Optimizing the tumor shrinkage threshold for evaluating immunotherapy efficacy for advanced non-small-cell lung cancer

Wei Du1,2,3 · Chen Chen1,2,4 · Lin-feng Luo1,2,3 · Li-na He1,2,3 · Yixing Wang1,2,3 · Xuanye Zhang1,2,3 · Yixin Zhou1,2,5 · Zuan Lin1,2,6 · Shaodong Hong1,2,3

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Abstract
Purpose The rise of immune checkpoint inhibitors (ICIs) in recent years has coincided with unusual clinical response patterns. Modification of the sum of longest diameters (SLD)-based threshold that reflecting dynamic change of the tumor burden and predicting response to ICIs, may markedly improve current treatment regimens.

Methods The baseline and post-treatment SLD of target lesion was recorded and the maximum percent change of the SLD from baseline was designated as SLD-change score. The optimal cut-off value was obtained using the X-tile program. The relationship between SLD-change score and survival outcome (PFS, OS) was evaluated.

Results 10% cut-off value of SLD-change score was found to be most distinctive for PFS. Responders defined according to this cut-off value showed a significant improvement for PFS and OS. Bone metastasis and brain metastasis were also two independent prognostic factors of PFS and OS, respectively.

Conclusions 10% SLD change score could discriminate for ICIs treatment response, which holds great promise in promoting the development of precise immunotherapeutic strategy.

Keywords Immunotherapy · Check point inhibitors · Non-small cell lung cancer · SLD · RECIST

Introduction
Lung cancer remains the leading cause of cancer mortality worldwide. More than 80% of lung cancers are classified as non-small cell lung cancer (NSCLC), and most of them are diagnosed with advanced stage at the time of presentation (Sung et al. 2020). The use of immunotherapy, or more specifically, immune checkpoint inhibitors (ICIs) targeting programmed death 1 (PD-1) or its ligand (PD-L1) has emerged as the standard therapy for most patients with advanced NSCLC. Several trials have showed consistent survival improvement with PD-L1 or PD-L1 inhibitor monotherapy compared with standard chemotherapy, with an acceptable toxicity profile (Reck et al. 2016; Lopes et al. 2018; Borghaei et al. 2015; Herbst et al. 2016; Rittmeyer et al. 2017).

Response Evaluation Criteria in Solid Tumors (RECIST) is the widely accepted methodology applied to the evaluation of treatment responses, based on the sum of the longest uni-dimensional diameters (SLD) of target lesions (Eisenhauer et al. 2009). RECIST-defined responder (RD-R) is defined by at least 30% decrease in SLD including complete response (CR) and partial response (PR). By contrast, stable disease (SD) and progressive disease (PD) were classified as RECIST-defined non-responder (RD-NR). Chemotherapy intended to generate cytotoxic effects on tumor cells, which, if effective,
results in a rapid reduction in lesion size. Conversely, ICIs attempt to suppress the interaction between PD-1 and PD-L1 and restore the functionality of exhausted T cells, thereby stimulating cell-mediated immunity to recognize and destroy cancer cells, frequently without an immediately obvious shrinkage of tumor size. The application of RECIST initially designed for cytotoxic chemotherapy to patients receiving immunotherapies falsely attests the disease process and subsequently fails to discriminate patient benefit; as a consequence, the clinical relevance of RECIST subsides.

To cope with these observations and the shortcomings of the conventional RECIST criteria, several evaluation criteria such as immune-related RECIST (irRECIST) and modified RECIST1.1 for immune-based therapeutics (iRECIST) have been proposed by the RECIST working group in cancer immunotherapy trials, but still maintained a − 30% threshold-defining response (Wolchok et al. 2009; Seymour et al. 2019). Preferred response threshold targeting immunotherapy needs to be proposed specifically. Herein, we seek to identify a cutoff value of SLD dynamic changes as an appropriate indicator to maximize beneficiaries in a population of ICIs-treated patients, so that tumor response better correlates with clinical benefit and survival outcomes.

