Nivolumab Retreatment in Non–Small Cell Lung Cancer Patients Who Responded to Prior Immune Checkpoint Inhibitors and Had ICI-Free Intervals (WJOG9616L)

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ABSTRACT

Purpose: To explore the efficacy of retreatment with immune checkpoint inhibitors (ICI) in patients with advanced non–small cell lung cancer (NSCLC) who responded to prior ICI and had adequate ICI-free interval.

Patients and Methods: Patients with advanced NSCLC who had achieved complete response (CR), partial response (PR), or stable disease for ≥6 months with prior ICI therapy preceding progression were prospectively enrolled. All patients should have had ICI-free interval ≥60 days before registration. Patients were treated with nivolumab (240 mg) every 2 weeks until progression. The primary endpoint was overall response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival, and safety (Trial Identifier, UMIN000028561).

Results: Sixty-one patients were enrolled during October 2017 to February 2020, with 59 analyzed for efficacy. Regarding prior ICI, 41 patients had CR or PR. Median treatment on ICI and median ICI-free intervals were 8.1 months and 9.2 months, respectively. Twenty patients experienced immune-related adverse events (irAE) that required discontinuation of prior ICI. Nivolumab retreatment demonstrated ORR of 8.5% [95% confidence interval (CI), 2.8–18.7%] and median PFS of 2.6 months (95% CI, 1.6–2.8 months) while 5 responders had 11.1 months of median PFS. In the multivariate analysis, ICI-free interval was the only predictive factor of PFS (HR, 2.02; $P = 0.02$), while prior efficacy or history of irAE was not. Common adverse events were skin disorders (23%), malaise (20%), and hypoalbuminemia (15%).

Conclusions: Even in patients who initially responded to prior ICI and had ICI-free interval, once resistance occurred, retreatment with nivolumab had limited efficacy.

Introduction

Immune checkpoint inhibitors (ICI) have become a key player in the treatment of advanced non–small cell lung cancer (NSCLC). However, recent follow-up of phase III studies demonstrated that ≥60% of patients who initially responded to either ICI alone or combined with chemotherapy ultimately acquired resistance and progressed (1, 2). Therefore, to develop an effective subsequent treatment is a critical unmet need.

For patients whose tumor had progressed with anti–programmed death 1 (anti–PD-1)/anti–programmed death ligand 1 (anti–PD-L1) inhibitors, adding anti-CTLA4 antibody has been investigated in various tumor types, but has shown modest benefit (3–5). Translational approaches have elucidated several mechanisms that may explain acquired resistance to ICIs, including mutational changes in tumor-specific neoantigens, PTEN loss, and/or β-catenin/Wnt signaling alterations (6–8). However, effective agents have not been approved yet.

Retreatment with anticancer drugs that showed efficacy during prior lines of therapy and had certain drug-free interval is commonly accepted in lung cancer. Although the duration of retreatment is typically relatively shorter compared with their initial administration (9, 10), the acceptable adverse events profiles of these agents allow clinicians to consider retreatment even in later line. However, data regarding the effectiveness of retreatment with ICIs have been conflicting. Another issue is the heterogeneity of patient population among studies. Schoenfeld and colleagues recently proposed a definition of acquired resistance to ICI in patients with advanced NSCLC as follows: (i) patients who received anti–PD-1/anti–PD-L1 inhibitor-containing regimen(s), (ii) those

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

WJOG9616L is the first study to explore the efficacy of nivolumab retreatment in patients with non–small cell lung cancer who responded to prior immune checkpoint inhibitors (ICI) and had adequate ICI-free interval. As a result, nivolumab retreatment had limited efficacy [overall response rate (ORR) 8.5% and median progression-free survival (PFS) 2.6 months] while 5 responders had 11.1 months of median PFS. In the multivariate analysis, ICI-free interval was the only predictive factor of PFS; neither prior ICI response nor history of immune-related adverse events was predictive. Interestingly, as the ICI-free interval extended, PFS with retreatment was significantly longer. In the exploratory research, although the number of circulating tumor cells (CTC) in peripheral blood increased among those who had progressive disease, changes in CTCs were not predictive of response.

who had complete response (CR) or partial response (PR) as their best response, and (iii) those who progressed within 6 months of prior ICI (11). While they encouraged ICI retreatment if patients progressed after ≥ 6 months of ICI-free interval, clinical data regarding the effectiveness of such retreatment is lacking.

