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PHASE III STUDIES

Early depth of tumor shrinkage and treatment outcomes in non-small cell lung cancer treated using Nivolumab

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Summary

Background It would be useful to have criteria for predicting long-term treatment responses to immune checkpoint inhibitors (ICIs). Maximum depth of response correlates with treatment outcomes among patients receiving programmed death protein 1 axis inhibitors for non-small cell lung cancer (NSCLC). We investigated associations between early depth of response and survival outcomes among patients receiving nivolumab for NSCLC. *Methods* Using records from prospective observational cohorts, we identified 83 previously treated advanced patients with NSCLC who received nivolumab during 2016–2017. Thirty-one patients who achieved disease control were analyzed. Tumor assessments followed the Response Evaluation Criteria in Solid Tumors (RECIST). Using Kaplan-Meier and receiver operating characteristic (ROC) curve analyses, treatment outcomes were compared with percent tumor reductions from baseline to the first evaluation (8–12 weeks after starting nivolumab). *Results* Early depth of response was predictive of 6-month progression-free survival (area under the ROC curve, 0.848). Based on ROC results, early tumor shrinkage was defined as a > 10% reduction by the first evaluation. Early tumor shrinkage was associated with significantly longer median progression-free survival (early tumor shrinkage: 16.6 months, 95% confidence interval [CI] 8.5 months–not reached; no early shrinkage: 5.1 months, 95% CI 3.9–6.8 months; $P < 0.001$) and significantly longer median overall survival ($P = 0.046$). *Conclusions* Early depth of tumor shrinkage was associated with outcomes after ICI treatment. Because of its simplicity and predictive ability, early tumor shrinkage may be a promising factor for use in clinical settings. However, confirmation of our results is needed.

Keywords Immune checkpoint inhibitor · Non-small cell lung cancer · Depth of response · Treatment outcome · Retrospective study

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Abbreviations

NSCLC	Non-small cell lung cancer
ICI	Immune checkpoint inhibitor
PD-1	Programmed death protein 1
PD-L1	Programmed death ligand 1
OS	overall survival
RECIST	Response Evaluation Criteria in Solid Tumors
PFS	Progression-free survival
EGFR	Epidermal growth factor receptor gene
TKI	Tyrosine kinase inhibitor
CT	Computed tomography
ROC	Receiver operating characteristic
CI	Confidence interval
PFS	Progression-free survival

Introduction

Lung cancer is the global leading cause of cancer-related death [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of lung cancer cases, and the majority of NSCLCs have already reached an advanced, unresectable, and metastatic disease stage by the time of the initial diagnosis [2]. Recent reports have described outstanding outcomes in patients with metastatic NSCLC who have been treated with immune checkpoint inhibitors (ICIs), such as antibodies targeting programmed death protein 1 (PD-1) or programmed death ligand 1 (PD-L1). Thus, PD-1 axis inhibitors have been established as a standard treatment for NSCLC [3–7].

In the clinical trial setting, we need criteria that can help to predict long-term outcomes after ICIs. These criteria are necessary because early-phase trials need to select appropriate surrogate endpoints that can be used instead of overall survival (OS), to inform the decision to proceed to phase 3 testing [8]. At present, the conventional Response Evaluation Criteria in Solid Tumors (RECIST) still play a leading role in assessments and evaluations of ICI treatment outcomes, which are used to guide the management of patients with NSCLC. In the RECIST criteria, treatment response is defined as a $\geq$ 30% decrease in the sum of the target lesions' longest diameters relative to baseline [9]. However, several previous studies revealed that the disease control rate was associated with OS, and therefore considered disease control as alternative early predictive endpoint among NSCLC patients treated with ICIs, although the objective response rate (ORR) was poorly correlated with OS in NSCLC patients who received ICIs [8, 10, 11]. These findings suggest that radiological RECIST-defined response is insufficient for predicting survival outcomes of ICIs, as tumor response patterns vary for conventional chemotherapeutic agents and targeted therapies. Therefore, it remains necessary to establish response criteria that can provide early predictions of survival outcomes among patients who receive ICIs.

Recently, it was reported that the maximum depth of response relative to baseline was associated with longer progression-free survival (PFS) and OS among NSCLC patients who received PD-1 axis inhibitors [12], although the degree of tumor shrinkage was not correlated with progression-free survival (PFS) and OS among epidermal growth factor receptor gene (*EGFR*)-positive NSCLC patients treated using EGFR-tyrosine kinase inhibitors (TKIs) [12, 13]. Additionally, in previous clinical trials, it was found that tumor response to treatment using PD-1 axis inhibitors can be evaluated at approximately 8 weeks after administration [3, 4, 6]. Thus, we hypothesized that the early depth of response may reflect long-term treatment outcomes in patients treated with ICIs. The present study aimed to address this issue by examining the association between early tumor shrinkage and long-term outcomes, as well as by identifying an optimal cut-off value for using tumor shrinkage to predict long-term outcomes after ICI treatment for NSCLC.

