquamous aNSCLC, regardless of tumour PD-L1 TPS cut-off [13]. KEYNOTE-407 study confirmed the benefit of adding pembrolizumab to chemotherapy in untreated squamous aNSCLC [14]. Similarly, the randomised phase III IMpower130 and IMpower150 studies showed the advantage of adding atezolizumab to chemotherapy [15], or chemotherapy and bevacizumab [16] in untreated nonsquamous aNSCLC. The CheckMate-227 study led to the FDA approval of the anti-PD1 nivolumab plus the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) ipilimumab, as first-line therapy in PD-L1-positive aNSCLC, while the CheckMate-9LA study to the approval of a combination of nivolumab plus ipilimumab with pemetrexed/paclitaxel and platinum [17].

To date, the available data examining combination of different immune-checkpoint inhibitors (ICIs) with chemotherapy or even with antiangiogenic agents has not provided clear evidence of synergy between those drugs, beyond the benefit of providing patients with multiple chances of response to a single agent [18]. This is particularly obvious in the PD-L1 high aNSCLC, where in the first line setting to date no randomised clinical trials support the addition of other agents over immunotherapy alone [19]. However, if we could separate patients who will do well as opposed to those who have a poor outcome, we could better undertake a focused evaluation of combinatorial strategies in cohorts enriched for high-risk patients and thus, there remains an urgent need for identifying new biomarkers to stratify the prognosis and predict treatment benefits for the non-oncogene addicted aNSCLC [20]. Beyond the quantification of PD-L1 expression [21], various inflammatory indices based on ratios between the cellular components of peripheral blood counts have demonstrated prognostic value in different cancer types treated with ICIs including the aNSCLC [22,23]. The neutrophil-to-lymphocyte ratio (NLR) entails quantitative variations of both neutrophils and lymphocytes, which are the two most relevant immune cell population participating in immune response [24,25]. It is part of combined prognostic scores, like the three-risk-class lung immuno-oncology prognostic score (LIPS) one which consists of NLR ≥ 4, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥ 2 and pretreatment steroids [19]. The LIPS score was developed in a large series of patients with PD-L1 ≥ 50% aNSCLC treated with immunotherapy alone [19], and confirmed with the possible addition of the lactate dehydrogenase (LDH) in the PS2 patient subgroup [26]. The systemic immune-inflammatory index (SII) includes the platelets, which play a relevant role in the tumour inflammation, and has demonstrated in other cancer types a higher prognostic accuracy than the NLR [27–29].

Here we assessed efficacy outcomes and how well blood inflammatory markers alongside other prognostic clinical prognostic variables identify patients with better vs poor outcomes, who are treated with chemo-immunotherapy in a real-life setting, outside of the highly selected patient groups evaluated in clinical trials.

2. Materials and methods

2.1. Study design and patients' eligibility

The Spinnaker study is a retrospective multicentre observational cohort study focusing on patients with aNSCLC in a real-world setting treated with first-line chemotherapy and pembrolizumab. Adult patients undergoing standard of care treatment with this regimen and an histologically confirmed aNSCLC (any histology), ECOG PS ≤ 1 at treatment start and known PD-L1 TPS were included. Patients with oncogene-addicted tumours (defined by the presence of EGFR, ALK, ROS1, or other actionable gene alterations) or those treated outside the current drug licences, were excluded. Patient data was collected from 6 UK cancer centres and 1 Swiss centre for patients treated between March 2018 and April 2021.

Pretreatment patients' demographic, clinical characteristics, tumour characteristics and staging, and standard blood results performed within 14 days of treatment start date were collected. NLR was calculated as the ratio between neutrophils and lymphocytes from the peripheral blood count; high NLR was considered a value ≥ 4 according to the literature reported cut-off [19]. The SII was calculated as the NLR times the platelets; high SII was defined as a value ≥ the median value. Efficacy outcome data were also collected, including survival and treatment response data.

This study was registered and approved as an audit by the multiple participating sites with the coordinating centre being Portsmouth Hospital University NHS Trust (UK). Clinical data was anonymized before sharing with the coordinating centre for analysis. The audit procedures were compliant with the Data Protection Act 2018, the precepts of Good Clinical Practice guidelines with regards to the collection, storage, processing and disclosure of personal information, and the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

2.2. Sample size and statistical analysis

A target sample size of at least 212 patients was required based on previous data from a cohort of aNSCLC patients with PD-L1 TPS ≥ 50% treated with first-line ICIs; although potentially different from the current study population for the exclusively high PD-L1 expression, these patients had shown a 2-year OS for the overall population and patients with low NLR of 52.0% and 62.0%, respectively [22]. With 80% power to detect a 10% difference in the proportion of patients achieving prolonged survival, at a one-sided α of 0.05, the enrolment of data from at least 193 patients was required to study the effect of NLR on outcome and other similar clinical variables. Considering a 10% drop for missing data, a cohort of 212 patients was planned.

The primary endpoints of the audit were to describe the survival outcomes (i.e., OS and PFS) and assess clinical prognostic factors, focusing on the NLR and SII inflammatory indexes. The exploratory endpoint was to develop a prognostic model based on factors significant in the multivariable analysis by using the entire patients' cohort as a training set.

