Cancer Science

WILEY | JCA JAPANESE CANCER ASSOCIATION

ORIGINAL ARTICLE OPEN ACCESS

Clinical Research

Four-Year Outcomes for Nivolumab With Chemotherapy and Bevacizumab in Patients With Nonsquamous NSCLC in the TASUKI-52

Jong-Seok Lee[1] | Shunichi Sugawara[2] | Jin-Hyoung Kang[3] | Hye Ryun Kim[4] | Naoki Inui[5] | Toyoaki Hida[6] | Ki Hyeong Lee[7] | Tatsuya Yoshida[8] | Hiroshi Tanaka[9] | Cheng-Ta Yang[10] | Takako Inoue[11] | Makoto Nishio[12] | Yasushi Goto[8] | Tomohide Tamura[13] | Nobuyuki Yamamoto[14] | Chong-Jen Yu[15] | Hiroaki Akamatsu[14] | Shigeru Takahashi[16] | Kazuhiko Nakagawa[17]

[1]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do, South Korea | [2]Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Miyagi, Japan | [3]Department of Medical Oncology, The Catholic University of Korea Seoul St. Mary's Hospital, Seoul, South Korea | [4]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University, College of Medicine, Severance Hospital, Yonsei University Health System, Seoul, South Korea | [5]Department of Pulmonary Medicine, Hamamatsu University Hospital, Hamamatsu, Shizuoka, Japan | [6]Department of Thoracic Oncology, Aichi Cancer Center, Nagoya, Aichi, Japan | [7]Department of Internal Medicine, Chungbuk National University Hospital, Cheongju-si, Chungcheongbuk-do, South Korea | [8]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan | [9]Department of Internal Medicine, Niigata Cancer Center Hospital, Niigata, Japan | [10]Department of Thoracic Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan | [11]Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan | [12]Department of Thoracic Medical Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Koto-ku, Tokyo, Japan | [13]Thoracic Center, St. Luke's International Hospital, Tokyo, Japan | [14]Internal Medicine III, Wakayama Medical University, Wakayama, Wakayama, Japan | [15]Department of Internal Medicine, National Taiwan University Hospital Hsin-Chu Branch, Hsinchu City, Hsinchu County, Taiwan | [16]Oncology Clinical Development Planning 1, Ono Pharmaceutical Co., Ltd., Osaka, Japan | [17]Department of Medical Oncology, Kindai University Faculty of Medicine, Osakasayama, Osaka, Japan

Correspondence: Kazuhiko Nakagawa (nakagawa@med.kindai.ac.jp)

Received: 15 August 2025 | **Revised:** 5 January 2026 | **Accepted:** 13 January 2026

Keywords: bevacizumab | carboplatin | nivolumab | NSCLC | paclitaxel

ABSTRACT

In the Phase III TASUKI-52 trial, nivolumab with carboplatin, paclitaxel (CP), plus bevacizumab significantly prolonged progression-free survival (PFS), and resulted in longer overall survival (OS) in patients with advanced nonsquamous non-small cell lung cancer (NSCLC). This final analysis evaluated 4-year treatment outcomes in terms of OS, PFS and duration of response (DOR) by investigator assessment and safety, as well as the background characteristics and treatment courses associated with 4-year survivors. Patients were randomized 1:1 to receive nivolumab ($n = 275$) or placebo ($n = 275$) in addition to CP plus bevacizumab. With a minimum follow-up of 53.1 months, nivolumab with CP plus bevacizumab continued to show improvement in OS (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.58–0.88) and PFS (HR: 0.61; 95% CI: 0.50–0.74) compared to placebo with CP plus bevacizumab. The 4-year OS rate was 34.7% in the nivolumab arm versus 22.1% in the placebo arm, and the 4-year PFS rate was 13.7% in the nivolumab arm versus 3.3% in the placebo arm. Among 4-year survivors, the median DOR was numerically longer in the nivolumab arm than in the placebo arm (34.7 vs. 13.5 months). No new safety signals were observed. Four-year survival in the nivolumab arm was associated with the absence of bone metastases and age < 65, but not with PD-L1 status and tumor size. In conclusion, treatment with nivolumab demonstrated long-term

Abbreviations: ALK, anaplastic lymphoma kinase; CP, carboplatin plus paclitaxel; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; IRRC, independent radiology review committee; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; ROS1, c-ros oncogene 1; VEGF, vascular endothelial growth factor.

survival benefit and durable response, which supports nivolumab with CP plus bevacizumab as a first-line treatment option for advanced nonsquamous NSCLC.
Trial Registration: ClinicalTrials.gov identifier: NCT03117049

1 | Introduction

The TASUKI-52 trial is a randomized, double-blind, placebo-controlled phase III trial to evaluate nivolumab in combination with carboplatin, paclitaxel (CP) plus bevacizumab in treatment-naive patients with stage IIIB/IV or recurrent nonsquamous non-small cell lung cancer (NSCLC) who were unsuitable for definitive radiation therapy. In this trial, nivolumab with CP plus bevacizumab significantly prolonged progression-free survival (PFS), the primary endpoint, as assessed by an independent radiology review committee (IRRC) and tended to prolong overall survival (OS) compared to placebo with CP plus bevacizumab [1, 2]. On the basis of these results, nivolumab with CP and bevacizumab was approved as first-line treatment for *EGFR*/*ALK* mutation-negative advanced or recurrent nonsquamous NSCLC and has become a standard treatment option for advanced and recurrent nonsquamous NSCLC. The Japanese Lung Cancer Society Guidelines give this regimen a grade 1 recommendation, the strongest possible recommendation, equaling that of combination regimens comprising immune checkpoint inhibitors (ICIs) plus chemotherapy.

The 3-year outcomes of patients from TASUKI-52 revealed that the clinical benefits of the treatment were stably maintained, with 3-year PFS rates for nivolumab with CP plus bevacizumab versus placebo with CP plus bevacizumab of 20.2% versus 4.9% (hazard ratio [HR], 0.59) and 3-year OS rates of 44.2% versus 32.3% (HR: 0.71) [3]. These results provided the first evidence for following up patients with NSCLC receiving ICIs plus chemotherapy plus bevacizumab for periods exceeding 3 years. Treatments with ICIs, including the TASUKI-52 regimen, have improved the survival of NSCLC patients, which in turn has led to a renewed interest in the factors that contribute to long-term clinical benefit; however, the background factors associated with the long-term survival of patients receiving combination therapy of ICIs plus bevacizumab are yet to be clarified [3–7]. Additionally, it has not been determined how the initial tumor response, course of the disease, or subsequent treatments impact the long-term survival outcomes.

Here, we report 4-year treatment outcomes of patients who received nivolumab with CP plus bevacizumab. This report is the final update of the results from TASUKI-52. Additionally, we analyzed background characteristics, efficacy, and status of subsequent treatment in 4-year survivors.

2 | Materials and Methods

2.1 | Patients

The eligibility criteria were as follows: age ≥ 20 years, unsuitable for definitive radiation therapy, histologically or cytologically confirmed stage IIIB/IV or recurrent nonsquamous NSCLC, no history of prior systemic therapy for metastatic disease, at least one measurable lesion defined by the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1, and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1. Patients with sensitizing *EGFR*, *ALK*, or *ROS1* mutations were excluded.