Materials and methods

We identified patients with previously treated advanced NSCLC (stage IIIB–IV) who received nivolumab at our hospital between January 2016 and December 2017. These patients had previously been enrolled in a prospective observational trial (UMIN 000021560). The exclusion criteria were patients with non-measurable lesions, no response evaluation, progressive disease, previous treatment using systemic glucocorticoids or other immunosuppressive agents, or active autoimmune disease. The chart review protocol was approved by the ethics committee of Kobe City Medical Center General Hospital.

Tumor assessments were performed according to RECIST ver 1.1. Response was defined as partial or complete response to therapy. Disease control was defined as stable disease, partial response, or complete response to therapy. In this study, tumor shrinkage assessments were conducted with computed tomography (CT), using scan slice thicknesses that were no greater than 5 mm. Tumor sizes were evaluated by at least 2 pulmonologists and, in any cases of disagreement, the tumor measurements were re-examined until consensus was reached. The patients had previously been enrolled in a prospective observational trial (UMIN 000021560) and had undergone CT within 30 days before starting nivolumab and then every 8–12 weeks to evaluate tumor response. Thus, we defined the first evaluation as the follow-up CT assessment at 8–12 weeks after starting nivolumab and determined the percent tumor size reduction at the first evaluation relative to the baseline evaluation.

Receiver operating characteristic (ROC) curve analysis was used to investigate whether tumor shrinkage at the first evaluation could predict 6-month PFS among patients with disease control, as previous reports have indicated that 6-month PFS is strongly correlated with OS and is a suitable surrogate endpoint [8, 10]. Patients who had disease progression at the first evaluation were excluded from this study because they were unable to experience 6-month PFS. Based on the ROC curve analysis, we identified the optimal cut-off value for the percent tumor shrinkage, with cases that achieved greater shrinkage being considered to have achieved "early tumor shrinkage". The optimal cut-off was selected to maximize the sum of specificity and sensitivity in the ROC analysis. The PFS interval was measured from the start of nivolumab treatment until the first instance of lung cancer progression, death from any cause, or the end of follow-up. The OS interval was measured from the start of nivolumab treatment until the first instance of death from any cause or the end of follow-up. The data cut-off date was June 30, 2018.

The expression of PD-L1 in NSCLC tumor cells was analyzed using immunohistochemical staining with the PD-L1 IHC 22C3 pharmDx antibody (clone 22C3; Dako North America, Inc. Carpinteria, CA). The antibody was used according to the DAKO-recommended detection method. We set 1% and 50% as the cut-off values according to the results of previous clinical trials [5, 6].

Statistical analysis

Continuous variables were analyzed using Wilcoxon's signed-rank test. Categorical variables were analyzed using the χ^2 test. The Kaplan-Meier method and log-rank test were used to compare survival outcomes. The ability of tumor shrinkage to predict 6-month PFS was determined using ROC analysis. A two-tailed *P* value of <0.05 was considered to indicate statistical significance, and all analyses were performed using JMP 14 software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

We identified 84 consecutive patients who received nivolumab at our institution, although 11 patients were excluded because they were previously treated using another ICI (*N* = 3) or they did not have RECIST-defined measurable lesions (*N* = 8). Furthermore, among the 73 evaluable patients who fulfilled the inclusion criteria, 42 patients were excluded because they had disease progression at the first evaluation (*N* = 42). Thus, 31 patients with disease control at the first evaluation were included in the study (Fig. 1), and their characteristics are summarized in Table 1. The median patient age was 69 years, and most patients were men (71%), had a smoking history (71%), had an Eastern Cooperative Oncology Group performance status of 0 or 1 (97%), and had adenocarcinoma (77%).

Tumor response and defining early tumor shrinkage

Figure 2 shows a waterfall plot of the percent change in the target lesions relative to baseline among the patients with disease control at the first evaluation. The median change was −20%, with an overall range of −94% to +17%. Among the 31 patients with disease control at the first evaluation, 18 patients (58%) had achieved RECIST-based response as their best response. The best response during the nivolumab therapy was different from the response status at the first evaluation in 6 patients. The median PFS was 12.1 months (95% confidence interval [CI]: 6.1–16.6 months) and the median OS was not reached (95% CI: not reached–not reached), with 22 patients (71%) not experiencing disease progression by 6 months after the start of nivolumab treatment.

Figure 3 shows the results of the ROC analysis for using tumor shrinkage to predict PFS at 6 months. The area under the ROC curve was 0.848 and the optimal cut-off for depth of shrinkage was 8%, which yielded a false-positive rate of 0.111 and a true positive rate of 0.818. Based on these results, we defined the cut-off for "early tumor shrinkage" as a − 10% change at the first evaluation.