Clinical data were analysed by descriptive statistics, using percentages for the binary variables, medians for the continuous variables, reporting their respective dispersion values. For the comparison of binary variables, the Chi-square test with an acceptable significance value of $p < 0.05$ was performed. The cut-off reported by the literature was

used for the NLR [19,26], whilst the unsupervised median value cut-off was accepted for the SII. Exploratory cut-offs for NLR and SII by receiver operating characteristic (ROC) curves were estimated. The best response to the treatment and progressive disease (PD) were assessed in each Centre, according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria version 1.1 [30]. The OS was calculated from the treatment start date until death or date of last follow-up; the PFS from treatment start date to disease progression or death from any cause. Patients who had not had any events at the time of the analysis were censored. OS and PFS were estimated using the Kaplan–Meier method and reported as medians with confidence limits (95% CI), and compared using a two-sided log-rank test with an acceptable significance value of $p < 0.05$ [31]. The prognostic value of clinical variables was explored by univariable analysis on OS and PFS by the Cox regression analysis. A multivariable stepwise Cox-regression analysis on OS and PFS of clinical baseline prognostic factors according to two models based on the NLR and SII was performed with a cut-off p-value < 0.10 for factors at the univariable analysis. Results were reported as the hazard ratio (HR) with 95% CI. An exploratory risk model based on independent prognostic factors was built to stratify patients' prognosis into three risk groups. Cox proportional hazard regression was used to compute the predicted probabilities for death according to the calculated scores to estimate Harrell's C statistic [32]. An interaction test between the SII, NLR and significantly related or otherwise relevant clinical variables was performed.

Internal validation of parameter estimates from the Cox models was performed. Five hundred bootstrap samples were randomly generated from the original sample, and from each of the Cox regression models that were built with the selected variables; the HRs with 95% CIs were re-estimated. Furthermore, the number of times each clinical characteristic was introduced in the multivariable model was calculated after the bootstrap procedures (software R v.4.0; package "rdm").

3. Results

3.1. Patients' characteristics

Three-hundred eight patients from seven centres were enrolled and data collected into the database. Their baseline characteristics are reported in Table 1. The median age was 65 (range, 37–84), 32% were 70 years or older, 52% were underweight or normal, 80% had adenocarcinoma histology, 56% PD-L1 negative, 56% PS 1, 33% ≥ metastatic sites, 11% pretreatment steroids. Fifty-three per cent had NLR ≥ 4; the median SII cut-off was 1444 (range, 161–11340).

3.2. Patients' outcomes

With a median follow-up of 18 months (95% CI, 15.9–20.1), the median OS was 12.7 months (95% CI, 10.2–15.2), and the median PFS was 8.0 months (95% CI, 7.1–8.8). Sixty-seven per cent of assessable patients reached a disease response to treatment, 18% stable disease, and 15% PD (see Table 1 and Supplementary Fig. 1).

3.3. Inflammatory indices segregated according to patient characteristics and outcomes.

A high NLR (≥4) or SII (≥1444) were similarly associated with a worse ECOG PS ($p = 0.0147$ and $p = 0.0018$, respectively), lower or normal BMI ($p = 0.0456$ and $p = 0.0062$), higher number of metastatic sites ($p = 0.0069$ and 0.0112), pretreatment steroids ($p = 0.0019$ and $p = 0.0017$), and poor treatment response ($p < 0.001$ for both) (see Table 2). Patients with high NLR or SII had significantly shorter OS (median 11.8 vs 14.9 months, $p = 0.02$; and 10.5 vs 16.1 months, $p = 0.001$, respectively) and PFS (median 6.6 vs 9.0 months, $p = 0.018$; and 6.0 v 9.6 months, p =< 0.001) than those with their low values (Table 2 and Fig. 1).

Table 1
Patients characteristics and outcomes (No. 308).

Characteristic	No. (%) [range]
Age, median	65 [37–84]
≥ 70 years	98 (32)
< 70 years	210 (68)
Gender	
Male/Female	171 (56) / 137 (44)
Smoking history	25 (8)
Never	192 (62) / 91 (30)
Former/Current	
Histology	51 (17)
Squamous	246 (80)
Adenocarcinoma	11 (3)
Other[a]	
ECOG PS	127 (41)
0	181 (59)
1	
Stage	24 (8) / 113 (37)
IIIB/IVA	171 (56)
IVB	
BMI, median[b]	24.8 [15.0–43.9]
Underweight/Normal	16 (5) / 146 (47)
Overweight/Obese	100 (32) / 46 (15)
Number of metastatic sites	205 (67)
<3	103 (33)
≥3	
Brain metastases	31 (10)
Liver metastases	37 (12)
PD-L1 IHC Ab	145 (49) / 151 (51)
22C3/SP263	165 (56)
Negative/	111 (37) / 20 (7)
Positive/High[c]	12 (4)
NA	
Oncogene (EGFR/ALK/ROS1)	3 (1)
Pre-treatment steroids	33 (11)
NLR, median	4.3 [0.4–84]
≥ 4	164 (53)
< 4	144 (47)
SII, median	1444 [161–11340]
≥ median (=1444)	154 (50)
< median (=1444)	154 (50)
Best response[d]	2 (1) / 197 (67)
CR/PR	52 (18)
SD	45 (15)
PD	12 (2)
NA	
Follow-up, median, mo. [95% CI]	18.0 [15.9–20.1]
OS, median, mo. [95% CI]	12.7 [10.2–15.2]
1 yr-OS [95% CI]	52.2 [50.7–53.9]
2 yr-OS [95% CI]	27.5 [26.6–28.5]
PFS, median, mo. [95% CI]	8.0 [7.1–8.8]

Abbreviations: Ab, antibody; BMI, body mass index; CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IHC, immunohistochemistry; mo., months; NA, not assessable; NLR, neutrophil-to-lymphocyte ratio; No. Number; OS, overall survival; PD-L1, programmed cell death-ligand-1; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SII, systemic immune-inflammatory index; TPS, tumour proportion score; yr, year.

[a] Including poorly differentiated (No. 6), undifferentiated (No. 2), sarcomatoid (No. 1), adenosquamous (No. 1), pleomorphic (No. 1) histology.