Patients and methods

Patients

We retrospectively reviewed electronic medical records of 284 consecutive patients diagnosed with NSCLC and treated with ICIs monotherapy as palliative treatment in Sun Yat-Sen University Cancer Center (SYSUCC) from August 2016 to October 2021. The inclusion criteria were listed as follows: (I) at least 18 years of age; (II) histologically or cytologically-confirmed stage IIIB-IV; (III) an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (3) obligatory to have at least one measurable tumor lesion according to the RECIST version 1.1, and (VI) having a life expectancy of at least 3 months.

Recorded data for each case were gathered, including information on sociodemographic variables [age, sex, Eastern Cooperative Oncology Group Performance status (ECOG-PS), smoking status]; pathologic data (histologic type, pathologic tumor, node, and metastasis status, driver mutation); and treatment-related data, including treatment lines and types of medication. Patients with missing values on these items were excluded. Written informed consent for participation was waived by the Institutional Review Board due to the retrospective nature of the study.

SLD-change score and follow-up

Computed tomography (CT) or magnetic resonance imaging (MRI) was carried out to measure target lesions periodically (mostly every 6 weeks) until immunotherapy termination due to any reasons. Patients lacking follow-up CT evaluation were excluded in the analyses. The maximum number of target lesions to be assessed was five, with a maximum of two per organ. The SLD of all targets for each patient were performed manually by two experienced radiologists on the original CT or MRI images using the calipers of a measurement tool on the workstation in strict accordance with RECIST 1.1. Non-solid part of target lesions (such as tumor necrosis, cavity, air) was not included. The variation in the SLD of all target lesions was calculated using \( \frac{\text{the minimum follow-up measurement} - \text{baseline measurement}}{\text{baseline measurement}} \times 100\% \). Hereafter the maximum percent change of the SLD from baseline are designated as SLD-change score.

Evaluation of tumor response according to RECIST 1.1

The best objective responses throughout ICI treatment were assessed by two physicians according to RECIST 1.1 by considering both target and non-target disease as well as the appearance of new lesions. Patients were classified into PR, SD and PD. In any cases of disagreement, the tumor measurements were re-examined until consensus was reached.

Selection of alternate response cut-off value

The optimal cutoff values of SLD-change score were stratified using X-tile version 3.6.1 (Yale University School of Medicine, New Haven, CT, USA) (Camp et al. 2004) to maximize PFS differentiation. Using the cutoff value of SLD-change score, patients were stratified into two groups, namely new threshold defined responder (ND-R) and new threshold defined non-responder (ND-NR) to process the data conveniently. Group explanation was shown in Fig. 1.

Statistics analysis

Sociodemographic and radiological characteristics were summarized as numbers and percentages for categorical variables, and as median and range for numeric variables. The distributions of the characteristics within the ND-R patients and ND-NR patients were compared using independent t-test for continuous variables and Fishers exact test or Chi-square test for categorical variables. The primary endpoint was Progression-free survival (PFS) and the secondary endpoint was
overall survival (OS). PFS was defined from the start of ICI therapies until the earliest occurrence of disease progression, death for any reason, or the end of follow-up. The OS interval was measured from the time of taking ICI therapies until the time of death for any reason or the end of follow-up. Kaplan–Meier curves were plotted for PFS and OS. The median PFS and OS with their 95% confidence intervals (CIs) for each subgroup was estimated. The survival distribution difference was evaluated using the log-rank test. A Cox proportional hazards regression model was used for univariate and multivariate analyses to identify independent risk factors and prognosis factors. Variables for PFS and OS with \( P \) value < 0.05 in the univariate cox regression analysis were analyzed in the multivariate Cox regression model in a stepwise procedure with alpha-to-remove, 0.05. All statistical analyses were performed using Empower (R) (http://www.empowerstats.com, X&Y solutions, Inc., Boston, MA) and R (http://www.R-project.org) and Statistical Package for Social Sciences (SPSS) 26.0 software (IBM, Armonk, NY). A two-tailed \( P \) value of < 0.05 was considered statistical significance.