On the basis of these backgrounds, we performed this multi-institutional, phase II trial of nivolumab retreatment in patients with advanced NSCLC who responded to prior anti–PD-1/anti–PD-L1 inhibitors and acquired resistance [West Japan Oncology Group (WJOG) 9616L].

Patients and Methods

Study design and eligibility criteria

We conducted this study as an open-label, multi-institutional, single-arm phase II study. Eligible patients were those with pathologically confirmed NSCLC who previously received at least one systemic anticancer treatment including ICI. Patients should have received clinical benefit from prior ICI-containing regimen preceding progression. We defined a clinical benefit as a CR, PR, or stable disease (SD) ≥ 6 months. To avoid those who recently progressed with prior ICI, patients must have had ICI-free interval ≥ 60 days. Additionally, patients had Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and had at least one measurable target lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients with brain metastases were allowed unless they were symptomatic. We excluded patients who had active autoimmune disease, however, those with controlled thyroid dysfunction or skin disease that did not require systemic therapy were allowed.

Treatment

All patients were intravenously administered nivolumab every 2 weeks until progression. The nivolumab dose was in accordance with that approved by the Japanese government. Initially, approved dose was 3 mg/kg but was changed to a 240-mg flat dose in August 2018.

Assessment

To assess efficacy, chest CT was performed every 6 weeks for up to 40 weeks and then every 12 weeks thereafter. Gadolinium-enhanced MRI of the brain was performed at baseline for all patients prior to registration. Tumor responses were based on the RECIST version 1.1. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

Endpoints and sample size calculation

The primary endpoint of the study was the overall response rate (ORR). After progression of ICI-containing regimen, the standard treatment was cytotoxic chemotherapy. The sample size was calculated on the basis of an assumption that retreatment with nivolumab would improve the ORR from 10% to 20% in the second- or later-line setting. As such, 60 patients were required to ensure a statistical power of 0.79 with a one-sided alpha error of 0.05. The secondary endpoints were progression-free survival (PFS), overall survival (OS), and adverse events.

Statistical analysis

The ORR estimates and 95% confidence intervals (CI) were calculated, and the 12-month PFS and OS were estimated using Kaplan–Meier curves and are reported with their 95% CIs. Differences in ORR and PFS according to clinical backgrounds were evaluated, with the significance level set to a two-sided alpha of 0.05. Univariate analyses were performed to identify factors predictive of ORR and PFS using a Cox proportional hazards model. The investigated covariates included clinical backgrounds (such as sex, smoking status, and histology) and ICI-related factors (such as PD-L1 expression level, history of immune-related adverse events (irAE), ICI-free interval, and duration of prior ICI). Continuous variables were dichotomized at the median. Covariates that were significantly correlated with PFS in the univariate analyses (defined as $P < 0.05$) were subjected to multivariate analyses. Statistical analyses were conducted using the JMP software (version 11; SAS Institute, Cary, NC) and Prism version 7.00 for Windows (GraphPad Software, San Diego, CA).

Biomarker analyses

We collected tumor tissue upon progression with prior ICI. PD-L1 and CD8+ lymphocytes were independently assessed using immunohistochemistry. PD-L1 (clone 22c3, Dako) and CD8 (clone SP57, Ventana/Roche) antibodies were used according to the manufacturers' guidelines. The tumor proportion score was calculated to quantify PD-L1 expression as previously described (12). To evaluate CD8, the density of stained lymphocytes was quantified by averaging the number of all lymphocytes counted in five high-power fields (400× magnification) and then categorizing them as minimal (average density <50), mild (50–75), and moderate (≥75) as described previously (13). According to our previous study (14), we also collected 20 mL of peripheral blood before and after treatment (6–8 weeks), and circulating tumor cells (CTC) were detected using a microcavity array system (Hitachi Chemical Co. Ltd., Chikusei, Japan).