[b] BMI was calculated using the formula of weight/height2 (kilograms/square meters) and categorized according to the World Health Organization (WHO) categories: underweight (BMI < 18.5), normal-weight (18.5 ≤ BMI ≤ 24.9), overweight (25 ≤ BMI ≤ 29.9), obese (BMI ≥ 30).

[c] Negative, TPS > 1%; positive, TPS 1–49%; high, TPS ≥ 50%.

[d] By RECIST version 1.1 criteria.

3.4. Regression analyses for prognostic factors

Significant prognostic factors in the univariable analysis of OS and PFS are reported in Supplementary Table 1. Notably, the chosen literature NLR (≥4) and median SII (≥1444) cut-offs and those we calculated based on ROC curves (of ≥ 5.2 for the NLR and ≥ 1655 for the SII)

Table 2
Association of NLR and SII with patients characteristics and outcomes.

Characteristic	NLR < 4 (No. 144) No. (%) [range]	NLR ≥ 4 (No. 164) No. (%) [range]	χ2 test (log-rank)	SII < median (No. 154) No. (%) [range]	SII ≥ median (No. 154) No. (%) [range]	χ2 test (log-rank)
Age						
≥ 70 years	49 (34)	49 (30)	0.4353	54 (35)	44 (29)	0.2212
< 70 years	95 (66)	115 (70)		100 (65)	110 (71)	
Gender						
Male	79 (55)	92 (56)	0.8275	92 (60)	79 (51)	0.1361
Female	65 (45)	72 (44)		62 (40)	75 (49)	
Smoking history						
Never	13 (9)	12 (7)	0.5833	14 (9)	11 (7)	0.5314
Former/Current	131 (91)	152 (93)		140 (91)	143 (93)	
Histology						
Squamous	26 (18)	25 (15)	0.5078	29 (19)	22 (14)	0.2833
Adenocarcinoma	113 (78)	133 (81)		122 (79)	124 (81)	
Other	5 (3)	6 (4)		3 (2)	8 (5)	
ECOG PS						
0	67 (47)	60 (37)	**0.0147**	73 (47)	54 (35)	**0.0018**
1	77 (53)	104 (63)		81 (53)	100 (65)	
Stage						
IIIB/IVA	71 (49)	66 (40)	0.1103	74 (48)	63 (41)	0.2072
IVB	73 (51)	98 (60)		80 (52)	91 (59)	
BMI						
Underweight/Normal	67 (47)	95 (58)	**0.0456**	69 (45)	93 (60)	**0.0062**
Overweight/Obese	77 (53)	69 (42)		85 (55)	61 (40)	
Number of metastatic sites						
<3	107 (74)	98 (60)	**0.0069**	113 (73)	92 (60)	**0.0112**
≥3	37 (26)	66 (40)		41 (27)	62 (40)	
Brain metastases	10 (7)	21 (13)	0.0881	11 (7)	20 (13)	0.0883
Liver metastases	13 (9)	24 (14)	0.1311	16 (10)	21 (14)	0.3809
PD-L1 IHC Ab[a]						
Negative	82 (59)	83 (53)	0.2896	86 (57)	79 (54)	0.5325
Positive/high	57 (41)	74 (47)		64 (43)	67 (46)	
NA	5 (3)	7 (4)		4 (3)	8 (5)	
Oncogene (EGFR/ALK/ROS1)	1 (1)	2 (1)	0.6397	2 (1)	1 (1)	0.5618
Pre-treatment steroids	7 (5)	26 (16)	**0.0019**	8 (5)	25 (16)	**0.0017**
Best response[b]			**<0.001**			**<0.001**
CR/PR	98 (71)	101 (64)		108 (72)	91 (62)	
SD	29 (21)	23 (15)		33 (22)	19 (13)	
PD	12 (9)	33 (21)		9 (6)	36 (25)	
NA	5 (3)	7 (4)		4 (3)	8 (5)	
OS, median, mo. [95% CI]	14.9 [11.8–18.1]	11.8 [9.4–14.2]	**(0.02)**	16.1 [13.5–18.7]	10.5 [8.1–13.0]	**(0.001)**
1 yr-OS [95% CI]	56.5 [54.0–59.1]	47.7 [45.8–49.7]		59.6 [57.1–62.3]	44.0 [42.2–45.9]	
2 yr-OS [95% CI]	34.4 [32.7–36.3]	19.5 [18.7–20.4]		33.6 [31.9–35.5]	19.7 [18.9–20.6]	
PFS, median, mo. [95% CI]	9.0 [7.4–10.6]	6.6 [5.3–7.9]	**(0.018)**	9.6 [8.0–11.2]	6.0 [4.8–7.1]	**(<0.001)**

Abbreviations: Ab, antibody; BMI, body mass index; CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IHC, immunohistochemistry; mo., months; No. Number; NA, not assessable; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PD, progressive disease; PD-L1, programmed cell death-ligand-1; PFS, progression-free survival; PR, partial response; SD; stable disease; SII, systemic immune-inflammatory index; yr, year. In bold statistically significant values.

[a] Negative, TPS > 1%; positive, TPS 1–49%; high, TPS ≥ 50%.

[b] By RECIST version 1.1 criteria.

(Supplementary Figs. 2 and 3) were either similarly prognostic on both OS and PFS (Supplementary Table 1). Better HRs and CIs for both OS and PFS were found with the median compared to ROC-based cut-off values in the univariable analysis (see Supplementary Table 1). The c-index for the SII median and ROC-based value cut-off were 0.5821 and 0.5634, respectively, further supporting the median value of 1444 as the SII cut-off.