2.2 | Study Design

TASUKI-52 is a multicenter, double-blinded, placebo-controlled randomized trial conducted at 135 sites in Japan, South Korea, and Taiwan. The study was registered in Japan Registry of Clinical Trials (jRCT2080223505).

The detailed study design was reported previously [1]. Between June 2017 and July 2019, a total of 550 patients were randomized 1:1 to either treatment with nivolumab with CP plus bevacizumab (the nivolumab combination) or treatment with placebo with CP plus bevacizumab (the placebo combination). The treatment was nivolumab 360 mg or placebo, in addition to paclitaxel 200 mg/m^2, carboplatin at an area under the curve of 6, and bevacizumab 15 mg/kg every 3 weeks for up to 6 cycles. After completing the cycles, patients were allowed to continue nivolumab or placebo (as randomized) and bevacizumab until any of the following occurred: progressive disease (PD) per RECIST v1.1, unacceptable toxicity, or withdrawal of consent. At randomization, patients were stratified by sex (male vs. female), ECOG PS (0 vs. 1), and tumor PD-L1 expression level (≥ 50% vs. 1%–49% vs. < 1%/indeterminate). Unblinding was permitted for patients whose overall response was determined as PD assessed by both investigators and IRRC, and the subsequent treatment was planned. Upon unblinding, patients in the placebo arm were allowed to receive nivolumab as subsequent treatment.

The study protocol was approved by the institutional review board or independent ethics committee at each site. This study was conducted in accordance with the International Council for Harmonization guideline for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from each participant.

2.3 | Assessment

This 4-year analysis was not prespecified in the statistical plan and was conducted post hoc. The primary endpoint was PFS assessed by IRRC; however, tumor assessments by IRRC were discontinued after the analysis performed at 3 years. Therefore, in the current analysis, we only examined PFS based on investigator assessment, which was one of the secondary endpoints. The other endpoints included OS, objective response rate (ORR), duration of response (DOR), and

TABLE 1 | Baseline characteristics of the ITT population.

	ITT	
	Nivolumab arm	**Placebo arm**
	***n* = 275**	***n* = 275**
Age, year, median (range)	66.0 (27–85)	66.0 (33–83)
< 65, *n* (%)	131 (47.6)	111 (40.4)
≥ 65, *n* (%)	144 (52.4)	164 (59.6)
Female, *n* (%)	70 (25.5)	69 (25.1)
ECOG PS, *n* (%)		
0	129 (46.9)	128 (46.5)
1	146 (53.1)	147 (53.5)
Smoking status, *n* (%)		
Current	196 (71.3)	200 (73.7)
Former	18 (6.5)	21 (7.6)
Never	61 (22.2)	54 (19.6)
Clinical stage[a], *n* (%)		
IIIB	15 (5.5)	14 (5.1)
IV	239 (86.9)	238 (86.5)
Recurrent	21 (7.6)	23 (8.4)
Country, *n* (%)		
Japan	188 (68.4)	183 (66.5)
South Korea	62 (22.5)	63 (22.9)
Taiwan	25 (9.1)	29 (10.5)
Tumor diameter, *n* (%)		
< 51 mm	83 (30.2)	87 (31.6)
51–< 80 mm	89 (32.4)	82 (29.8)
≥ 80 mm	84 (30.5)	93 (33.8)
Missing	19 (6.9)	13 (4.7)
Metastases, *n* (%)		
Bone	56 (20.4)	83 (30.2)
Liver	19 (6.9)	20 (7.3)
Brain	36 (13.1)	41 (14.9)
Number of metastatic organs[b], *n* (%)		
0	22 (8.0)	30 (10.9)
1	76 (27.6)	75 (27.3)
2	87 (31.6)	77 (28.0)
3 or more	90 (32.7)	93 (33.8)
Tumor PD-L1 expression, *n* (%)		
< 1% or indeterminate	120 (43.6)	120 (43.6)
1%–49%	82 (29.8)	81 (29.5)
≥ 50%	73 (26.5)	74 (26.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; PS, performance status.
[a]Clinical stage was classified according to the Union for International Cancer Control-TNM Classification of Malignant Tumors, 7th edition.
[b]The number of lung metastases was counted by lung site (right upper lobe, right middle lobe, right lower lobe, left upper lobe, left lower lobe, unknown, and other).

safety. Tumor response was evaluated every 6 weeks for the first 48 weeks and every 12 weeks thereafter until PD was confirmed by imaging. Safety was assessed based on the adverse events (AEs) that occurred until 100 days had elapsed from the final administration. The AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events ver. 4.0 [8].

2.4 | Statistical Analysis

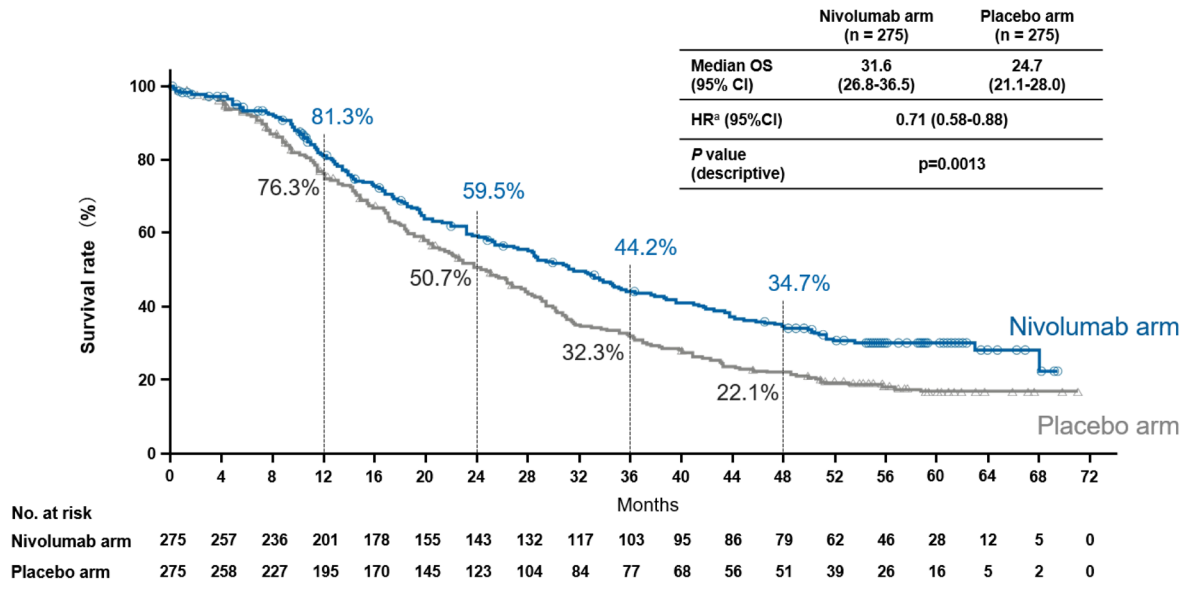
PFS and OS were assessed in the intention-to-treat (ITT) population, whereas safety was assessed in patients who received ≥ 1 dose of study treatment. Additionally, we examined PFS and DOR in subgroups of 4-year survivors and non-survivors. The Kaplan–Meier method was used to estimate PFS, OS, and DOR, and the Brookmeyer–Crowley method with double log transformation was used to calculate the corresponding 95% confidence intervals (CIs). A Cox proportional hazards model stratified by the randomization factors was used for calculating hazard ratios (HRs). To explore factors associated with long-term survival, the chi-square test was used to compare characteristics between 4-year survivors and non-survivors. All statistical analyses were performed using Statistical Analysis Software (ver. 9.4; SAS Institute, Cary, NC, USA).