Ethical considerations

The study was conducted in compliance with the principles of the Declaration of Helsinki, and the institutional review board of each participating institution approved the protocol. Written informed consent was obtained from all patients before any screening or inclusion procedure. This protocol was registered in the University Hospital Medical Information Network, Japan (protocol identification no. UMIN000028561).

Data availability statement

The data generated in this study are available upon request from the corresponding authors.

Results

Sixty-one patients were enrolled between October 2017 and February 2020. One dropped out before commencing nivolumab and another was excluded from efficacy analysis because this patient did not meet eligibility criteria after registration (Supplementary Fig. S1). The median follow-up interval for the 59 patients who were evaluated for efficacy was 19.5 months (range, 2.2–30.7 months). At the time of data cut-off, 56 patients had discontinued nivolumab retreatment. The median number of administrations was five (range, 1–31).

The baseline characteristics of 59 patients are described in **Table 1**. Median age was 70 years (range, 38–81). Most patients were male ($n = 43$, 73%) and smokers ($n = 49$, 83%). Median number of prior regimen was three (range, 1–6). Regarding prior ICI, most patients ($n = 54$, 92%) received monotherapy and 41 (70%) achieved CR or PR. Median duration of prior ICI was 8.1 months (range, 0.8–37.0 months) and median ICI-free interval was 9.2 months (range, 2.4–29.4 months). Prior ICI was discontinued in 20 patients due to irAEs (9 pneumonitis, 4 colitis, 2 thyroid dysfunction, and 5 other AEs).

Tumor shrinkage owing to nivolumab retreatment is shown in **Fig. 1**. Five patients achieved PR, 25 had SD, 28 had progressive disease, and 1 was not evaluable. Thus, the ORR was 8.5% (95% CI, 2.8%–18.7%), which failed to meet the primary endpoint. Median PFS was 2.6 months (95% CI, 1.6–2.8 months), and PFS rate at 12 months was 4.8% (95% CI, 1.0%–13.6%; **Fig. 2A**). Median OS was 11.0 months (95% CI, 9.0–14.5 months), and OS rate at 12 months was 46.4% (95% CI, 32.8%–59.0%; Supplementary Fig. S2A).

Table 1. Patients' characteristics.

	***n* = 59**
Age	
Median (range)	70 (38–81)
Sex, *n* (%)	
Male/Female	43 (73)/16 (27)
Smoking status, *n* (%)	
Never/(ex-) smoker	10 (17)/49 (83)
ECOG performance status, *n* (%)	
0/1	22 (37)/37 (63)
Histology, *n* (%)	
Non-Sq/Sq	38 (64)/21 (36)
EGFR WT/MT/unknown	30 (51)/2 (3)/6 (10)
ALK WT/MT/unknown	30 (51)/0/8 (14)
Clinical stage at registration, *n* (%)	
IIIB-C/IV/postoperative relapse	6 (10)/38 (64)/15 (25)
Prior chemotherapy lines, median (range)	3 (1–6)
Prior radiotherapy, *n* (%)	
Yes/No	32 (54)/27 (46)
PD-L1 expression (TPS); < 50%/≥50%/unknown, *n* (%)	
At diagnosis	20 (34)/17 (29)/22 (37)
At registration	8 (14)/1 (1)/50 (85)
Types of prior ICI, *n* (%)	
Monotherapy (Nivo/Pembro/Durva/Atezo)	30 (51)/21 (36)/2 (3)/1 (1)
ICI +cytotoxic chemotherapy	5 (9)
Best response of prior ICI, *n* (%)	
CR/PR/SD ≥ 6 months	2 (3)/39 (66)/18 (31)
Duration of prior ICI, median (range), months	8.1 (0.8–37.0)
ICI-free interval, median (range), months	9.2 (2.4–29.4)
History of irAE that required discontinuation of prior ICI, *n* (%)	
Yes/No	20 (34)/39 (66)

Abbreviations: Atezo, atezolizumab; Durva, durvalumab; MT, mutation; Nivo, nivolumab; Non-Sq, non-squamous; Pembro, pembrolizumab; PS, performance status; Sq, Squamous; TPS, tumor proportion score; WT, wild-type.