In the stepwise multivariate analysis, according to two models including either the NLR or the SII, independent prognostic factors for both OS and PFS were the number of metastatic sites (≥3 vs < 3, $p < 0.001$ and $p = 0.002$, respectively), histology (squamous vs adenocarcinoma, $p = 0.035$ and $p = 0.013$), and pretreatment steroids (yes vs no, $p = 0.03$ and $p = 0.045$) for the NLR model. In contrast, the number of metastatic sites ($p < 0.001$ and $p = 0.002$), histology ($p = 0.033$ and $p = 0.013$), and the SII ($p = 0.031$ and $p = 0.009$) resulted as independent prognostic factors for both OS and PFS in the SII model (see Table 3).

The internal bootstrap validation of the multivariable models confirmed the prognostic value of the number of metastatic sites and histology for all models. SII with median value cut-off was confirmed as a prognostic factor for both OS and PFS, ECOG PS for OS only. Pre-treatment steroids was not confirmed. Three to four prognostic factors were included in the multivariable model for OS in>70% of replications (see Supplemental Table 2). Similarly, two to three factors were included for PFS models with the same frequencies.

No potential interactions between SII, NLR and other relative clinical variables were observed except for the nutritional status defined by the BMI and the SII on OS ($p = 0.025$), with an adverse effect for overweight/obesity (BMA ≥ 25) (Fig. 2).

3.5. Prognostic models

Our cohort did not include patients with an ECOG PS 2, we therefore were unable to classify our patients into three reported LIPS score [19] risk groups. Furthermore, the LIPS score was developed in a population with only high PD-L1 tumours treated with first-line immunotherapy alone. Nevertheless, a significantly longer OS (median 14.9 vs 11.9 months, $p = 0.014$) and PFS (median 9.0 vs 6.9 months, $p < 0.001$) were observed between favourable- (0 risk factors) and intermediate/poor-

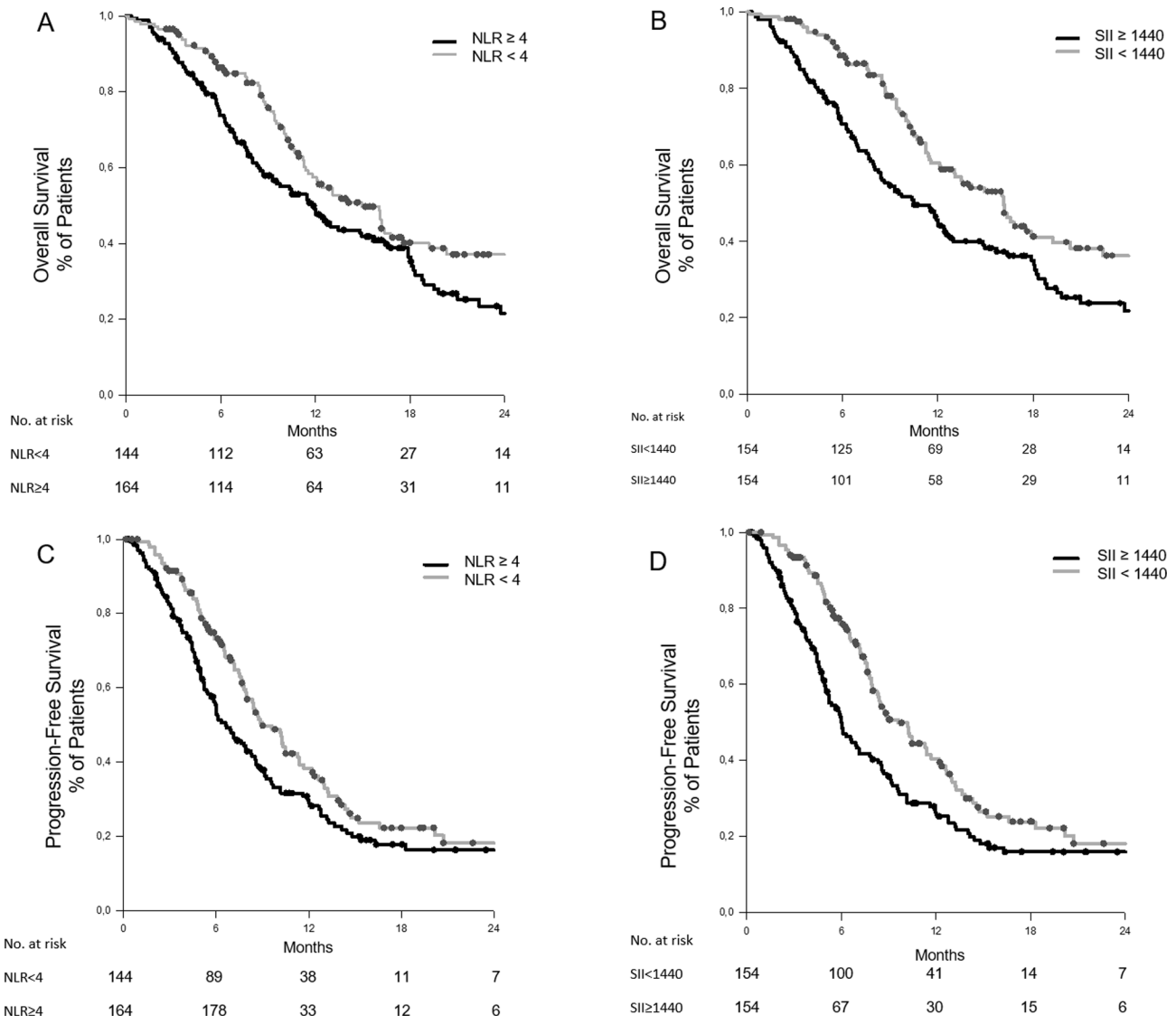


Fig. 1. OS and PFS by NLR and SII (cut-offs from literature or unsupervised) in patients with aNSCLC treated with chemoimmunotherapy. Abbreviations: aNSCLC, advanced non-small-cell-lung cancer; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression-free survival; SII, systemic immune-inflammatory index.

risk (1–2 factors) LIPS risk patients (see Fig. 2). C-index for the LIPS score was 0.605 and 0.581 for OS and PFS, respectively.