Treatment outcomes and early tumor shrinkage

Among the 31 patients, 18 patients achieved early tumor shrinkage, and the baseline characteristics of patients with

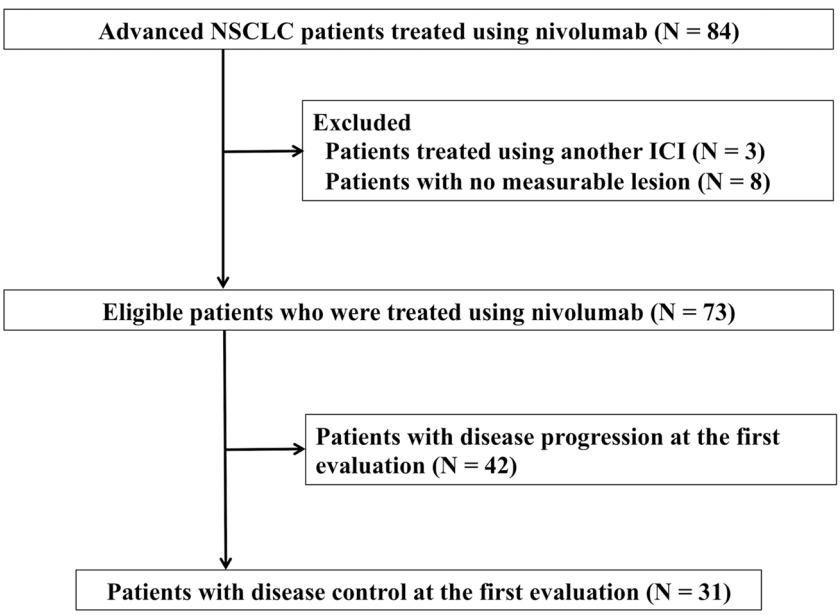

Fig. 1 Study flowchart. NSCLC: non-small cell lung cancer; ICI: immune checkpoint inhibitor

Table 1 Patient characteristics at the first evaluation, according to early tumor shrinkage ($N = 31$)

	Patients with disease control ($N = 31$)	With early tumor shrinkage ($N = 18$)	Without early tumor shrinkage ($N = 13$)	*P* value
Age (years)				
Median (range)	69 (41–92)	70.5 (41–92)	69 (47–80)	0.645
Sex, n (%)				
Male	22 (71)	15 (83)	7 (54)	0.074
Female	9 (29)	3(17)	6 (46)	
Smoking status, n (%)				
Never-smoker	9 (29)	4 (22)	5 (38)	0.326
Current or former smoker	22 (71)	14 (78)	8 (62)	
ECOG PS, n (%)				
0–1	30 (97)	18 (100)	12 (92)	0.232
2	1 (3)	0 (0)	1 (8)	
Histology, n (%)				
Adenocarcinoma	24 (77)	13 (72)	11 (85)	0.415
Squamous cell carcinoma	6 (19)	4 (22)	2 (15)	
Other	1 (3)	1 (6)	0 (0)	
EGFR mutation status, n (%)				
Positive	2 (6)	1 (6)	1 (8)	0.811
Negative or not investigated	29 (94)	17 (94)	12 (92)	
ALK translocation, n (%)				
Positive	1 (3)	0 (0)	1 (8)	0.232
Negative or not investigated	30 (97)	18 (100)	12 (92)	
Stage, n (%)				
IIIB	2 (6)	2 (11)	0 (0)	0.214
IV	29 (94)	16 (89)	13 (100)	
Treatment line, n (%)				
Second	15 (48)	11 (61)	4 (31)	0.095
Third or later	16 (52)	7 (39)	9 (69)	
PD-L1 status, n (%)				
≥ 50%	6 (19)	5 (28)	1 (8)	0.122[a]
1–49%	11 (35)	7 (39)	4 (31)	
< 1%	8 (26)	2 (11)	6 (46)	
Not known	6 (19)	4 (22)	2 (15)	

ECOG PS Eastern Cooperative Oncology Group performance status, *EGFR* epidermal growth factor receptor gene, *ALK* anaplastic lymphoma kinase gene, *PD-L1* programmed death ligand 1

P values were calculated by comparing the patients with and without early tumor shrinkage

[a] Patients with PD-L1 expression of 50% or more and less than 50% were compared

and without early tumor shrinkage are summarized in Table 1. No significant differences were detected in the baseline characteristics of these two subgroups. However, early tumor shrinkage was associated with significantly longer median PFS (early shrinkage: 16.6 months [95% CI: 8.5 months–not reached], no early shrinkage: 5.1 months [95% CI: 3.9–6.8 months], $P < 0.001$) (Fig. 4a). Furthermore, the PFS rate at 6 months was significantly higher for patients with early tumor shrinkage than patients without early shrinkage (94% vs. 38%, $P < 0.001$). Moreover, early tumor shrinkage was associated with significantly longer median OS (early shrinkage: median not reached [95% CI: not reached–not reached], no early shrinkage: not reached [95% CI: 15.3 months–not reached], $P = 0.046$) (Fig. 4b).