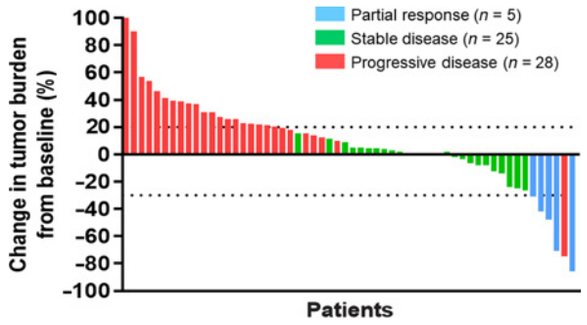

Figure 1.
Waterfall plot of tumor burden in patients receiving nivolumab retreatment.

The clinical backgrounds of the 5 patients who experienced PR are described in Supplementary Table S1. Despite the small number of patients, it was notable that their median PFS was 11.1 months (**Fig. 2A**), and most of them were alive at the time of analysis (**Fig. 2B**; Supplementary Fig. S2B).

We performed univariate and multivariate analyses to identify the predictive factor of response to nivolumab retreatment (**Table 2**). None of the clinical backgrounds significantly influenced ORR (Supplementary Fig. S3). However, non-squamous histology, duration of prior ICI (>8.1 months), ICI-free interval (>9.2 months), and history of irAE were associated with significantly longer PFS (Supplementary Fig. S4). Multivariate analysis revealed that ICI-free interval was the only significant predictor of longer PFS (≤9.2 vs. >9.2 months; HR, 2.02; 95% CI, 1.10–3.73; $P = 0.02$), while prior ICI response or history of irAE was not. As shown in **Fig. 3**, ICI-free intervals were correlated with longer PFS in a duration-dependent manner. Median PFS values according to ICI-free intervals were 1.4, 1.6, 4.3, 2.8, and 8.4 months among ICI-free intervals with 2–6, 6–12, 12–18, 18–24, and 24–30 months, respectively.

Adverse events related to nivolumab retreatment are summarized in Supplementary Table S2. Nine grade 3 and three grade 4 events were observed, while no treatment-related deaths occurred. Frequent adverse events were skin disorders ($n = 14$, 23%), malaise ($n = 12$, 20%), and hypoalbuminemia ($n = 9$, 15%). Various irAEs were observed, among which pneumonitis and colitis were the most common irAEs. Other severe irAEs included myocarditis (grade 4, $n = 1$), pancreatitis (grade 3, $n = 1$), vasculitis (grade 3, $n = 1$), and adrenal insufficiency (grade 3, $n = 1$). Of 20 patients who discontinued prior ICI due to irAEs, 4 had severe irAEs by nivolumab retreatment. Thus, the history of irAEs with prior ICI was not related to the occurrence of severe irAE with nivolumab retreatment.

As an exploratory analysis, we planned to collect tissue samples immediately before retreatment. However, a fresh biopsy was challenging in this heavily pretreated patient population. Two specimens were obtained from responders of retreatment: one had high PD-L1 expression (tumor proportion score >90%) with lower $CD8^+$ cells, while the other expressed neither PD-L1 or $CD8^+$ cells (data not shown). The median number of CTCs at baseline was zero (range, 0–512), with this count being higher among patients who had progressive disease (Supplementary Fig. S5). Changes in CTCs at 6 to 8 weeks were not predictive because most patients had lower CTC counts. PD-L1 expression on CTCs was detected in 11 cases at baseline and in only one case at 6 to 8 weeks.