Considering the three independent prognostic factors obtained from the multivariable analysis, we defined the NHS-Lung prognostic score where N stands for the number of metastatic sites (cut-off $\geq$ 3), H for histology (i.e., squamous), and S for the SII ($\geq$1440), we identified three significantly separated prognostic groups in OS and PFS ($p < 0.001$ for both). Patients with no risk factors (91, 30%), namely at favourable risk, had the longest median OS and PFS, of 20.3 and 11.3 months, respectively; those with one risk factor (133, 43%), at intermediate risk, of 12.4 and 7.9 months; poor-risk patients (84, 27%), with two or three risk factors, of 8.4 and 5.7 months (Fig. 3). C-index for the NHS-Lung score was 0.623 and 0.613 for OS and PFS, respectively.

4. Discussion

We reported one of the largest and homogeneously treated real-world series of patients with treatment-naïve EGFR/ALK/ROS1-wild-type aNSCLC treated with the first-line combination of chemotherapy plus pembrolizumab within the approved indications.

As far as efficacy outcomes are concerned, our work brings to light similar PFS but surprisingly different OS when contrasting Real World Evidence (RWE) data with the clinical trial ones, specifically the KEYNOTE-189 [13] and KEYNOTE-407 [14] phase III randomised studies. Indeed, the median PFS of our patients was 8.0 months, similarly to the 8.0 and 9.0 months observed in the KEYNOTE-189 [13] and KEYNOTE-407 [14] studies, respectively. Unexpectedly, the median OS of 12 months we observed in our patients was dramatically shorter than the 22.0 and 17.2 months reported by those studies [13,14]. At least three different reasons might be explanatory for this inconsistency. To begin with, the median follow-up time in our series was adequate, but a longer median OS might be seen with a more prolonged follow-up. For instance, in the KEYNOTE-189 study the median OS was not reached and 22.0 months at the first and late follow-up analysis, respectively, with a median follow-up of 10.5 and 23.1 months [13]. However, our data argue that this is unlikely as at 2 years the number of patients at risk are small, at only 25, accounting for only 8% of the total population. Secondly, clinical trial eligibility criteria are stricter than those adopted to select our population. Although our series did not include patients with an ECOG PS 2, about one-third of patients were aged $\geq$ 70 years and had

Table 3
Multivariable stepwise analysis of clinical baseline prognostic factors: NLR and SII models.[a]

	NLR-model		SII-model	
	OS	PFS	OS	PFS
Variable	**HR (95% CI); p-value[b]**	**HR (95% CI); p-value[b]**	**HR (95% CI); p-value[b]**	**HR (95% CI); p-value[b]**
Histology				
SCC vs Adeno	**1.53 (1.03–2.28); p = 0.035**	**1.62 (1.11–2.37); p = 0.013**	**1.54 (1.03–2.29); p = 0.033**	**1.62 (1.11–2.36); p = 0.013**
ECOG PS				
1 vs 0	**1.48 (1.07–2.05); p = 0.017**	–	**1.46 (1.06–2.02); p = 0.022**	–
Number of met sites				
≥3 vs < 3	**1.76 (1.29–2.40); p < 0.001**	**1.58 (1.18–2.11); p = 0.002**	**1.74 (1.27–2.37); p < 0.001**	**1.59 (1.19–2.12); p = 0.002**
Pre-treatment steroids				
Yes vs No	**1.69 (1.05–2.70); p = 0.030**	**1.57 (1.01–2.45); p = 0.045**	**1.61 (1.00–2.59); p = 0.048**	1.49 (0.96–2.34); p = 0.078
NLR	1.21	1.29		
≥ 4 vs < 4	(0.88–1.65); p = 0.25	(0.97–1.72); p = 0.078	–	–
SII, median				
≥ 1444 vs < 1444	–	–	**1.41 (1.03–1.93); p = 0.031**	**1.45 (1.10–1.93); p = 0.009**

Abbreviations: Ab, antibody; Adeno, adenocarcinoma; BMI, body mass index; 95% CI, 95% confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; met, metastatic; NLR, neutrophil-to-lymphocyte ratio; No. Number; OS, overall survival; PD-L1, programmed cell death-ligand-1; PFS, progression-free survival; SCC, squamous cell carcinoma; SII, systemic immune-inflammatory index.
In bold statistically significant values.
[a] Only variables with p-value < 0.10 reported.
[b] Cox regression analysis.

≥ 3 metastatic sites; about ten per cent had brain or liver metastases associated with poor outlook in NSCLC [33–35] or received concomitant steroids, often used for the palliation of symptoms such as loss of appetite and energy, and also identifying a high-risk group. Thirdly, our series was enriched by patients with PDL1 negative tumours. PD-L1 is known to be an adverse prognostic and is the major molecular determinant of clinical benefit from immunotherapy: high PD-L1 expression (≥50%) leads to greater efficacy from anti-PD-1/anti-PD-L1 agents [5,36]. More than half of our patients had PD-L1 negative (i.e., <1%) tumours, whereas in the KEYNOTE-189 [13] and KEYNOTE-407 [14] studies, this population represented only one-third of the enrolled subjects. Notably, the late analysis of the KEYNOTE-024 study [37], with a median follow-up of 25.2 months, showed an impressive median OS of 30.0 months for patients treated with pembrolizumab, but also remarkable 14.2 months with chemotherapy.