3 | Results

3.1 | Patient Characteristics and Treatment Status

We enrolled 550 patients: 371 from Japan, 125 from South Korea, 54 from Taiwan, and randomly assigned them to either the nivolumab arm (*n* = 275) or placebo arm (*n* = 275). Of the 275 patients in the nivolumab arm, 273 received the assigned treatment, whereas all 275 patients in the placebo arm received the assigned treatment. The patient characteristics were well balanced between the arms (Table 1). As of the data cutoff on December 4, 2023, the minimum follow-up period was 53.1 months. Due to study completion, study treatment was discontinued in 17 patients in the nivolumab arm and 1 patient in the placebo arm.

a.



b.

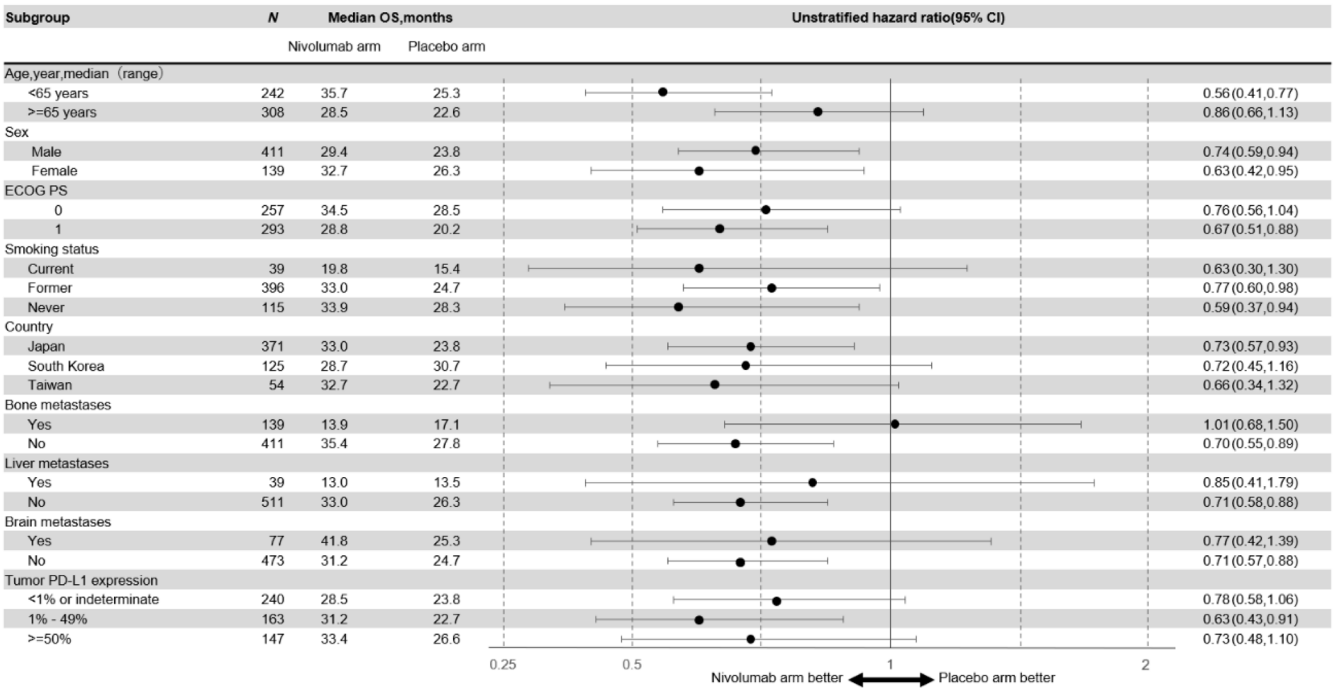


FIGURE 1 | Overall survival (OS). (a) Kaplan–Meier for OS of the intention-to-treat (ITT) population in the nivolumab and placebo arms. [a]Stratified hazard ratio (HR). (b) Forest plot of subgroup analysis for OS. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; PS, performance status.

3.2 | Efficacy

The nivolumab combination continuously demonstrated a survival benefit versus the placebo combination (hazard ratio [HR] 0.71; 95% CI: 0.58–0.88) (Figure 1a). The 4-year OS rates were 34.7% in the nivolumab arm and 22.1% in the placebo arm. The OS improved with a higher level of PD-L1 expression: the 4-year OS rates were 30.5% versus 21.1% (HR: 0.78; 95% CI: 0.58–1.06) for PD-L1 < 1% or indeterminate in the nivolumab versus placebo arms; 34.2% versus 18.9% (HR: 0.63; 95% CI: 0.43–0.91) for PD-L1 1%–49%; and 42.5% versus 27.6% (HR: 0.73; 95% CI 0.48–1.10) in those with PD-L1 ≥ 50% (Figure S1). Overall survival favored the nivolumab combination across subgroups by patient characteristics, except for those with bone metastases (Figure 1b).

PFS by investigator assessment favored the nivolumab combination over the placebo combination (HR: 0.61; 95% CI: 0.50–0.74), with a median PFS of 9.9 months versus 8.2 months