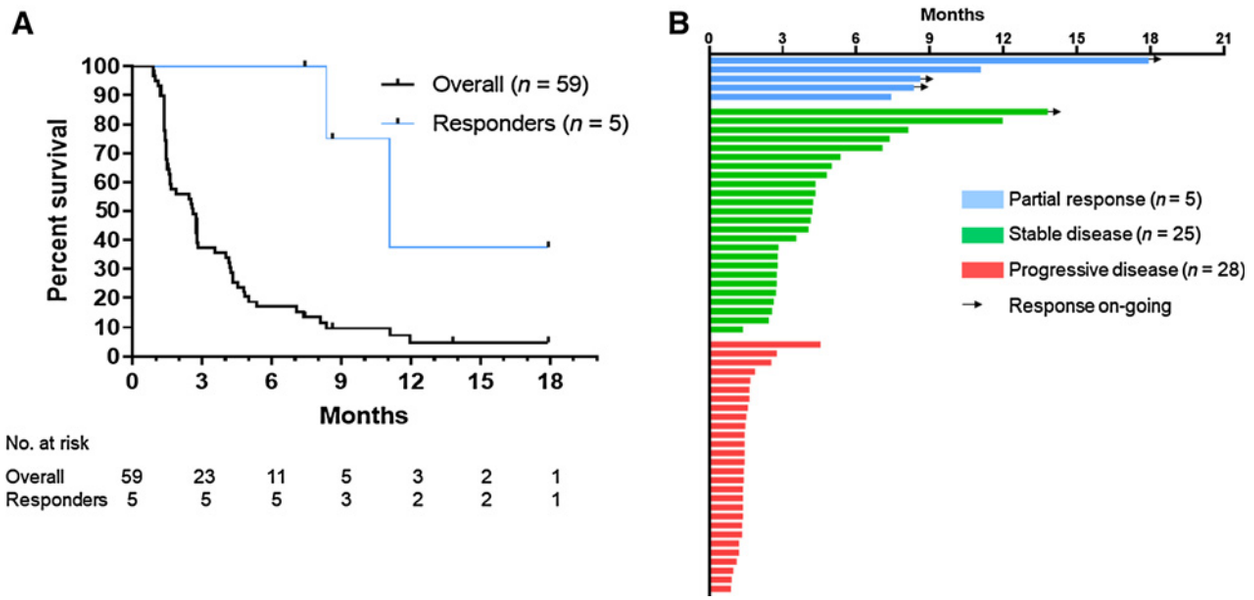

Figure 2.
Kaplan–Meier curves (**A**) of PFS among overall (black line, $n = 59$) and responders (blue line, $n = 5$) and Swimmer's plot (**B**).

Discussion

The rationale of retreatment is from the hypothesis that chemotherapy-sensitive tumor cells ultimately revive through drug-free interval (15) as clinically replicated in patients with small cell lung cancer (16). However, it has not been investigated whether ICI retreatment could show efficacy in patients who responded to prior ICI after ICI-free intervals.

Several studies already demonstrated the safety of ICI retreatment in patients with NSCLC even after the occurrence of irAEs (17, 18), however, its efficacy has not been properly assessed. A retrospective case series of 18 patients with NSCLC that included both ICI responders and nonresponders showed that retreatment with PD-L1 inhibitor was not effective (19). Meanwhile, a *post hoc* analysis of phase III studies revealed ORRs of 15% to 33% with pembrolizumab retreatment (2, 20). It should be noted that participants in the latter report were highly selective, as they were allowed to receive pembrolizumab retreatment only after they had completed two years of pembrolizumab. Such heterogeneity of patient population made it difficult to interpret these results.