Evidence for an incremental efficacy of pembrolizumab with increasing PD-L1 values was provided by the KEYNOTE-042 study [9,10], retrospectively [22,38], or through inter-trials comparisons [2]. In KEYNOTE-024 and KEYNOTE-042 studies, pembrolizumab monotherapy in PD-L1 ≥ 50% TPS squamous/nonsquamous tumours yielded to 3-year OS rate ranging from 31% to 44%, whereas in KEYNOTE-189 PD-L1 ≥ 50% nonsquamous tumour subgroup pembrolizumab plus chemotherapy lead to a 3-year OS of 44%. However, the latter caused higher incidence of grade 3–5 treatment-related adverse events (TRAEs) compared to PD-L1 monotherapy (52% vs 31%) [2]. Network *meta*-analyses failed to provide OS benefit from the addition of chemotherapy to ICIs in high PD-L1 aNSCLC [39,40]. According to this evidence, with the current lack of data from randomised comparisons, single agent immunotherapy appears to be most suitable for patients with high PD-L1 tumours as opposed to use with chemotherapy or with a further ICI, like an anti-CTLA-4 antibody; these combinations additionally also significantly increase the risk of more severe TRAEs [2]. Conversely, an FDA pooled analysis conducted on 2108 patients with low PD-L1 (i.e., 1–49%) aNSCLC suggested the combination of chemotherapy with ICIs may improve PFS and OS over ICI alone in most subgroups of patients with low PD-L1 (i.e., PD-L1 score 1–49%) aNSCLC [41]. The ongoing INSIGNA (NCT03793179) trial will shed light on the issue of adding chemotherapy to ICI in high PD-L1 aNSCLC. Meanwhile, both treatment strategies are considered standard of care and the therapeutical approach in this category of patients is based on clinical judgment as no validated predictive biomarkers are available. In our RWE series, twenty patients (7%) with high PD-L1 tumours received a combination of chemotherapy and pembrolizumab instead of an ICI alone. It is, of course, a small proportion of patients but confirms some patients are selected for treatment intensification based on clinical considerations. Hence, there is a real need to find reliable prognostic factors or models that could aid clinicians in their therapeutic decisions.

In this context, peripheral blood inflammatory indices alone, or in combination with other clinical and/or pathological factors may offer easily accessible and relatively inexpensive prognostic tools [5]. Several prognostic scores were built based on the prognostic value of the NLR, or the derived NLR (dNLR) (i.e., absolute neutrophil counts / [white blood cell count – absolute neutrophil counts]) [42]. The Lung Immune Prognostic Index (LIPI) (defined as higher LDH levels plus dNLR > 3) was specifically associated with worse outcomes with ICIs [43]. We had previously reported the ability of the LIPS score, based on the NLR ≥ 4, ECOG PS 2 and use of pretreatment steroids, to accurately stratify the prognosis of patients with high PD-L1 aNSCLC treated with pembrolizumab [19]. Combining NLR ≥ 4 and pretreatment steroids +/- high serum LDH confirmed prognostic discrimination in the ECOG PS 2 subgroup of 128 patients from the LIPS series [26]. Patients with LIPS poor prognosis might benefit from the addition of chemotherapy. Moreover, although in a different low PD-L1 population, the FDA pooled analysis above discussed indicated the addition of chemotherapy to ICI was particularly beneficial in patients with worse ECOG PS [41]. By a propensity score matching analysis of 423 patients with high PD-L1 aNSCLC, the Advanced Lung cancer Inflammation index (ALI) score, calculated as the BMI × serum albumin / NLR, alongside the LIPI, confirmed their correlation with OS in patients treated with pembrolizumab but not when platinum-based chemotherapy was added to pembrolizumab [44]. Similarly, high ALI values predicted longer OS for patients receiving ICI monotherapy but not chemoimmunotherapy in a retrospective study, and the correlation between OS and the ALI was weaker in the chemotherapy only control cohort [45]. Here we confirmed the role of NLR might be flattened by the addition of platinum-based chemotherapy to pembrolizumab, as the it did not result as an independent prognostic factor by the multivariable analysis; however, the prognostic value of the LIPS score was validated on both OS and PFS. Conversely, the SII maintained its prognostic value on both OS and PFS regardless of the addition of chemotherapy to pembrolizumab. The SII is a ratio that considers the platelets besides the NLR and is associated with worse OS in many solid tumours, including the