**Results**

**Patient demographics and clinicopathologic features**

Among 284 NSCLC patients treated with ICI monotherapy, 180 individuals were eligible for the retrospective analysis (Fig. 2). The baseline characteristics of all patients are summarized in Table 1. The median age was 57 years (range 28–79 years) and majority of patients (73.9%) were male. Among these patients, 99 (55.0%) were nonsmokers and 159 (88.3%) had at least 2 metastatic sites. 166 patients (92.2%) had disease of stage IV, 171 (95.0%) patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, and 105 (58.3%) patients were adenocarcinoma. 97 (53.9%) of these individuals were treated with ICI as first-line or second-line treatment. With regard to the gene mutation, 19 patients (10.6%) had EGFR mutation while 5 patients (2.8%) had ALK translocation. Pembrolizumab and nivolumab accounted for over a half of treatment regimen. 45.6% patients had two target lesions with median baseline tumor burden of 76 mm. The median SLD-change score was 4%, with an overall range of 78% decrease to 125% increase. Figure 3 shows a waterfall plot of the SLD-change score of target lesions relative to baseline evaluation.

**Response analysis**

As for best overall response, 26 (14.4%) patients were classified to PR. 64 (35.6%) patients were SD and half of them are PD. According to RECIST criteria, the objective response rate (ORR) (CR + PR) was 14.4%.

The optimal cutoff value of SLD-change score in terms of PFS was identified as 10% (\( X^2 = 87.730, P < 0.0001 \))
According to 10.0% SLD-change score, 104 (57.8%) patients were considered ND-R with SLD-change score less than this threshold, whereas 76 (42.2%) patients with SLD-change score exceeding this threshold were deemed as ND-NR. Table 2 shows the characteristics of patients in each subgroup according to the 10% cutoff. The patient demographics and disease characteristics were well-balanced for most variables except that ND-NR patients tended to have hepatic ($P = 0.006$) metastasis.
Survival analysis

PFS

The median PFS of all patients was 2.550 months. when referring to RECIST, 17.600 months PFS for RD-R patients, and 2.133 months for RD-NR patients ($P < 0.001$). Similarly, the median PFS for ND-R was significantly longer than that for ND-NR (ND-NR vs. ND-R, 1.833 months vs. 8.367 ($P < 0.001$, Fig. 5). In the univariate analysis, 10% SLD-change score (unadjusted HR 0.176, 95% CI 0.117–0.264, $P < 0.001$) had statistically significant correlations with PFS. Besides, stage, hepatic metastasis, bone metastasis, total number of metastatic sites were associated with the PFS. Multivariate analyses further revealed that 10% SLD-change score was an independent prognostic factor of PFS after adjusting the potential confounding factors (adjusted HR 0.181, 95% CI 0.120–0.272, $P < 0.001$). In addition, bone metastasis was also valid prognostic factors of PFS (Table 3).

OS

The median OS of all patients was 11.950 months, but that for patients with CR + PR was 47.633 months, and 22.767 months for patients with SD + PD ($P = 0.022$). Kaplan–Meier survival analysis and log-rank test revealed that the median OS of ND-NR patients was notably shorter than that of ND-R patients (ND-NR vs. ND-R, 14,800 (95% CI 9.228–20.372) months vs. 31,633 (95% CI 19.455–43.811) months) ($P < 0.001$, Fig. 5). According to the univariate analysis of OS, brain metastasis and 10% SLD-change score (unadjusted HR 1.00 (ref.) vs. 0.442; 95% CI 0.265–0.683, $P < 0.001$) as valid prognostic factors (Table 4).

Discussion

ICIs have transformed the therapeutic landscape of various cancers. However, despite compelling clinical responses, durable response is limited to only a fraction of patients. Furthermore, the new immunomodulatory approach to cancer treatment comes with unusual patterns of treatment response such as pseudoprogression, delayed response and potentially severe toxicity (Lesterhuis et al. 2017; Topalian et al. 2016; Nishino et al. 2017; Havel et al. 2019), indicating an urgent need for a reliable predictive biomarker.