Our key eligibility criteria mostly fulfilled with the aforementioned definition of acquired resistance to ICI (11): 70% of our patients had CR/PR with prior ICI, and the median ICI-free interval was 9.2 months. Given this point, our result suggested that retreatment with ICI is not a mainstay treatment even if prior ICI had shown response for a period of time. Subgroup analysis showed that patients with non-squamous histology, longer duration with prior ICI, longer ICI-free interval, or history of irAE tended to have longer PFS. Among these factors, multivariate analysis found that a longer ICI-free interval was the only predictor of improved PFS. Interestingly, as the ICI-free interval extended, PFS was significantly longer (**Fig. 3**). This study suggested

Table 2. Cox-proportional hazard regression analysis for PFS.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≤70/>70)	1.10 (0.64–1.87)	0.73		
Sex (male/female)	1.25 (0.69–2.29)	0.47		
Smoking history (yes/no)	1.55 (0.75–3.18)	0.23		
ECOG PS (0/1)	0.73 (0.42–1.28)	0.28		
Histology (non-Sq/Sq)	0.45 (0.25–0.81)	0.01	0.57 (0.31–1.05)	0.07
Stage (III, IV/recurrence)	1.35 (0.72–2.53)	0.35		
PD-L1 expression at diagnosis (<50%/≥50%)	1.24 (0.89–1.70)	0.59		
Response with prior ICI (CR, PR/SD ≥ 6 months)	0.85 (0.48–1.49)	0.56		
Duration of prior ICI (≤8.1 months/>8.1 months)	1.83 (1.02–3.30)	0.04	1.27 (0.68–2.38)	0.46
ICI-free interval (≤9.2 months/>9.2 months)	2.61 (1.47–4.64)	0.001	2.02 (1.10–3.73)	0.02
History of irAE with prior ICI (yes/no)	0.51 (0.28–0.91)	0.02	0.69 (0.37–1.29)	0.24

Abbreviations: Non-Sq, non-squamous; PS, performance status; Sq, squamous.

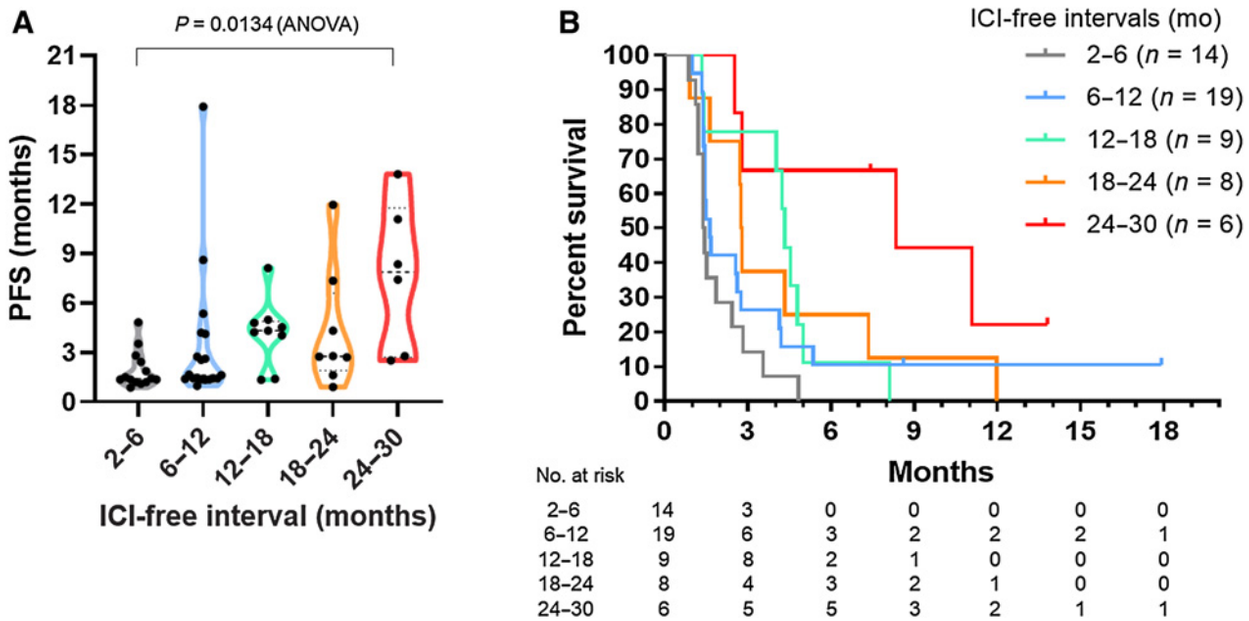

Figure 3.