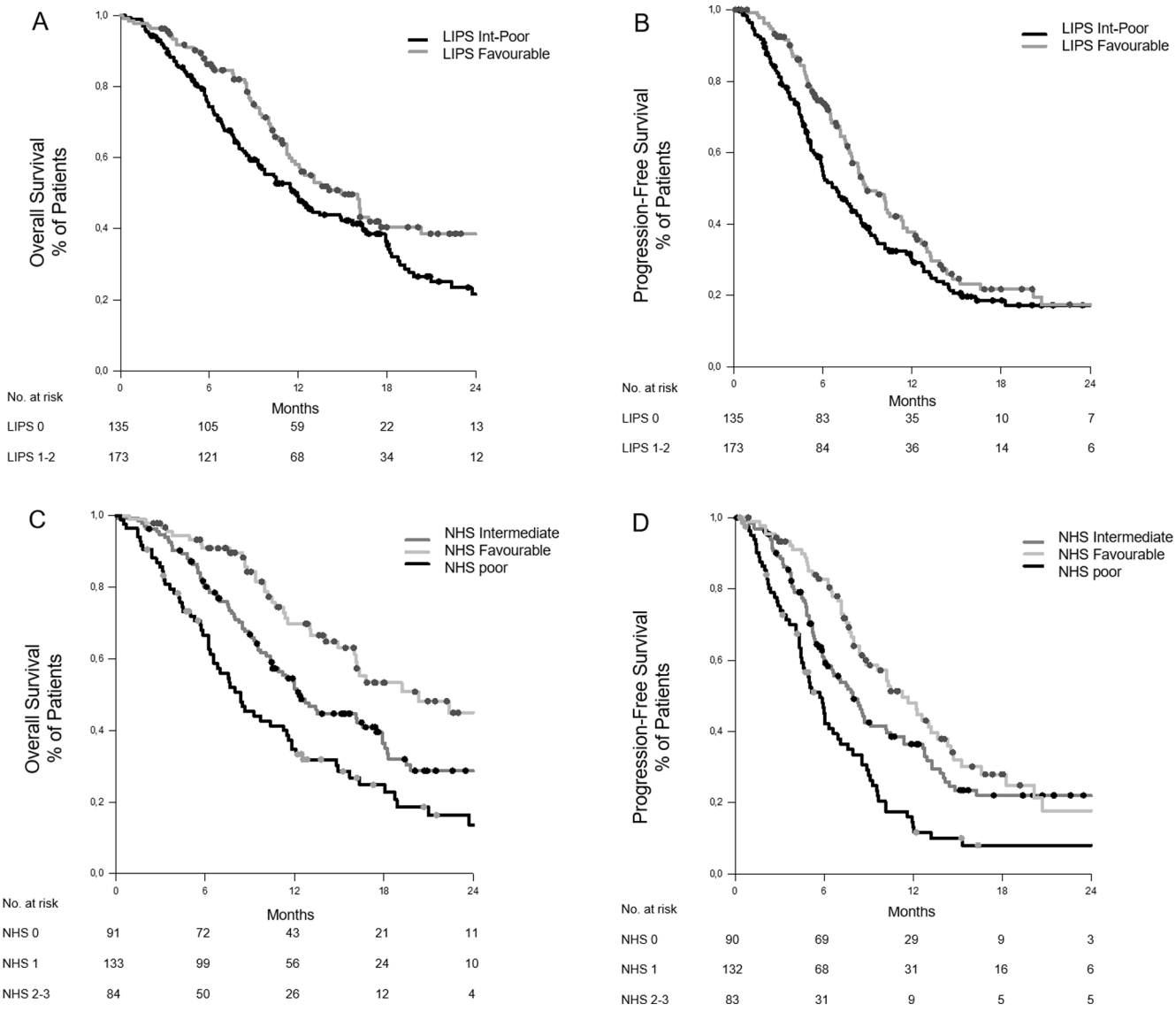
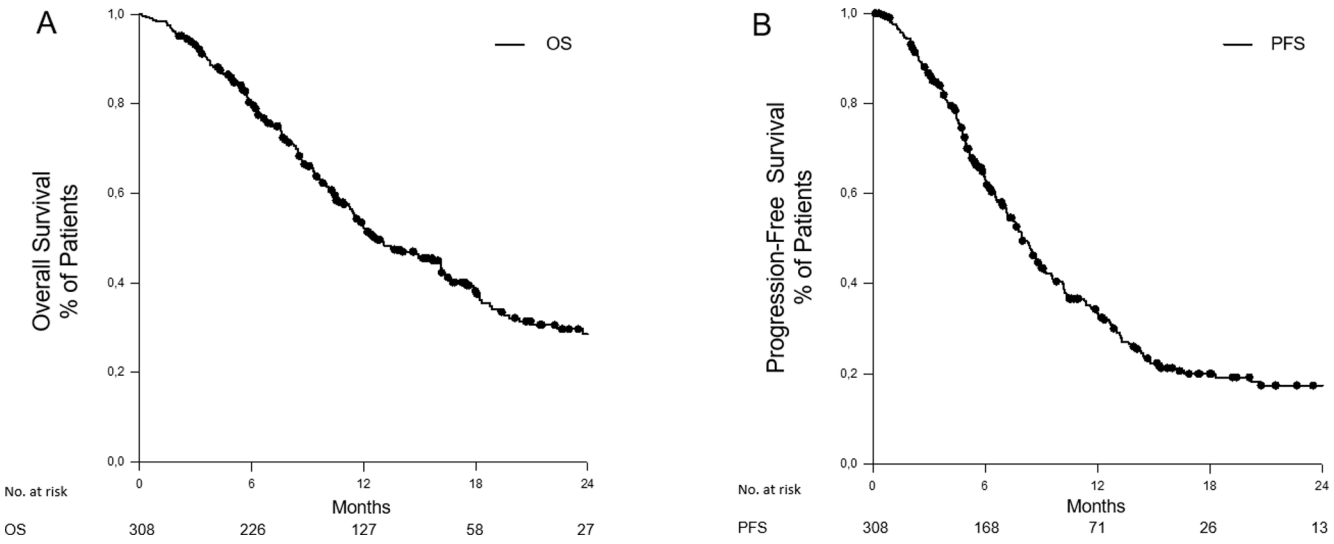


Fig. 2. OS and PFS by adapted LIPS[a] and the NHS-Lung[b] score in patients with aNSCLC treated with chemoimmunotherapy.