Treatment outcomes and RECIST-defined response at the first evaluation

Among the 31 patients who achieved disease control at the first evaluation, 12 patients achieved RECIST-based response at the first evaluation, and the baseline characteristics of patients with and without RECIST-based response are

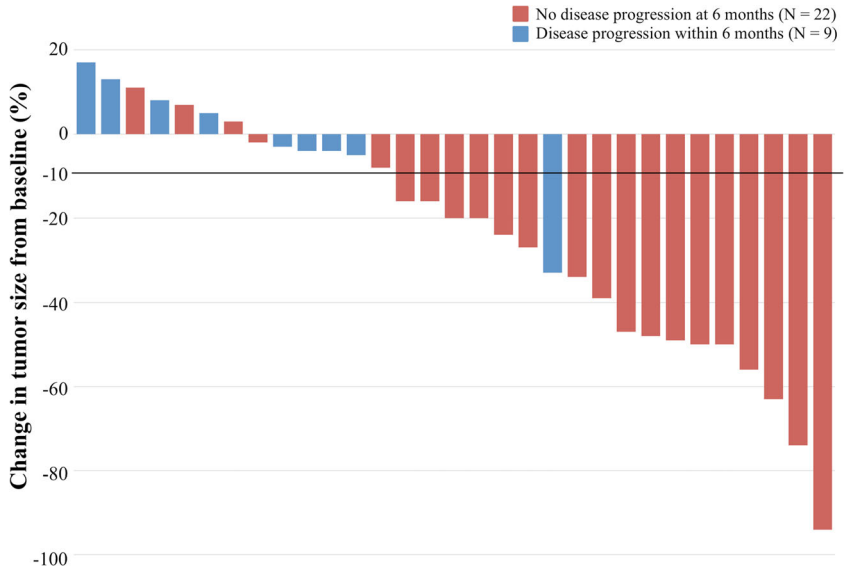

Fig. 2 Waterfall plot of the 31 patients with disease control at the first evaluation

summarized in Table 2. The patients who had RECIST-based response were significantly more likely to have ≥50% PD-L1 expression than were the patients who did not have RECIST-based response (42% vs. 5%, respectively; $P = 0.006$). Interestingly, achieving RECIST-based response was only marginally associated with improved median PFS (response: 14.9 months [95% CI: 6.5 months–not reached], no response: 6.8 months [95% CI: 4.1–16.8 months], $P = 0.096$) (Fig. 4c). However, the PFS rate at 6 months was significantly higher among patients who achieved response than among patients who did not (92% vs. 58%, $P = 0.032$). Further, achieving RECIST-based response was only marginally associated with improved median OS (response: not reached [95% CI: not reached–not reached], no response: not reached [95% CI: 17.3 months–not reached], $P = 0.0501$) (Fig. 4d).

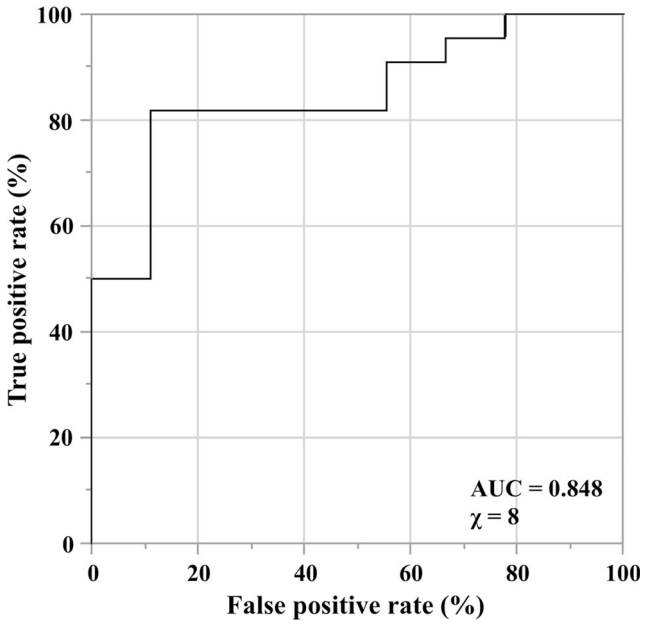

Fig. 3 Receiver operating characteristic curve for the 31 patients with early tumor shrinkage. AUC: area under the curve

Subgroup analysis of patients with stable disease at the first evaluation

We also analyzed the 19 patients who achieved RECIST-defined stable disease at the first evaluation. Among these patients, early tumor shrinkage was still associated with significantly longer median PFS (early shrinkage: 24.0 months [95% CI: 8.5–24.0 months], no early shrinkage: 5.1 months [95% CI: 3.9–6.8 months], $P = 0.006$) (Online Resource 1: Supplementary Figure).