Correlation between ICI-free interval and PFS with ICI rechallenge (**A**) and Kaplan–Meier curves (**B**) of PFS by ICI-free intervals. As we could not collect the exact date of finishing prior ICI in 3 patients, the total number in this figure is 56.

that sufficient ICI-free interval might provide a clue to achieve efficacy with ICI retreatment, however, the optimal duration is still unknown. Moreover, even though patients with ICI-free interval of 24 to 30 months had 8.4 months of median PFS, we could not deny the possibility that their tumor simply progressed slowly.

Despite our negative data, it was noteworthy that 5 patients had durable responses with ICI retreatment. These patients exhibited no distinct characteristics, but all of them had achieved PR with prior ICI and most had a relatively long ICI-free interval. To better understand their biological traits, we planned to collect tumor samples just before retreatment. However, it was difficult to obtain tissues from heavily treated patients. Alternatively, we also examined whether the number of CTCs at baseline of retreatment could be a possible predictor of response. Unfortunately, we could not extract useful information regarding CTC counts or PD-L1 expression therein.

This study had several limitations. First, its single-arm nature could not rule out selection bias. For example, prior treatment such as chemotherapy or radiotherapy may affect the result despite setting the appropriate interval before enrollment. However, regarding the 5 responders in this study, 3 did not receive any treatment after prior ICI. Although the other 2 completed chemotherapy 33 and 45 days before enrollment, it may not be unusual for the delayed efficacy of chemotherapy to persist for almost a year. Furthermore, it is more important that this was the first prospectively designed investigation with formal statistical calculation of power to evaluate the utility of ICI retreatment among patients with NSCLC. Second, the lack of independent radiological review could have influenced the efficacy data. However, antitumor activity is rarely underestimated because of this drawback.

In conclusion, even in patients who initially responded to prior ICI and had ICI-free interval, once resistance was acquired, retreatment with nivolumab had limited efficacy. Only a small proportion of patients achieved durable responses, thus identifying biomarkers that are predictive of favorable responses to ICI retreatment is warranted.

Authors' Disclosures

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Authors' Contributions

H. Akamatsu: Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, investigation, visualization, writing–original draft, project administration, writing–review and editing. **S. Teraoka:** Resources. **S. Takamori:** Resources, data curation. **S. Miura:** Resources, data curation. **H. Hayashi:** Resources, data curation. **A. Hata:** Resources, data curation. **Y. Toi:** Resources. **Y. Shiraishi:** Resources. **N. Mamesaya:** Resources. **Y. Sato:** Resources. **N. Furuya:** Resources, data curation. **J. Oyanagi:** Resources, formal analysis. **Y. Koh:** Data curation, formal analysis, supervision, writing–review and editing. **T. Misumi:** Formal analysis. **N. Yamamoto:** Conceptualization, data curation, supervision. **K. Nakagawa:** Supervision.