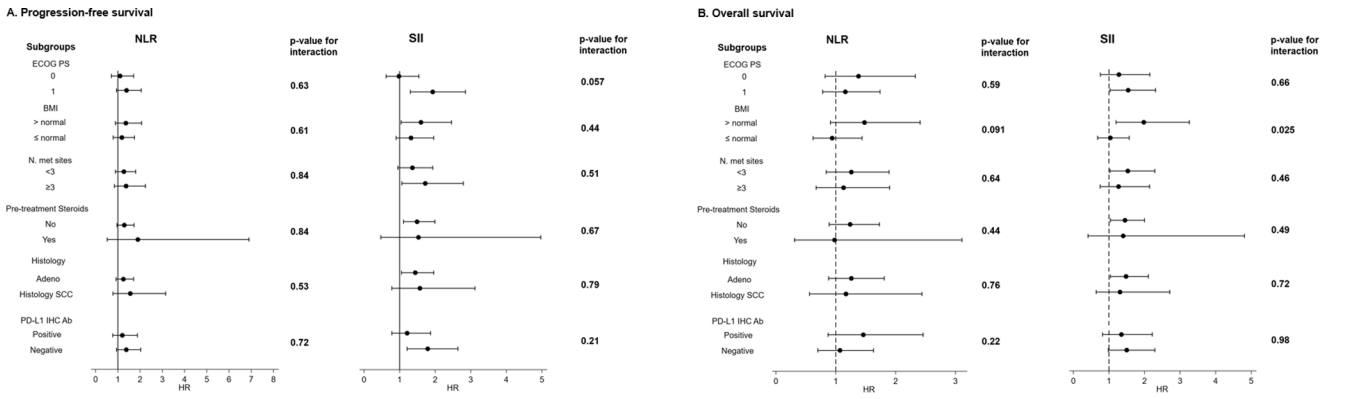


Fig. 3. Interaction by SII and NLR with relevant clinical variables in patients with aNSCLC treated with chemoimmunotherapy. Abbreviations: Adeno, adenocarcinoma; aNSCLC, advanced non-small-cell-lung cancer; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IHC Ab, immunohistochemistry antibody; N, number; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed cell death ligand1; SCC, squamous cell carcinoma; SII, systemic immune-inflammatory index.

aNSCLC [46]. The prognostic role of high platelet count in patients with cancer has been emerging [47]. Here we showed that both the NLR and SII similarly reflected a category of patients with a pro-inflammatory clinical condition associated with higher tumour burden (i.e., the number of metastatic sites), concomitant conditions requiring steroids, worse performance status and lower BMI. The interaction we found between the BMI and SII on OS is noteworthy, suggesting the relationship between cachexia and the pro-inflammatory condition indicated by the SII. This connection might be biologically relevant in the interplay between cachexia and inflammation concerning immunotherapy and chemotherapy. Immunotherapy has been demonstrated to be more effective in patients with high BMI [48], but this was not confirmed when chemotherapy was added to it [49]. Intriguingly, the multivariable model, including the SII, weaken the prognostic role of pretreatment steroids, particularly on PFS, confirming again a relevant still unknown role of platelets in the inflammatory process.

By combining the three clinical variables emerging from the multivariable analysis as significant factors on both the OS and PFS, we developed a prognostic model, namely the NHS-Lung score consisting of the number of metastatic sites and the histology and SII. A more favourable outcome for patients with adenocarcinoma histology was found in the abovementioned propensity score matching analysis and included in a five-factor prognostic score based on dNLR [44]. The NHS-Lung score overperformed the LIPS score by relying on the SII instead of NLR and two different clinical factors. It allowed an accurate stratification in three prognostic groups and deserved external validation.

The main limitations of this study are its retrospective nature and the absence of a control cohort to explore the potential predictive value of the prognostic variables. Furthermore, we developed a prognostic model in a training set without testing it in a validation series. Another potential limitation could rely on the sample size calculation which had been made on data from patients with high PD-L1 tumour expression and, consequently, possibly different prognosis from the study population; however, the number of enrolled patients largely exceeded the preplanned sample size.

In conclusion, we confirmed the efficacy of first-line chemoimmunotherapy in a real-world series of patients with non-oncogene addicted aNSCLC. We confirmed the significant prognostic value of adverse clinical variables, like the number of metastatic sites and squamous histology and the SII as peripheral blood inflammatory index overperforming the NLR. We developed a prognostic model based on those three variables, namely the NHS-Lung score. It could be a valuable tool for categorising patients with treatment-naïve aNSCLC based on their predicted outcomes of chemoimmunotherapy.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: G. L.B. received grant consultancies from Astrazeneca and Astellas Pharma. A.C. received speaker fees and grant consultancies by Astrazeneca, MSD, BMS, Roche, Novartis and EISAI. A.A. received consulting fees from BMS, Astrazeneca, Boehringer-Ingelheim, Roche, MSD, Pfizer, Eli Lilly and Astellas; speakers fees from Eli Lilly and Astrazeneca. D.J.P. received lecture fees from ViiV Healthcare, Bayer Healthcare, BMS, Roche, EISAI, Falk Foundation, travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, EISAI, Roche, Avamune, Exact Sciences, Mursla, DaVolterra and Astra Zeneca; research funding (to institution) from MSD and BMS. CO reports personal fees from BMS. All other authors declare no competing interests.

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Contributorship statement

All authors have made substantial contribution to: the conception and design of the study, or acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; final approval of the submitted version.

Appendix A. Supplementary material

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Glossary

aNSCLC: advanced non-small cell lung cancer
ECOG PS: Eastern Cooperative Oncology Group performance status
HR: hazard ratio
ICI: immune checkpoint inhibitors
LIPS: lung immuno-oncology prognostic score
MVA: multivariate analysis
NHS-Lung prognostic score: N = number of metastatic sites (cut-off ≥3), H = histology (i.e., squamous), S = SII (≥1440)
NLR: neutrophils-to-lymphocytes ratio
OS: overall survival
SII: systemic immune-inflammatory index
PD-1: programmed death-1
PD-L1: programmed death ligand-1
PFS: progression-free survival
RECIST: Response Evaluation Criteria in Solid Tumours
ROC: receiver operating characteristic curves
TPS: tumour proportion score
TRAEs: treatment-related adverse events
UVA: univariable analysis