Discussion

To the best of our knowledge, this is the first study to reveal an association between early tumor shrinkage and survival outcomes after nivolumab treatment for NSCLC. Based on our findings, tumor shrinkage of at least −10% at the first evaluation (8–12 weeks after starting treatment) predicted good survival outcomes after nivolumab treatment. Furthermore, the present study revealed that early tumor shrinkage was strongly associated with the 6-month PFS rate after nivolumab treatment for NSCLC. In contrast, a previous study revealed that depth of response at week 6 or 12 had little-to-no associations with long-term outcomes after EGFR-TKI treatment or chemotherapy for NSCLC, which suggests that the depth of response may not be a useful marker for predicting response to non-ICI therapies [14]. Therefore, it is conceivable that the clinical benefits of early tumor shrinkage differ between patients who are treated with ICIs and non-ICI therapies. These differences may be related to the unique anticancer

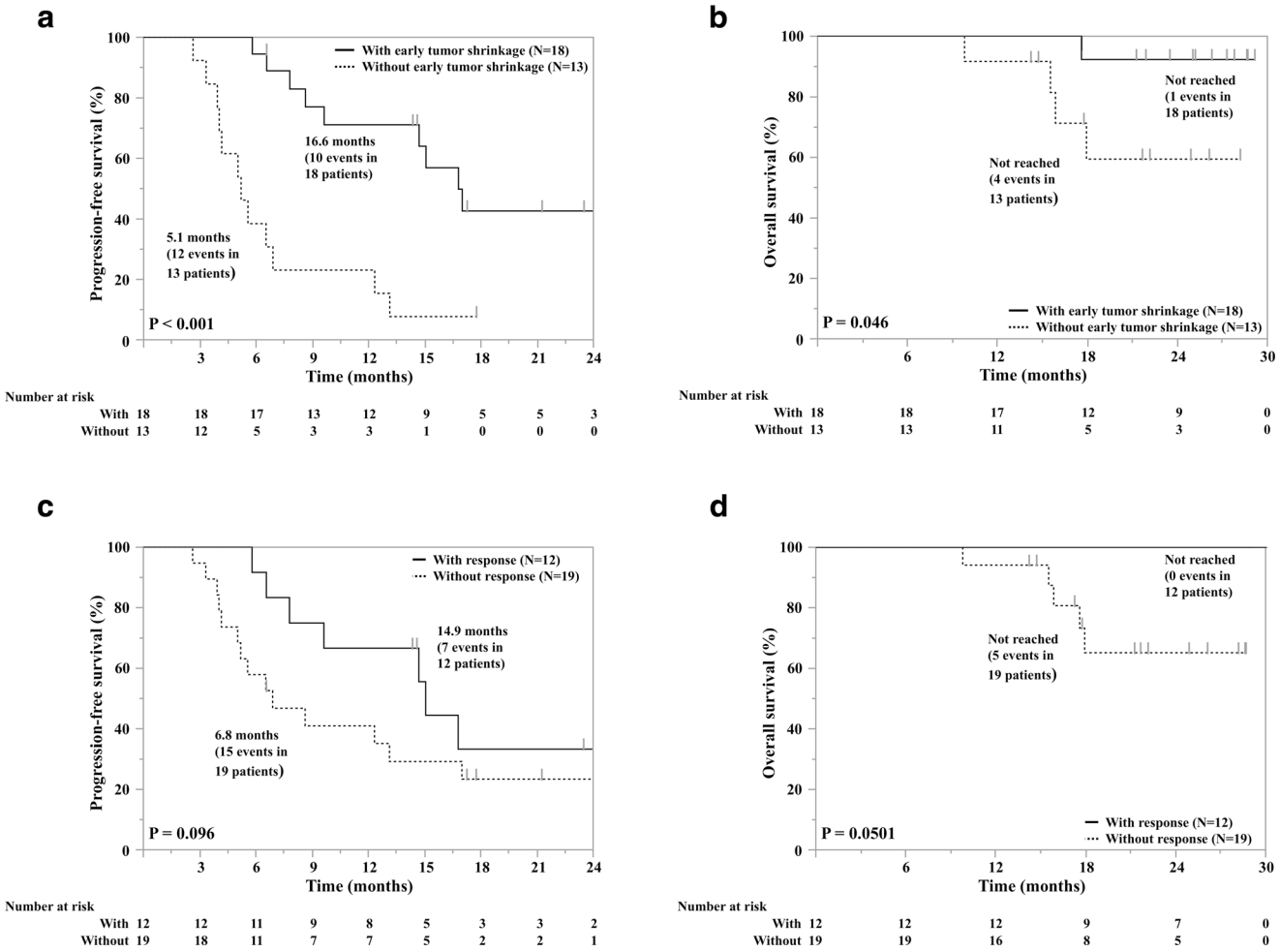

Fig. 4 Kaplan-Meier curves for the patients with disease control ($N = 31$). **a** Progression-free survival and **b** overall survival have been stratified by early tumor shrinkage (present vs. absent). For comparison, **c** progression-free survival and **d** overall survival have also been stratified by RECIST-based response (present vs. absent). Each survival curve is labelled with the median survival time, the total number events, and the total number of patients