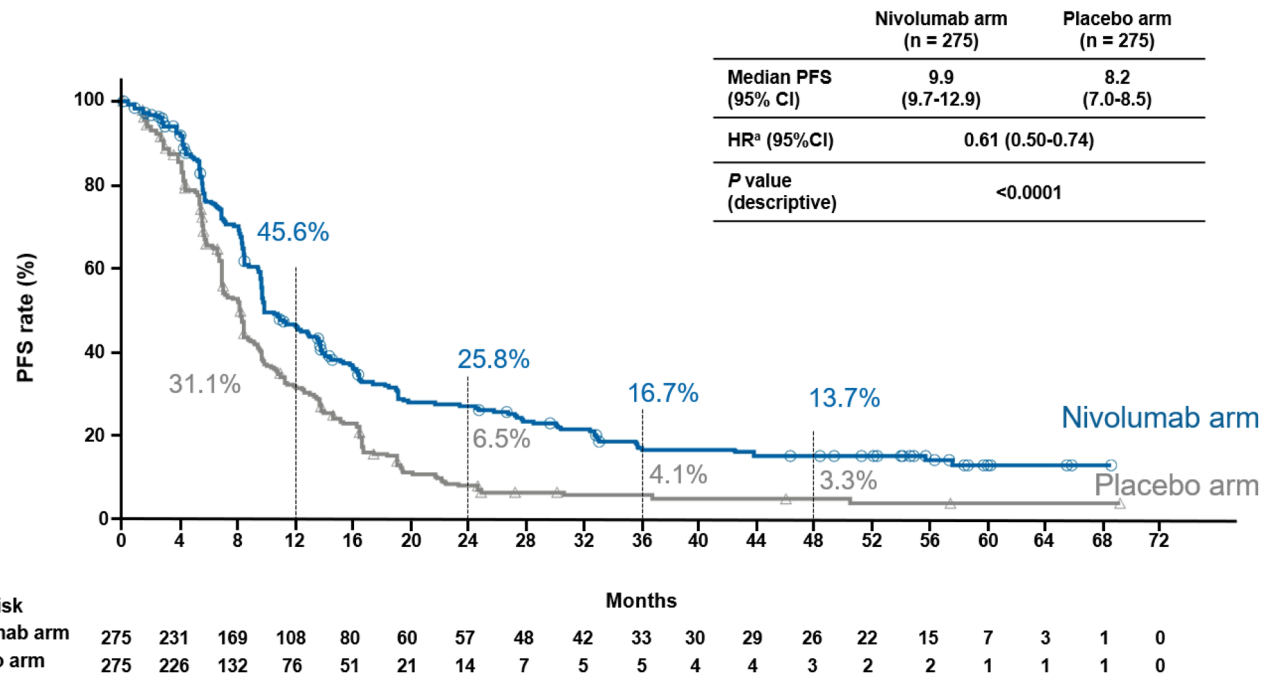


FIGURE 2 | Progression-free survival (PFS) by investigator assessment. Kaplan–Meier for PFS of the intention-to-treat (ITT) population in the nivolumab and placebo arms. [a]Stratified hazard ratio (HR). CI, confidence interval.

TABLE 2 | ORR, DOR, and PFS in the ITT population and 4-year survivors.

	ITT		4-year survivors	
	Nivolumab arm ($n=275$)	Placebo arm ($n=275$)	Nivolumab arm ($n=79$)	Placebo arm ($n=51$)
ORR, % (n)	67.3 (185)	55.6 (153)	87.3 (69)	78.4 (40)
95% CI	61.4–72.8	49.5–61.6	78.0–93.8	64.7–88.7
Median DOR, months	11.8	7.2	34.7	13.5
95% CI	8.6–13.7	6.7–8.5	22.2–54.0	8.0–20.7
4-year DOR rate, %	17.0	4.2	43.9	18.2
95% CI	11.8–23.1	1.6–8.8	31.6–55.4	7.6–32.4
Median PFS, months	9.9	8.2	30.4	15.0
95% CI	9.7–12.9	7.0–8.5	23.6–56.2	9.9–19.4
4-year PFS rate, %	13.7	3.3	39.4	14.6
95% CI	9.5–18.6	1.3–6.8	28.1–50.5	5.5–27.9

Abbreviations: CI, confidence interval; DOR; duration of treatment; ITT, intention-to-treat; ORR, objective response rate; PFS, progression-free survival.

(Figure 2). The 4-year PFS rates were 13.7% in the nivolumab arm and 3.3% for the placebo arm. The nivolumab combination extended the PFS regardless of PD-L1 expression: the 4-year PFS rates were 13.8% versus 4.9% (HR: 0.68; 95% CI: 0.51–0.91) for PD-L1 < 1% or indeterminate; 9.5% versus 1.8% (HR: 0.57; 95% CI: 0.40–0.81) for PD-L1 1%–49%; and 17.7% versus 2.7% (HR: 0.50; 95% CI: 0.34–0.72) for PD-L1 ≥ 50% (Figures S1, S2).

The ORR was 67.3% in the nivolumab arm and 55.6% in the placebo arm. In the ITT population, the median DOR and the proportion of patients with ongoing response at 4 years were 11.8 months and 17.0% with the nivolumab combination, respectively, and 7.2 months and 4.2% with the placebo combination, respectively (Table 2).

3.3 | Subsequent Therapies

In the ITT population, 62.2% of the nivolumab arm and 78.2% of the placebo arm received subsequent therapies (Table S1a). Systemic therapy was administered in 55.3% of the nivolumab

arm and 57.8% in the placebo arm. Note that the proportion of patients who received immunotherapy was higher in the placebo arm (51.3%) compared to the nivolumab arm (14.9%).

3.4 | Patient Characteristics, Efficacy, and Subsequent Therapies in 4-Year Survivors

A total of 79 patients in the nivolumab arm and 51 patients in the placebo arm survived for ≥4 years after treatment initiation (Table 3). We compared the baseline characteristics of 4-year survivors and non-survivors. In the nivolumab arm, the 4-year survivors included a higher proportion of patients aged <65 years and those with recurrent disease compared to the non-survivors. In the placebo arm, the 4-year survivors included a higher proportion of patients with ECOG PS 0 compared to the non-survivors, and non-survivors also included a higher proportion of patients with a large tumor diameter in the placebo arm. In both treatment arms, the 4-year survivors included a higher proportion of patients without bone metastasis and with fewer organ metastases than non-survivors in the respective arms.

Regarding efficacy in 4-year survivors, the median PFS was 30.4 months (95% CI: 23.6–56.2) in the nivolumab arm and 15.0 months (95% CI: 9.9–19.4) in the placebo arm (Table 2). The 4-year PFS rate was 39.4% (95% CI: 28.1–50.5) in the nivolumab arm and 14.6% (95% CI: 5.5–27.9) in the placebo arm. Among the 4-year survivors, more sustained responses were observed in the nivolumab arm compared to the placebo arm: the ORR was 87.3% (95% CI: 78.0–93.8) in the nivolumab arm and 78.4% (95% CI: 64.7–88.7) in the placebo arm; the median DOR was 34.7 months (95% CI: 22.2–54.0) in the nivolumab arm and 13.5 months (95% CI: 8.0–20.7) in the placebo arm. The proportion of patients with an ongoing response at 4 years was 43.9% (95% CI: 31.6–55.4) in the nivolumab arm and 18.2% (95% CI: 7.6–32.4) in the placebo arm (Table 2).

Regarding subsequent treatment, 58.2% (46 of 79 patients) of the 4-year survivors in the nivolumab arm and 88.2% (45 of 51 patients) of the 4-year survivors in the placebo arm received subsequent systemic treatment. Subsequent immunotherapy was administered to 64.7% (33 of 51 patients) of the 4-year survivors in the placebo arm. In the 4-year survivors in the nivolumab arm, 3 patients underwent surgery and 18 received radiation therapy, whereas in the placebo arm, 1 patient underwent surgery and 11 received radiation therapy (Tables S1b and S3).

The 4-year survivors in the nivolumab arm who received subsequent local treatment ($n=20$) included 15 patients who had achieved partial response (PR) and 2 patients who had achieved complete response (CR) under the study treatment (Figure S3a). The 4-year survivors in the placebo arm who received subsequent local treatment ($n=12$) included 9 patients who had achieved PR and 1 patient who had achieved CR under the study treatment (Figure S3b).