In this study, we evaluated the clinical significance of SLD-change score and identified 10% as an optimal tumor response threshold in advanced NSCLC patients treated with ICIs monotherapy. The results indicate that 10% SLD-change score is a reliable predictive indicator for survival outcomes.

With new-cutoff of 10.0%, the advocated ND-R and the RD-R in this study were reached in 57.8% and 14.4% of cases, respectively. It demonstrated that the 10% threshold had a very high specificity, expanding the number of responder population who might benefit from immunotherapy. Among the additional patients who may benefit, 70% of them are from SD group and 30% from PD group. In other words, the major beneficiary was from SD group. As we mentioned before, durable SD after completion of treatment is one of the new patterns in cancer immunotherapies (Wolchok et al. 2009). Many patients in SD group may also obtain long time survival in the era of immunotherapy. Long-term survival outcomes in
CheckMate 017/057 showed that 4-year OS rate for SD patients with nivolumab was as high as 19%, while that for patients with docetaxel was only 2%. Sure, the 4-year OS rate for PR + CR patients was still much higher than that for SD patients (58% VS 12%) (Brahmer et al. 2019). In the phase 2 randomized NEOSTAR trial of neoadjuvant ICIs in 44 NSCLC patients, 20% patients with SD/PD radiographically achieved major pathologic response (MPR) or achieved marked pathologic tumor regression at surgery (Cascone et al. 2021). Collectively, the survival benefit of a fair percentage of SD patients was undervalued since the range of RECIST defined SD is not granular enough, with tumor reductions ranging from – 30 to + 20%. Besides, survival analysis also confirmed that SLD-change score was significantly correlated with better PFS and OS, which was aligned with Hopkins et al. (2020) who demonstrated that ETS (> 10% decrease in SLD at 6 weeks) are strongly associated with improved survival in patients with atezolizumab treatment for advanced NSCLC. Taken together, these results implied that 10% SLD-change score indicated

| Table 2 | Characteristics of patients according to the SLD-change score on the evaluation of response |
|---------|-------------------------------------------------------------------------------------------|
| Factor                                                                 | Training cohort (n = 180) (%) |  |
| Age (years)                                                                 | Responder (N = 104) | Non-responder (N = 76) | P |
| Median (range)                                                                 | 57.50 (43) | 54.00 (46) | 0.068 |
| Gender, n (%)                                                                 |  |
| Male                                                                 | 82 (78.8) | 51 (67.1) | 0.077 |
| Female                                                                | 22 (21.2) | 25 (32.9) |  |
| Stage, n (%)                                                                 |  |
| III                                                                   | 11 (10.6) | 3 (3.9) | 0.101 |
| IV                                                                    | 93 (89.4) | 73 (96.1) |  |
| Type of histology, n (%)                                                                 |  |
| Adenocarcinoma                                                        | 63 (60.6) | 42 (55.3) | 0.475 |
| Non-adenocarcinoma                                                    | 41 (39.4) | 34 (44.7) |  |
| ECOG PS, n (%)                                                                 |  |
| 0–1                                                                  | 98 (94.2) | 73 (96.1) | 0.835 |
| 2                                                                    | 6 (5.8) | 3 (3.9) |  |
| Smoking status, n (%)                                                                 |  |
| Never-smoker                                                          | 56 (53.8) | 43 (56.6) | 0.716 |
| Current or former smoker                                              | 48 (46.2) | 33 (43.4) |  |
| Treatment lines, n (%)                                                                 |  |
| 1–2 regimen                                                          | 59 (56.7) | 38 (50.0) | 0.371 |
| ≥ 3 regimens                                                         | 45 (43.3) | 38 (50.0) |  |
| EGFR mutation status, n (%)                                                                 |  |
| Positive                                                              | 11 (10.6) | 8 (10.5) | 0.694 |
| Negative or not investigated                                          | 93 (89.4) | 68 (89.5) |  |
| ALK translocation, n (%)                                                                 |  |
| Positive                                                              | 3 (2.9) | 2 (2.6) | 1.000 |
| Negative or not investigated                                          | 101 (97.1) | 74 (97.4) |  |
| Metastasis, n (%)                                                                 |  |
| Hepatic metastases                                                   | 15 (14.4) | 24 (31.6) | 0.016 |
| Lung metastases                                                       | 40 (38.5) | 40 (52.6) | 0.059 |
| Bone metastases                                                       | 34 (32.7) | 29 (38.2) | 0.448 |
| Brain metastases                                                      | 24 (23.1) | 19 (25.0) | 0.765 |
| Adrenal gland metastases                                              | 15 (14.4) | 8 (10.5) | 0.439 |
| Distant lymph nodes metastasis                                        | 26 (25.0) | 20 (26.3) | 0.842 |
| No. of metastatic sites, n (%)                                                                 |  |
| 0–1                                                                  | 15 (14.4) | 6 (7.9) | 0.178 |
| ≥ 2                                                                  | 89 (85.6) | 70 (92.1) |  |