mechanism of ICIs, relative to target therapies or chemotherapy, which involve indirect or direct tumor cell inhibition. In patients treated with ICIs, the depth of early response may reflect the magnitude of immune system activation and subsequent tumor response, which could predict a durable response to ICI treatment. Thus, early tumor shrinkage may be useful for early decision-making in clinical practice or trials that involve ICI treatment.

Our study revealed that the RECIST-based classification of early tumor response was not able to accurately predict the outcomes of nivolumab treatment. In contrast, early tumor shrinkage of at least −10% by the first evaluation could be used to predict the likelihood of 6-month PFS. Other studies have also revealed that disease control correlates with OS and might be more suitable than ORR as an early endpoint for predicting response to ICI treatment among NSCLC patients [10, 11]. A large multicenter study of real-world experience has also revealed that patients who achieved stable disease during nivolumab treatment tended to experience good survival outcomes [15]. Furthermore, updated analyses from the CheckMate 017 and CheckMate 057 trials have demonstrated that nivolumab prolonged OS in patients who achieved both disease response and stable disease, which indicated that tumor response is not a prerequisite for an OS benefit [16]. These findings suggest that ICIs can help improve outcomes among patients with RECIST-defined stable disease. Relatedly, our findings indicated that, among 19 patients with RECIST-defined stable disease, superior outcomes were still associated with early tumor shrinkage of at least −10%. Nonetheless, it is unknown whether −10% is the optimal cut-off value for depth of response. In the present study, the evaluation of predictive performance showed that the −10% cut-off value was associated with moderate, but not high accuracy. Additionally, 6-months PFS rates were similar for patients who showed early tumor shrinkage of at least −10% and for those who showed RECIST-based response (6-month PFS: 94% and 92%, respectively). However, the results of our study highlight that early tumor shrinkage may provide useful

Table 2 Patient characteristics at the first evaluation, according to RECIST-defined response ($N = 31$)

	Patients with disease control ($N = 31$)	With RECIST-based response ($N = 12$)	Without RECIST-based response ($N = 19$)	P value
Age (years)				
Median (range)	69 (41–92)	70.5 (41–82)	69 (47–92)	0.919
Sex, n (%)				
Male	22 (71)	9 (75)	13 (68)	0.694
Female	9 (29)	3 (25)	6 (32)	
Smoking status, n (%)				
Never-smoker	9 (29)	3 (25)	6 (32)	0.694
Current or former smoker	22 (71)	9 (75)	13 (68)	
ECOG PS, n (%)				
0–1	30 (97)	12 (100)	18 (95)	0.419
2	1 (3)	0 (0)	1 (5)	
Histology, n (%)				
Adenocarcinoma	24 (77)	8 (67)	16 (84)	0.255
Squamous cell carcinoma	6 (19)	3 (25)	3 (16)	
Other	1 (3)	1 (8)	0 (0)	
EGFR mutation status, n (%)				
Positive	2 (6)	1 (8)	1 (5)	0.735
Negative or not investigated	29 (94)	11 (92)	18 (95)	
ALK translocation, n (%)				
Positive	1 (3)	0 (0)	1 (5)	0.419
Negative or not investigated	30 (97)	12 (100)	18 (95)	
Stage, n (%)				
IIIB	2 (6)	1 (8)	1 (5)	0.735
IV	29 (94)	11 (92)	18 (95)	
Treatment line, n (%)				
Second	15 (48)	6 (50)	9 (47)	0.886
Third or later	16 (52)	6 (50)	10 (53)	
PD-L1 status, n (%)				
≥ 50%	6 (19)	5 (42)	1 (5)	0.006[a]
1–49%	11 (35)	3 (25)	9 (47)	
< 1%	8 (26)	1 (8)	7 (37)	
Not known	6 (19)	3 (25)	3 (16)	

RECIST Response Evaluation Criteria in Solid Tumors, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EGFR* epidermal growth factor receptor gene, *ALK* anaplastic lymphoma kinase gene, *PD-L1* programmed death ligand 1

P-values were calculated by comparing patients with and without RECIST-based response

[a] Patients with PD-L1 expression of 50% or more and less than 50% were compared

predictions of long-term efficacy. Further, the study results suggest that the RECIST-based classification of early tumor response may not be capable of accurately predicting long-term outcomes in NSCLC patients treated with nivolumab. Thus, further studies are needed to refine the cut-off value such that it provides optimal predictions of outcomes after ICI treatment, based on the depth of tumor shrinkage.