3.5 | Safety

In the nivolumab and placebo arms, Grade 3 and 4 treatment-related AEs (TRAEs) were observed in 76.2% and 74.9% of patients, respectively; serious TRAEs were observed in 45.4% and 27.3%, respectively; and TRAEs leading to death were observed in 2.2% and 1.5%, respectively (Table S2). We identified no new safety signals or TRAEs leading to death during this extended follow-up.

4 | Discussion

This is the final report from TASUKI-52 with 4 years of follow-up, which is the longest observational period in a Phase 3 trial of ICIs with chemotherapy and bevacizumab in NSCLC. The 4-year OS rates were 34.7% in the nivolumab arm and 22.1% in the placebo arm, which demonstrated continued OS improvement with the nivolumab combination. Durable PFS benefit by investigator assessment was also observed. During this extended follow-up, we identified no new safety signals or TRAEs leading to death.

The favorable 4-year OS results not only in the nivolumab arm but also in the placebo arm may be due to the current study setting in Asian countries. Results from previous global studies of ICIs combined with chemotherapy suggest generally longer survival is achieved in Asian populations than in populations from other regions [9–11]. Such ethnic differences in the survival rate were also identified in a meta-analysis of randomized controlled trials of chemotherapy in advanced NSCLC, whereas other factors such as differences in culture, socioeconomic status, or medical care environment may also influence the outcomes [9].

As an ICI plus bevacizumab combination regimen as first-line treatment for patients with NSCLC, atezolizumab with CP plus bevacizumab, studied in the global phase III IMpower150 trial, was reported [12]. As a notable difference between IMpower150 and TASUKI-52, IMpower150 allowed enrollment of patients with EGFR/ALK mutation positivity if patients had received prior TKI therapy, whereas TASUKI-52 excluded patients with EGFR/ALK mutation positivity. Median OS in IMpower150 was 19.2 months in the atezolizumab arm and 14.7 months in the placebo arm (HR: 0.78). Median OS in TASUKI-52 was 31.6 months in the nivolumab arm and 24.7 months in the placebo arm (HR: 0.78). The difference in median OS between these trials may result from differences in study design, such as eligibility for patients with EGFR/ALK mutation-positive NSCLC, prior TKI therapy, as well as differences in study regions.

In this study, although the high rate of immunotherapy as subsequent treatment in the placebo arm (51.3%) may have improved OS in the placebo arm, OS benefit was still observed in the nivolumab arm. The higher objective response and durable response of nivolumab with CP plus bevacizumab may contribute OS benefit for the nivolumab arm compared to the placebo arm. Similarly, the 5-year analysis of KEYNOTE-189 reported that the pembrolizumab arm showed continuously longer OS than the placebo arm, despite the rate of crossover to anti-PD-(L)1 therapy of 57.3% in the placebo arm [6].

The nivolumab combination demonstrated long-term PFS improvement as well as OS regardless of PD-L1 expression. VEGF

TABLE 3 | Baseline characteristics of the ITT population and 4-year survivors/non-survivors in the (a) nivolumab arm (b) placebo arm.

(a)

	Nivolumab arm			
	ITT, *n* = 275	**4-year survivors, *n* = 79**	**Non-4-year survivors, *n* = 196**	***p*[a]**
Age, year, median (range)	66.0 (27–85)	62.0 (34–78)	67.0 (27–85)	
< 65, *n* (%)	131 (47.6)	47 (59.5)	84 (42.9)	0.0161
≥ 65, *n* (%)	144 (52.4)	32 (40.5)	112 (57.1)	
Female, *n* (%)	70 (25.5)	19 (24.1)	51 (26.0)	0.7624
ECOG PS, *n* (%)				
0	129 (46.9)	44 (55.7)	85 (43.4)	0.0823
1	146 (53.1)	35 (44.3)	111 (56.6)	
Smoking status, *n* (%)				
Current	196 (71.3)	4 (5.1)	14 (7.1)	0.7603
Former	18 (6.5)	59 (74.7)	137 (69.9)	
Never	61 (22.2)	16 (20.3)	45 (23.0)	
Clinical stage[b], *n* (%)				
IIIB	15 (5.5)	6 (7.6)	9 (4.6)	0.0012
IV	239 (86.9)	60 (75.9)	179 (91.3)	
Recurrent	21 (7.6)	13 (16.5)	8 (4.1)	
Country, *n* (%)				
Japan	188 (68.4)	60 (75.9)	128 (65.3)	0.1635
South Korea	62 (22.5)	12 (15.2)	50 (25.5)	
Taiwan	25 (9.1)	7 (8.9)	18 (9.2)	
Tumor diameter, *n* (%)				
< 51 mm	83 (30.2)	27 (34.2)	56 (28.6)	0.8460
51–< 80 mm	89 (32.4)	26 (32.9)	63 (32.1)	
≥ 80 mm	84 (30.5)	24 (30.4)	60 (30.6)	
Missing	19 (6.9)	2 (2.5)	17 (8.7)	
Metastases, *n* (%)				
Bone	56 (20.4)	6 (7.6)	50 (25.5)	0.0008
Liver	19 (6.9)	3 (3.8)	16 (8.2)	0.2933
Brain	36 (13.1)	14 (17.7)	22 (11.2)	0.1679
Number of metastatic organs[c], *n* (%)				
0	22 (8.0)	12 (15.2)	10 (5.1)	0.0104
1	76 (27.6)	20 (25.3)	56 (28.6)	
2	87 (31.6)	29 (36.7)	58 (29.6)	
3 or more	90 (32.7)	18 (22.8)	72 (36.7)	

(Continues)

TABLE 3 | (Continued)

(a)

	Nivolumab arm			
	ITT, *n* = 275	**4-year survivors, *n* = 79**	**Non-4-year survivors, *n* = 196**	***p*[a]**
Tumor PD-L1 expression, *n* (%)				
< 1% or indeterminate	120 (43.6)	32 (40.5)	88 (44.9)	0.4994
1%–49%	82 (29.8)	22 (27.8)	60 (30.6)	
≥ 50%	73 (26.5)	25 (31.6)	48 (24.5)	

(b)