ECOG PS Eastern Cooperative Oncology Group performance status
true change in tumor size with prognostic value in ICIs monotherapy.

Besides primary tumor lesion, metastatic lesion spectrum is an important part of systemic tumor burden. Studies on the relationship between cancer cells and the invaded host organ have revealed that the immune contexture differs greatly in different organs, which will no doubt influence anti-tumor immunity (Jimenez-Sanchez et al. 2017). In our cohort, more metastatic sites were associated with shorter PFS ($P = 0.013$) and tended to be associated with worse OS ($P = 0.264$) in univariate analysis. It corresponded with the previous study about the effect of baseline number of metastatic lesions on PD-1/PD-L1 inhibitor monotherapy (Miyawaki et al. 2020). With regard to metastatic sites, bone metastasis was significantly associated with shorter PFS both in univariate analysis (HR 1.607, $P = 0.006$) and multivariate analysis (HR 1.436, $P = 0.039$). Brain metastasis was significantly associated with shorter OS in univariate analysis (HR 1.846, $P = 0.015$) and multivariate analysis (HR 1.950, $P = 0.009$). Specifically for bone metastasis, it was considered as one of the negative prognostic factors. A previous study suggested that presence of bone metastasis could impair nivolumab efficacy with lower ORR, shorter PFS and OS in both nonsquamous and squamous NSCLC (Landi et al. 2019). Bone metastasis as well as skeletal-related events (SREs) such as bone pain or pathologic fracture have a detrimental impact on the survival of patients with advanced NSCLC (Kuchuk et al. 2013; Sugiura et al. 2008). As regards brain metastasis, it is a tough and challenging case in the treatment of lung cancer together with poor prognosis. The probable inability of ICI to cross the blood-tumor-barrier (BTB) due to their size, the use of steroids and the high risk of pseudoprogression might influence the ICIs treatment potency (Hochmair et al. 2017; Parvez et al. 2014; Doherty et al. 2015). Collectively, the occurrence of specific organ metastases is negative predictive biomarker for patients treated with ICI monotherapy, and could provide medication guidance for advanced NSCLC.

Tumor shrinkage, as a parameter reflecting tumor burden, has always been a useful metric to predict benefit from treatment and guided treatment decision-making in oncology (Kim et al. 2021). Analyses have been carried out in several solid tumors identifying an optimal threshold as an earlier assessment of the treatment response. It was investigated and validated in metastatic renal cell carcinoma that $-10\%$ tumor shrinkage in the SLD appears to be a reliable threshold for identifying patients benefiting from angiogenesis Inhibitors (Thiam et al. 2010; Krajewski et al. 2014). Preceding studies have recommended setting $-10.0\%$ tumor shrinkage as a reliable outcome predictor of advanced NSCLC patients with chemotherapy plus targeted agents (Luo et al. 2019). To the best of the authors’ knowledge, this is the first study to evaluate SLD-change score for treatment response in advanced NSCLC patients under ICIs monotherapy. Such changes of tumor burden only relied on post-therapy imaging manifest superiority and effectiveness for medication guidance. Regarding accessibility, baseline and post-treatment SLD are routinely measured and objective, strengthening its potential use as a prognostic marker in clinical day-to-day decision making for patients. As for stability, unlike blood-based biomarkers, SLD-change score would not be easily disturbed by the short-term physical condition or affected by infection, trauma, or the usage of glucocorticoids, etc. (Li et al. 2020).
It should be noted that our study population is moderate and homogeneous ensuring robust size analysis and that all the radiological data were reviewed and assessed independently ensuring high-quality data collection. The 10% SLD-change score, an indicator of prognosis to treatment, could therefore bring broader and more accurate clinical application. Based on our findings, patients with SLD-change score ≤ 10% could benefit from continuation of treatment to reach optimal response. For those with SLD-change score > 10%, there has been none evidence of treatment benefit, enabling these patients to consider other therapies and possibly address primary resistance. However, the generalizability is limited by the restricted monotherapy of ICIs and settings evaluated. Prospective evaluations are needed to further explore and validate our findings and how it compares with traditional RECIST measures of tumor response.