Some patients who receive ICIs exhibit an unconventional imaging-based pattern of tumor response that is known as pseudoprogression. In these patients, the pseudoprogression involves an initial increase in the burden of the primary tumor or new lesions, with a subsequent response based on possible immune cell infiltrates within the growing lesion [17–20]. Radiological pseudoprogression is initially indistinguishable from true disease progression and presents a challenge to accurately assessing the response to ICI treatment [20–22]. However, this event is uncommon among NSCLC patients treated using anti-PD-1 therapy, as it is only detected at approximately 2% of the initial radiological assessments [23]. In addition, the KEYNOTE 024, Checkmate 017, and Checkmate 057 trials have revealed a median time to response of 2.1–2.2 months, which is nearly the time to the first tumor

assessment in most clinical trial protocols [3, 4, 6]. In our original cohort of 73 patients, only 1 patient had experienced pseudoprogression. Therefore, for most patients treated using ICIs, it appears that the tumor response at the first evaluation reflects the best overall response and is a reasonable option for predicting long-term treatment outcomes.

The present study has several limitations. First, the study had a single-center design with a small sample size. Thus, although the results of our study are clinically important, they have the potential to be affected by selection bias. Second, the study included only Japanese patients, which precludes the generalization of our findings to broader patient groups. Third, our patients only received nivolumab as second-line or later treatment. Therefore, large prospective studies with broader patient selection criteria and treatment protocols are needed to validate our findings and determine whether they can be used in clinical practice.

In conclusion, we found that early tumor shrinkage (based on the depth of response at the first evaluation) was associated with long-term outcomes among patients who received nivolumab for NSCLC. Early tumor shrinkage could be a simple predictive factor for use in clinical settings, although further studies are needed to confirm our results.

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Compliance with ethical standards

Disclosure of potential conflicts of interest Dr. Kawachi has received lecture fees from Ono Pharmaceutical Co., Ltd., Chugai Pharmaceutical, Merck Sharp and Dohme, and Taiho Pharmaceutical. Dr. Fujimoto has received lecture fees from Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb K.K., Chugai Pharmaceutical, AstraZeneca, Merck Sharp and Dohme, and Taiho Pharmaceutical. Dr. Hosoya has received lecture fees from Chugai Pharmaceutical, Merck Sharp and Dohme, and Taiho Pharmaceutical. Dr. Sato has received lecture fees from Ono Pharmaceutical Co., Ltd. Dr. Tomii has received lecture fees from Chugai Pharmaceutical, AstraZeneca, and Taiho Pharmaceutical. The remaining authors have declared that they have no conflicts of interest.

Ethical approval All study procedures complied with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

References

1. Siegel RL, Miller KD, Jemal A (2017) Cancer statistics, 2017. CA Cancer J Clin 67:7–30
2. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA (2008) Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 83:584–594
3. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhaufl M, Arrieta O, Burgio MA, Fayette J, Lena H, Poddubskaya E, Gerber DE, Gettinger SN, Rudin CM, Rizvi N, Crino L, Blumenschein GR Jr, Antonia SJ, Dorange C, Harbison CT, Graf Finckenstein F, Brahmer JR (2015) Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 373:1627–1639
4. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Aren Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR (2015) Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373:123–135
5. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, Molina J, Kim JH, Arvis CD, Ahn MJ, Majem M, Fidler MJ, de Castro G Jr, Garrido M, Lubiniecki GM, Shentu Y, Im E, Dolled-Filhart M, Garon EB (2016) Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 387:1540–1550
6. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR (2016) Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375:1823–1833
7. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gadgeel SM, Hida T, Kowalski DM, Dols MC, Cortinovis DL, Leach J, Polikoff J, Barrios C, Kabbinavar F, Frontera OA, DeMarinis F, Turna H, Lee JS, Ballinger M, Kowanetz M, He P, Chen DS, Sandler A, Gandara DR (2017) Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 389:255–265
8. Ritchie G, Gasper H, Man J, Lord S, Marschner I, Friedlander M, Lee CK (2018) Defining the most appropriate primary end point in phase 2 trials of immune checkpoint inhibitors for advanced solid cancers: a systematic review and meta-analysis. JAMA Oncol 4:522–528
9. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 11). Eur J Cancer 45:228–247
10. Shukuya T, Mori K, Amann JM, Bertino EM, Otterson GA, Shields PG, Morita S, Carbone DP (2016) Relationship between overall survival and response or progression-free survival in advanced non-small cell lung cancer patients treated with anti-PD-1/PD-L1 antibodies. J Thorac Oncol 11:1927–1939
11. Nishino M, Dahlberg SE, Adeni AE, Lydon CA, Hatabu H, Janne PA, Hodi FS, Awad MM (2017) Tumor response dynamics of advanced non-small cell lung cancer patients treated with pd-1 inhibitors: imaging markers for treatment outcome. Clin Cancer Res 23:5737–5744
12. McCoach CE, Blumenthal GM, Zhang L, Myers A, Tang S, Sridhara R, Keegan P, Pazdur R, Doebele RC, Kazandjian D (2017) Exploratory analysis of the association of depth of response and survival in patients with metastatic non-small-cell lung cancer treated with a targeted therapy or immunotherapy. Ann Oncol 28:2707–2714
13. Takeda M, Okamoto I, Nakagawa K (2014) Survival outcome assessed according to tumor response and shrinkage pattern in patients with EGFR mutation-positive non-small-cell lung cancer treated with gefitinib or erlotinib. J Thorac Oncol 9:200–204
14. Lee CK, Lord S, Marschner I, Wu YL, Sequist L, Rosell R, Fukuoka M, Mitsudomi T, Asher R, Davies L, Gebski V, Gralla