	Placebo arm			
	ITT *n* = 275	**4-year survivors *n* = 51**	**Non-4-year survivors *n* = 224**	***p*[a]**
Age, year, median (range)	66.0 (33–83)	69.0 (46–78)	66.0 (33–83)	
< 65, *n* (%)	111 (40.4)	15 (29.4)	96 (42.9)	0.0839
≥ 65, *n* (%)	164 (59.6)	36 (70.6)	128 (57.1)	
Female, *n* (%)	69 (25.1)	13 (25.5)	56 (25.0)	1.0000
ECOG PS, *n* (%)				
0	128 (46.5)	32 (62.7)	96 (42.9)	0.0126
1	147 (53.5)	19 (37.3)	128 (57.1)	
Smoking status, *n* (%)				
Current	200 (73.7)	2 (3.9)	19 (8.5)	0.5593
Former	21 (7.6)	40 (78.4)	160 (71.4)	
Never	54 (19.6)	9 (17.6)	45 (20.1)	
Clinical stage[b], *n* (%)				
IIIB	14 (5.1)	2 (3.9)	12 (5.4)	0.1219
IV	238 (86.5)	41 (80.4)	197 (87.9)	
Recurrent	23 (8.4)	8 (15.7)	15 (6.7)	
Country, *n* (%)				
Japan	183 (66.5)	38 (74.5)	145 (64.7)	0.4597
South Korea	63 (22.9)	9 (17.6)	54 (24.1)	
Taiwan	29 (10.5)	4 (7.8)	25 (11.2)	
Tumor diameter, *n* (%)				
< 51 mm	87 (31.6)	26 (51.0)	61 (27.2)	0.0048
51–< 80 mm	82 (29.8)	14 (27.5)	68 (30.4)	
≥ 80 mm	93 (33.8)	10 (19.6)	83 (37.1)	
Missing	13 (4.7)	1 (2.0)	12 (5.4)	
Metastases, *n* (%)				
Bone	83 (30.2)	8 (15.7)	75 (33.5)	0.0116
Liver	20 (7.3)	2 (3.9)	18 (8.0)	0.3871
Brain	41 (14.9)	11 (21.6)	30 (13.4)	0.1888
Number of metastatic organs[c], *n* (%)				

(Continues)

TABLE 3 | (Continued)

(b)

	Placebo arm			
	ITT $n=275$	**4-year survivors $n=51$**	**Non-4-year survivors $n=224$**	**p[a]**
0	30 (10.9)	10 (19.6)	20 (8.9)	0.0285
1	75 (27.3)	17 (33.3)	58 (25.9)	
2	77 (28.0)	14 (27.5)	63 (28.1)	
3 or more	93 (33.8)	10 (19.6)	83 (37.1)	
Tumor PD-L1 expression, *n* (%)				
< 1% or indeterminate	120 (43.6)	20 (39.2)	100 (44.6)	0.5209
1%–49%	81 (29.5)	14 (27.5)	67 (29.9)	
≥ 50%	74 (26.9)	17 (33.3)	57 (25.4)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; PS, performance status.
[a]Calculated by χ^2 test.
[b]Clinical stage was classified according to the Union for International Cancer Control-TNM Classification of Malignant Tumors, 7th edition.
[c]The number of lung metastases was counted by lung site (right upper lobe, right middle lobe, right lower lobe, left upper lobe, left lower lobe, unknown, and other).

inhibitors including bevacizumab are reported to hinder the formation of tumor vasculature, thereby promoting the infiltration of CD8-positive T cells into the tumor microenvironment [13–16]. Additionally, VEGF is known to inhibit the maturation of dendritic cells, which in turn suppresses T cell priming. By inhibiting VEGF, the maturation of T cells may be supported by enhancing the overall immune response against the tumor. In this study, the synergistic effect of bevacizumab and nivolumab on the cancer-immunity cycle might have positively affected the favorable PFS and OS results in the nivolumab arm.

In the 4-year survivors, a certain proportion of patients remain on treatment, and the higher ORR, rate of ongoing response, and PFS rate were observed in the nivolumab arm compared to the placebo arm. These results suggest that the durable response to the study treatment was the primary factor influencing the improvement in OS. The trend of a higher rate of durable response in long-term survivors treated with nivolumab was also observed in other cancer types [17–19]. Among 4-year survivors, 58.2% (46 of 79 patients) in the nivolumab arm and 88.2% (45 of 51 patients) in the placebo arm received subsequent anti-cancer therapy. In the 4-year survivors who received subsequent local treatment, the proportion of patients who achieved PR or CR was 85.0% (17 of 20 patients) in the nivolumab arm and 83.3% (10 of 12 patients) in the placebo arm. The proportion of patients who achieved PR or CR tended to be favorable in both arms. Furthermore, among the patients who received subsequent treatment, 43.5% of the patients received subsequent local treatment (radiotherapy, 39.1%; surgery, 6.5%; other, 2.2%) in the nivolumab arm, which was greater than that in the placebo arm, 26.7% (radiotherapy, 24.4%; surgery, 2.2%). As a result, the addition of nivolumab might have contributed to creating the opportunities for performing local treatment. Although the proportions of patients who achieved PR or CR in the 4-year survivors who received subsequent local treatment were similar between the nivolumab arm and the placebo arm, considering that the PFS, ORR, and rate of ongoing response among 4-year survivors were higher in the nivolumab arm than in the placebo arm, it is possible that a durable tumor response contributed to the opportunities for performing local treatment.

Previous reports suggest that bone metastases are a poor prognostic factor in NSCLC. Consistently, in this study, patients with bone metastases at baseline were more enriched in non-4-year survivors than in 4-year survivors and exhibited shorter OS than those without bone metastases, regardless of the treatment. Alteration in tumor microenvironment caused by bone metastases is thought to make NSCLC less responsive to ICIs [20–22]. Accordingly, ICIs combined with anti-VEGF effectively suppress disease progression in bone metastases but fail to improve PFS or OS in patients with NSCLC [23], suggesting that the add-on effect of ICIs to an anti-VEGF is limited to local disease control. Recently, a retrospective study demonstrated that patients with NSCLC exhibited longer OS when treated with ICIs combined with denosumab, anti-RANKL (receptor activator of nuclear factor-kB) antibody [24]. This promising effect of ICIs plus denosumab on NSCLC is now being evaluated in clinical trials: the DENIVOS study (NCT03669523) and the POPCORN study (ACTRN12618001121257). Due to the absence of comprehensive reports on the efficacy of ICIs combined with or without anti-VEGF therapy for NSCLC patients with bone metastases, further research is needed to reach a conclusive understanding.

The 4-year survivors in the nivolumab arm consisted of a higher proportion of younger patients (aged < 65 years). The relationship between the long-term efficacy of ICIs plus chemotherapy and age remains controversial, with some previous reports finding an association while others did not [12, 25, 26]. This inconsistency indicates the need for further research to clarify how age influences the effectiveness of additive ICIs.

Large tumor diameters are associated with a poor prognosis in NSCLC. However, previous studies involving combination therapy with ICIs and chemotherapy demonstrated favorable PFS regardless of tumor burden in the target lesion [27, 28]. In

agreement with these results, our analysis showed that in the nivolumab arm, among 4-year survivors and non-survivors there was no marked difference in the proportion of patients with different tumor diameters, whereas in the placebo arm, 4-year survivors included more patients with a smaller tumor diameter than non-survivors. Therefore, the survival benefit of the nivolumab combination regardless of the tumor size may be attributed to the common trait of combining ICIs with chemotherapy in counteracting the negative impact of tumor size on treatment outcomes.