### Table 3 Prognostic univariate and multivariable Cox regression analyses in PFS

| Factor                     | Univariate analysis | Multivariate analysis |
|---------------------------|---------------------|-----------------------|
|                           | HR 95% CI           | HR 95% CI             |
|                           | P value             | P value               |
| Age (years) diagnosis     |                     |                       |
| Gender                    |                     |                       |
| Male                      | 1.000 (ref.)        |                       |
| Female                    | 1.401 0.985–1.992   | 0.061                 |
| Stage                     |                     |                       |
| III                       | 0.358 0.147–0.874   | 0.024                 |
| IV                        | 1.000 (ref.)        |                       |
| Type of histology         |                     |                       |
| Adenocarcinoma            | 1.042 0.752–1.444   | 0.805                 |
| Non-adenocarcinoma        | 1.000 (ref.)        |                       |
| ECOG PS                   |                     |                       |
| 0–1                       | 1.000 (ref.)        |                       |
| 2                         | 1.032 0.505–2.106   | 0.932                 |
| Smoking status            |                     |                       |
| Never-smoker              | 1.000 (ref.)        |                       |
| Current or former smoker  | 0.853 0.617–1.178   | 0.335                 |
| Treatment lines           |                     |                       |
| 1–2 regimen               | 1.000 (ref.)        |                       |
| ≥ 3 regimens              | 1.218 0.883–1.680   | 0.229                 |
| EGFR mutation status      |                     |                       |
| Positive                  | 1.386 0.832–2.309   | 0.210                 |
| Negative or not investigated| 1.000 (ref.)      |                       |
| ALK translocation         |                     |                       |
| Positive                  | 1.843 0.677–5.014   | 0.231                 |
| Negative or not investigated| 1.000 (ref.)      |                       |
| Metastasis                |                     |                       |
| Hepatic metastases        | 1.768 1.213–2.579   | 0.003                 |
| Lung metastases           | 1.319 0.958–1.814   | 0.089                 |
| Bone metastases           | 1.607 1.143–2.258   | 0.006 1.436 1.019–2.025| 0.039 |
| Brain metastases          | 1.292 0.893–1.871   | 0.174                 |
| Adrenal gland metastases  | 0.902 0.558–1.460   | 0.676                 |
| Distant lymph nodes metastasis | 1.281 0.901–1.822 | 0.168                 |
| No. of metastatic sites   |                     |                       |
| 0–1                       | 1.000 (ref.)        |                       |
| ≥ 2                       | 2.177 1.177–4.025   | 0.013                 |
| SLD-change score          |                     |                       |
| Non-responder patients    | 1.000 (ref.)        | 1.000 (ref.)          |
| Responder patients        | 0.176 0.117–0.264   | <0.001 0.181 0.120–0.272| <0.001 |

ECOG PS Eastern Cooperative Oncology Group performance status
Some limitations of our study should be acknowledged, the first of which was its retrospective, non-randomized, single-center nature. The likelihood of an unintentional patient selection bias could therefore yield. Secondly, the SLD-change score was calculated on limited number of lesions (up to 5) which are subjectively selected. Moreover, non-target lesions were not taken into account. Thus, it could not fully reflect the biological behavior of tumors. Thirdly, there was insufficient information regarding PD-L1 status and TMB level. Both of them are regarded as biomarkers for ICIs, and, therefore, collecting this genetic information would have made the results more valuable. Last, the influence of prior chemotherapy or radiotherapy was not considered in this study, which may affect the changes in target lesion size during ICI therapy.