R, Mok T, Chih-Hsin Yang J (2018) The value of early depth of response in predicting long-term outcome in EGFR-mutant lung cancer. J Thorac Oncol 13:792–800

15. Fujimoto D, Yoshioka H, Kataoka Y, Morimoto T, Kim YH, Tomii K, Ishida T, Hirabayashi M, Hara S, Ishitoko M, Fukuda Y, Hwang MH, Sakai N, Fukui M, Nakaji H, Morita M, Mio T, Yasuda T, Sugita T, Hirai T (2018) Efficacy and safety of nivolumab in previously treated patients with non-small cell lung cancer: a multicenter retrospective cohort study. Lung Cancer 119:14–20
16. Horn L, Spigel DR, Vokes EE, Holgado E, Ready N, Steins M, Poddubskaya E, Borghaei H, Felip E, Paz-Ares L, Pluzanski A, Reckamp KL, Burgio MA, Kohlhaeufl M, Waterhouse D, Barlesi F, Antonia S, Arrieta O, Fayette J, Crino L, Rizvi N, Reck M, Hellmann MD, Geese WJ, Li A, Blackwood-Chirchir A, Healey D, Brahmer J, WEberhardt EE (2017) Nivolumab versus docetaxel in previously treated patients with advanced non-small-cell lung cancer: two-year outcomes from two randomized, open-label, phase iii trials (CheckMate 017 and CheckMate 057). J Thorac Oncol 35: 3924–3933
17. Hodi FS, Hwu WJ, Kefford R, Weber JS, Daud A, Hamid O, Patnaik A, Ribas A, Robert C, Gangadhar TC, Joshua AM, Hersey P, Dronca R, Joseph R, Hille D, Xue D, Li XN, Kang SP, Ebbinghaus S, Perrone A, Wolchok JD (2016) Evaluation of immune-related response criteria and RECIST v11 in patients with advanced melanoma treated with pembrolizumab. J Clin Oncol 34: 1510–1517
18. Nishino M, Giobbie-Hurder A, Manos MP, Bailey N, Buchbinder EI, Ott PA, Ramaiya NH, Hodi FS (2017) Immune-related tumor response dynamics in melanoma patients treated with pembrolizumab: identifying markers for clinical outcome and treatment decisions. Clin Cancer Res 23:4671–4679
19. Nishino M, Tirumani SH, Ramaiya NH, Hodi FS (2015) Cancer immunotherapy and immune-related response assessment: the role of radiologists in the new arena of cancer treatment. Eur J Radiol 84:1259–1268
20. Chiou VL, Burotto M (2015) Pseudoprogression and immune-related response in solid tumors. J Clin Oncol 33:3541–3543
21. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS (2009) Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 15:7412–7420
22. Hoos A, Eggermont AM, Janetzki S, Hodi FS, Ibrahim R, Anderson A, Humphrey R, Blumenstein B, Old L, Wolchok J (2010) Improved endpoints for cancer immunotherapy trials. J Natl Cancer Inst 102:1388–1397
23. Katz SI, Hammer M, Bagley SJ, Aggarwal C, Bauml JM, Thompson JC, Nachiappan AC, Simone CB, Langer CJ (2018) Radiologic pseudoprogression during anti-PD-1 therapy for advanced non-small cell lung cancer. J Thorac Oncol 13:978–986

Summary headings

- RECIST-based tumor shrinkage may not predict outcomes from ICI treatment.
- A > 10% decrease in tumor size predicted good outcomes from nivolumab.
- Early tumor shrinkage may be a simple and useful marker in the clinical setting.