This study enrolled only Asian patients, which limits the generalizability to other ethnic populations and is a major limitation of this study. As another limitation, the characteristics of 4-year survivors were analyzed for exploratory purposes only; therefore, the observed associations should be interpreted with caution. Efficacy comparisons between the nivolumab and placebo arms in 4-year survivors are subject to immortal time bias. The comparison of baseline characteristics between 4-year survivors and non-survivors may be affected by selection bias and confounding factors. Further research is needed to verify whether the patient characteristics identified in this analysis contribute to long-term survival.

In conclusion, during this extended follow-up of 53.1 months, the nivolumab combination continued to demonstrate long-term PFS and OS benefits in patients with advanced nonsquamous NSCLC, whereas no new safety signals were identified. The nivolumab arm showed favorable OS and PFS compared to the placebo arm regardless of the PD-L1 expression level. Among the 4-year survivors in the nivolumab arm, more patients experienced a sustained response compared to those in the placebo arm. These findings support nivolumab with CP plus bevacizumab as a first-line treatment option for advanced and recurrent nonsquamous NSCLC.

Author Contributions

Jong-Seok Lee: investigation, resources, writing – original draft, writing – review and editing. **Shunichi Sugawara:** investigation, resources, writing – review and editing. **Jin-Hyoung Kang:** investigation, resources, writing – review and editing. **Hye Ryun Kim:** conceptualization, investigation, methodology, resources, writing – review and editing. **Naoki Inui:** investigation, resources, writing – review and editing. **Toyoaki Hida:** investigation, resources, writing – review and editing. **Ki Hyeong Lee:** investigation, resources, writing – review and editing. **Tatsuya Yoshida:** investigation, resources, writing – review and editing. **Hiroshi Tanaka:** investigation, resources, writing – review and editing. **Cheng-Ta Yang:** investigation, resources, writing – review and editing. **Takako Inoue:** conceptualization, investigation, methodology, resources, writing – review and editing. **Makoto Nishio:** conceptualization, investigation, methodology, resources, writing – review and editing. **Yasushi Goto:** conceptualization, investigation, methodology, resources, writing – review and editing. **Tomohide Tamura:** conceptualization, investigation, methodology, resources, writing – review and editing. **Nobuyuki Yamamoto:** conceptualization, investigation, methodology, resources, writing – review and editing. **Chong-Jen Yu:** conceptualization, investigation, methodology, resources, writing – review and editing. **Hiroaki Akamatsu:** conceptualization, investigation, methodology, resources, writing – review and editing. **Shigeru Takahashi:** conceptualization, data curation, formal analysis, methodology, writing – original draft, writing – review and editing. **Kazuhiko Nakagawa:** conceptualization, investigation, methodology, project administration, resources, supervision, writing – original draft, writing – review and editing.

Acknowledgments

The authors thank all the participants, their families, and healthcare professionals who contributed to the study. Taihei Nishiyama, PhD from Ono Pharmaceutical Co. Ltd. provided medical writing support.

Funding

This study was funded by Ono Pharmaceutical Co. Ltd. and Bristol Myers Squibb (BMS).

Ethics Statement

The Institutional Review Board or Independent Ethics Committee at each study site approved the protocol and subsequent amendments. This study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines. The registration number of the study/trial: Japan Registry of Clinical Trials No. jRCT2080223505.

Consent

All patients provided written informed consent.

Conflicts of Interest

J.S.L. and C.-J.Y. has nothing to disclose. S.S. reported grants or contracts received by their institution from AnHeart Therapeutics, AstraZeneca, Chugai, MSD, Daiichi Sankyo, BMS, Nippon Boehringer Ingelheim, AbbVie, Amgen, Taiho, Accerise, A2 Healthcare, Parexel International, EPS, PPD-SNBL, and Syneos Health; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, Chugai, Ono, BMS, MSD, Nippon Boehringer Ingelheim, Pfizer, Taiho, Eli Lilly, Novartis, Kyowa Kirin, Takeda, Nippon Kayaku, Merck, Amgen, Thermo Fisher Scientific, Sysmex, and Eisai. J.-H.K. reported research funding received by their institution from Bayer; consulting fees from Janssen and Yuhan; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Roche, Bayer, and Boehringer Ingelheim; and support for attending meetings and/or travel from Boehringer Ingelheim; and participation on a data safety monitoring board or advisory board for Daiichi Sankyo. H.R.K. reported research funding received by their institution from Genentech/Roche, AstraZeneca, MSD, and Merck; and honoraria for lectures from AstraZeneca and Yuhan. N.I. reported grants or contracts from AstraZeneca and Boehringer Ingelheim; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Astra Zeneca, Chugai, Eli Lilly Japan, MSD, Ono, and Takeda. T.H. reported honoraria from Ono, BMS, Chugai, MSD, and AstraZeneca. K.H.L. reported research funding from Merck and consulting fees from BMS, MSD, Pfizer, AstraZeneca, Eli Lilly, Merck, Yuhan, Daiichi Sankyo, Boehringer Ingelheim, Johnson & Johnson/Janssen, Amgen, and Takeda. T.Y. reported grants or contracts from Novartis, AbbVie, Amgen, Daiichi Sankyo, AstraZeneca, MSD, Chugai, Astellas Pharma, Boehringer Ingelheim, BMS, Ono, and Merck Biopharma; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Novartis, Daiichi Sankyo, AstraZeneca, MSD, Chugai, BMS, Ono, Takeda, Pfizer, Eli Lilly, and Merck Biopharma; and participation on a data safety monitoring board or advisory board for Novartis, MSD, Amgen, Chugai, Daiichi Sankyo, Pfizer, and Boehringer Ingelheim. H.T. reported grants received by their institution from AstraZeneca, Chugai, MSD, Ono, BMS, Daiichi Sankyo, Eli Lilly, Takeda, Taiho, Merck, Boehringer Ingelheim, Amgen, and AbbVie; and honoraria for lectures from AstraZeneca, Chugai, MSD, Ono, BMS, Daiichi Sankyo, Eli Lilly, Takeda, Taiho,