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Hiroaki Akamatsu, the principal investigator had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Rodríguez-Abreu D, Powell SF, Hochmair MJ, Gadgeel S, Esteban E, Felip E, et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. Ann Oncol 2021;32:881–95.
2. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non–small cell lung cancer with PD-L1 tumor proportion score ≥ 50%. J Clin Oncol 2021;39:2339–49.
3. Schoenfeld JD, Giobbie-Hurder A, Ranasinghe S, Kao KZ, Lako A, Tsuji J, et al. Durvalumab plus tremelimumab alone or in combination with low-dose or hypofractionated radiotherapy in metastatic non–small cell lung cancer refractory to previous PD(L)-1 therapy: an open-label, multicenter, randomized, phase II trial. Lancet Oncol 2022;23:279–91.
4. Calabro L, Rossi G, Morra A, Rosati C, Cutaia O, Daffina MG, et al. Tremelimumab plus durvalumab retreatment and 4-year outcomes in patients with mesothelioma: a follow-up of the open label, non-randomized, phase II NIBIT-MESO-1 study. Lancet Respir Med 2021;9:969–76.
5. Olson DJ, Eroglu Z, Brockstein B, Poklepovic AS, Bajaj M, Babu S, et al. Pembrolizumab plus ipilimumab following anti–PD-1/L1 failure in melanoma. J Clin Oncol 2021;39:2647–55.
6. Anagnostou V, Smith KN, Forde PM, Niknafs N, Bhattacharya R, White J, et al. Evolution of neoantigen landscape during immune checkpoint blockade in non–small cell lung cancer. Cancer Discov 2017;7:264–76.
7. George S, Miao D, Demetri GD, Adeegbe D, Rodig SJ, Shukla S, et al. Loss of PTEN is associated with resistance to anti–PD-1 checkpoint blockade therapy in metastatic uterine leiomyosarcoma. Immunity 2017;46:197–204.
8. Spranger S, Bao R, Gajewski TF. Melanoma-intrinsic β-catenin signaling prevents antitumor immunity. Nature 2015;523:231–5.
9. Ichihara E, Hotta K, Ninomiya K, Kubo T, Ohashi K, Rai K, et al. Re-administration of osimertinib in osimertinib-acquired resistant non–small cell lung cancer. Lung Cancer 2019;132:54–8.
10. Baize N, Monnet I, Greillier L, Geier M, Lena H, Janicot H, et al. Carboplatin plus etoposide versus topotecan as second-line treatment for patients with sensitive relapsed small-cell lung cancer: an open-label, multicenter, randomized, phase III trial. Lancet Oncol 2020;21:1224–33.
11. Schoenfeld AJ, Antonia SJ, Awad MM, Felip E, Gainor J, Gettinger SN, et al. Clinical definition of acquired resistance to immunotherapy in patients with metastatic non–small cell lung cancer. Ann Oncol 2021;32:1597–607.

12. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non–small cell lung cancer. N Engl J Med 2015;372:2018–28.
13. Juergens RA, Hao D, Ellis PM, Tu D, Mates M, Kollmannsberger C, et al. A phase IB study of durvalumab with or without tremelimumab and platinum-doublet chemotherapy in advanced solid tumors: Canadian Cancer Trials Group Study IND226. Lung Cancer 2020;143:1–11.
14. Koh Y, Yagi S, Akamatsu H, Kanai K, Hayata A, Tokudome N, et al. Heterogeneous expression of programmed death receptor-ligand 1 on circulating tumor cells in patients with lung cancer. Clin Lung Cancer 2019;20:270–7.
15. Gobbini E, Charles J, Toffart AC, Leccia MT, Moro-Sibilot D, Lervra MG. Current opinions in immune checkpoint inhibitors rechallenge in solid cancers. Crit Rev Oncol Hematol 2019;144:102816.
16. Giaccone G, Ferrati P, Donadio M, Testore F, Calciati A. Reinduction chemotherapy in small cell lung cancer. Eur J Cancer Clin Oncol 1987;23:1697–9.
17. Simonaggio A, Michot JM, Voisin AL, Le Pavec J, Collins M, Lallart A, et al. Evaluation of readministration of immune checkpoint inhibitors after immune-related adverse events in patients with cancer. JAMA Oncol 2019;5:1310–7.
18. Dolladille C, Ederhy S, Sassier M, Cautela J, Thuny F, Cohen AA, et al. Immune checkpoint inhibitor rechallenge after immune-related adverse events in patients with cancer. JAMA Oncol 2020;6:865–71.
19. Fujita K, Uchida N, Yamamoto Y, Kanai O, Okamura M, Nakatani K, et al. Retreatment with anti–PD-L1 antibody in advanced non–small cell lung cancer previously treated with anti–PD-1 antibodies. Anticancer Res 2019;39:3917–21.
20. Cho BC, Wu YL, Lopes G, Kudaba I, Kowalski DM, Turna HZ, et al. KEYNOTE-042 3-year survival update: 1L pembrolizumab vs platinum-based chemotherapy for PD-L1+ locally advanced/metastatic NSCLC. J Thorac Oncol 2021;16:S225–6.