### Table 4 Prognostic univariate and multivariable Cox regression analyses in OS

| Factor                        | Univariate analysis | Multivariate analysis |
|-------------------------------|---------------------|-----------------------|
|                               | HR 95%CI            | HR 95%CI P value       |
| Age (years) diagnosis         | 1.007 0.984–1.031   | 0.527                 |
| Gender                        |                     |                       |
| Male                          | 1.000 (ref.)        |                       |
| Female                        | 0.975 0.581–1.637   | 0.924                 |
| Stage                         |                     |                       |
| III                           | 0.263 0.036–1.901   | 0.186                 |
| IV                            | 1.000 (ref.)        |                       |
| Type of histology             |                     |                       |
| Adenocarcinoma                | 0.751 0.467–1.209   | 0.239                 |
| Non-adenocarcinoma            | 1.000 (ref.)        |                       |
| ECOG PS                       |                     |                       |
| 0–1                           | 1.000 (ref.)        |                       |
| 2                             | 0.978 0.239–4.006   | 0.975                 |
| Smoking status                |                     |                       |
| Never-smoker                  | 1.000 (ref.)        |                       |
| Current or former smoker      | 0.929 0.579–1.492   | 0.762                 |
| Treatment lines               |                     |                       |
| 1–2 regimen                   | 1.000 (ref.)        |                       |
| ≥ 3 regimens                  | 1.100 0.686–1.764   | 0.692                 |
| EGFR mutation status          |                     |                       |
| Positive                      | 0.469 0.171–1.287   | 0.142                 |
| Negative or not investigated  | 1.000 (ref.)        |                       |
| ALK translocation             |                     |                       |
| Positive                      | 0.883 0.277–2.816   | 0.833                 |
| Negative or not investigated  | 1.000 (ref.)        |                       |
| Metastasis                    |                     |                       |
| Hepatic metastases            | 1.545 0.895–2.667   | 0.119                 |
| Lung metastases               | 1.109 0.695–1.768   | 0.664                 |
| Bone metastases               | 1.264 0.772–2.071   | 0.351                 |
| Brain metastases              | 1.846 1.125–3.028   | 0.015 1.950 1.184–3.211 | 0.009 |
| Adrenal gland metastases      | 0.890 0.408–1.944   | 0.771                 |
| Distant lymph nodes metastasis| 0.795 0.460–1.375   | 0.412                 |
| No. of metastatic sites       |                     |                       |
| 0–1                           | 1.000 (ref.)        |                       |
| ≥ 2                           | 1.786 0.646–4.937   | 0.264                 |
| SLD-change score              |                     |                       |
| Non-responder patients        | 1.000 (ref.)        | 1.000 (ref.)          |
| Responder patients            | 0.442 0.276–0.707   | 0.001 0.426 0.265–0.683 | < 0.001 |

*ECOG PS* Eastern Cooperative Oncology Group performance status
Despite these limitations, we have demonstrated that ND-R defined by 10% SLD-change score was associated with better PFS and OS, suggesting that it could be used in future clinical practice to evaluate the treatment response as a useful tool.

**Conclusion**

This study revealed the predictive capacity of 10% SLD-change score in metastatic NSCLC patients receiving ICIs monotherapies, which could discriminate between favorable and poor outcomes for PFS and OS. 10% SLD-change score could be a simple predictive factor for use in clinical settings, although further studies are needed to confirm our results.

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**Author contributions**

SH: conceptualization, study design, methodology, project administration, supervision. WD, CC: resources, investigation, formal analysis. XZ, YZ, ZL: data curation, visualization. WD, CC: writing—original draft. SH, YZ and ZL: writing—reviewing and editing. All authors: final approval of the manuscript.

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**Declarations**

**Conflict of interest**

All authors have no conflicts of interest to declare.

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