Merck, Boehringer Ingelheim, Sun, Eisai, Novartis, Pfizer, and Celltrion. C.-T.Y. reported consulting fees for presentations from Boehringer Ingelheim, AstraZeneca, Ono, MSD, Roche, Eli Lilly, Merck, and Chugai. T.I. reported payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, BMS, Chugai, MSD, and Ono; and unpaid leadership or committee roles in the following organizations: academic committee member and safety committee vice chairperson of the Japan Society for Respiratory Endoscopy, and patient guideline subcommittee member of the Japan Lung Cancer Society. M.N. reported payment or honoraria for lectures from Ono, Chugai, Taiho, BMS, Daiichi Sankyo, Eli Lilly Japan, AstraZeneca, Merck/MSD, AbbVie, Takeda, Pfizer Japan, Boehringer Ingelheim, Novartis, Nippon Kayaku, Merck Biophama, and Janssen. Y.G. is an editorial board member of Cancer Science and reported grants or contracts received by their institution from IQVIA Services Japan, MSD, Astellas Pharma, AstraZeneca, AbbVie, Amgen, Syneos Health, Sysmex, CMIC, Novartis, Bayer, BMS, Medpace Japan, Janssen, Clinical Research Support Center Kyushu, SATOMI Clinical Research Project, Ono, Daiichi Sankyo, Takeda, Chugai, Thoracic Oncology Research Group, Eli Lilly Japan, and Preferred Networks; personal grants or contracts received from AstraZeneca, AbbVie, Eli Lilly, Pfizer, BMS, Ono, Novartis, Kyorin, Daiichi Sankyo, MSD, Guardant Health, and Preferred Networks; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Eli Lilly, Chugai, Taiho, Boehringer Ingelheim, Ono, BMS, Pfizer, MSD, Novartis, Merck, and Thermo Fisher Scientific; participation on a data safety monitoring board or advisory board for AstraZeneca, Chugai, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Taiho, Pfizer, Novartis, Kyorin, Guardant Health, Illumina, Daiichi Sankyo, Merck, MSD, Ono, and Janssen; and paid or unpaid leadership or fiduciary role in other board, society, committee or advocacy group for CancerNet Japan and Japanese Association of Medical Technologists. T.T. reported payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from CMIC Shift Zero, Chugai, and Eli Lilly. N.Y. reported grants or contracts received by their institution from A2 Healthcare, Amgen, AstraZeneca, Eli Lilly Japan, Mebix, AbbVie, Janssen, BMS, RPM, Pfizer R&D Japan, Chugai, MSD, Nippon Boehringer Ingelheim, PRiME-R, IQVIA Solutions Japan, Novartis Japan, EPS, Medpace Japan, and Syneos Health; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Amgen, AstraZeneca, Chugai, AbbVie, Janssen, Accuray Japan, Guardant Health Japan, Taiho Oncology, Tsumura & Co., Nippon Kayaku, Merck Biopharma, Otsuka, Miyarisan, Kyowa Kirin, MSD, Nippon Boehringer Ingelheim, Eli Lilly Japan, Novartis Japan, BMS, Ono, Daiichi Sankyo, Takeda, Terumo, Pfizer Japan, USACO, Kyorin, Medical Review, and Kowa; and payments or honoraria received by their institution for participation on a data safety monitoring board or advisory board for MSD, Amgen, Daiichi Sankyo, USACO, AstraZeneca, Ono, and Novartis Japan. C.-J.Y. has nothing to disclose. H.A. reported grants or contracts from Amgen, Chugai, and Novartis; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Amgen, AstraZeneca, Nippon Boehringer Ingelheim, BMS, Chugai, Eli Lilly Japan, MSD, Nippon Kayaku, Novartis, Ono, Pfizer, Takeda, Taiho, and Daiichi Sankyo; participation on a data safety monitoring board or advisory board for Amgen, Janssen, MSD, and Sandoz; and paid or unpaid leadership or committee role in the WCLC Patient Advocacy Committee. S.T. is an employee of Ono. K.N. reported grants or contracts received by their institution from IQVIA Services Japan, Syneos Health, EPS, Nippon Kayaku, Takeda, MSD, Amgen, Taiho, BMS, Janssen, CMIC, Pfizer R&D Japan, Labcorp Development Japan, Kobayashi, Pfizer Japan, AbbVie, Japan Clinical Cancer Research Organization, Eisai, EP-CRSU, Shionogi, Otsuka, GlaxoSmithKline, Sanofi, Chugai, Nippon Boehringer Ingelheim, SRL Medisearch, PRA Health Sciences, Astellas Pharma, Ascent Development Services, Eisai, Bayer, AstraZeneca, A2 Healthcare, and Thoracic Oncology Research Group; consulting fees from Ono and Eli Lilly Japan; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Ono, Daiichi Sankyo, AstraZeneca, Chugai, Eli Lilly Japan, MSD, Pfizer Japan, Nippon Boehringer Ingelheim, Incyte Biosciences Japan, Otsuka, Hisamitsu, Patientricity MedPartners, Merck Biopharma, Bayer, Novartis, BMS, Janssen, Taiho, Medical Mobile Communications, Yodosha, M3, Global Health Consulting Japan, The Yomiuri Shimbun, and 3H Medi Solution.

Data Availability Statement

Qualified researchers may request individual patient-level data from clinical studies conducted by Ono Pharmaceutical Co. Ltd. through Vivli (https://vivli.org/). For more information on Ono Pharmaceutical Co. Ltd.'s Global Policy for the Disclosure of Clinical Study Data, please visit the following website (https://www.ono-pharma.com/en/company/policies/clinical_trial_data_transparency_policy.html).

References

1. S. Sugawara, J. S. Lee, J. H. Kang, et al., "Nivolumab With Carboplatin, Paclitaxel, and Bevacizumab for First-Line Treatment of Advanced Nonsquamous Non-Small-Cell Lung Cancer," *Annals of Oncology* 32 (2021): 1137–1147, https://doi.org/10.1016/j.annonc.2021.06.004.

2. H. R. Kim, S. Sugawara, J. S. Lee, et al., "First-Line Nivolumab, Paclitaxel, Carboplatin, and Bevacizumab for Advanced Non-Squamous Non-Small Cell Lung Cancer: Updated Survival Analysis of the ONO-4538-52/TASUKI-52 Randomized Controlled Trial," *Cancer Medicine* 12 (2023): 17061–17067, https://doi.org/10.1002/cam4.6348.

3. K. H. Lee, J. S. Lee, S. Sugawara, et al., "First-Line Nivolumab Plus Platinum Chemotherapy and Bevacizumab for Advanced Nonsquamous Non-Small Cell Lung Cancer: A 3-Year Follow-Up of the Phase 3 Randomized TASUKI-52 Trial," *Lung Cancer* 201 (2025): 108109, https://doi.org/10.1016/j.lungcan.2025.108109.

4. M. Reck, T. E. Ciuleanu, M. Schenker, et al., "Five-Year Outcomes With First-Line Nivolumab Plus Ipilimumab With 2 Cycles of Chemotherapy Versus 4 Cycles of Chemotherapy Alone in Patients With Metastatic Non-Small Cell Lung Cancer in the Randomized CheckMate 9LA Trial," *European Journal of Cancer* 211 (2024): 114296, https://doi.org/10.1016/j.ejca.2024.114296.

5. J. R. Brahmer, J. S. Lee, T. E. Ciuleanu, et al., "Five-Year Survival Outcomes With Nivolumab Plus Ipilimumab Versus Chemotherapy as First-Line Treatment for Metastatic Non-Small-Cell Lung Cancer in CheckMate 227," *Journal of Clinical Oncology* 41 (2023): 1200–1212, https://doi.org/10.1200/JCO.22.01503.

6. M. C. Garassino, S. Gadgeel, G. Speranza, et al., "Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study," *Journal of Clinical Oncology* 41 (2023): 1992–1998, https://doi.org/10.1200/JCO.22.01989.

7. S. Novello, D. M. Kowalski, A. Luft, et al., "Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study," *Journal of Clinical Oncology* 41 (2023): 1999–2006, https://doi.org/10.1200/JCO.22.01990.

8. National Cancer Institute, "Common Terminology Criteria for Adverse Events (CTCAE) Version 6.0," (n.d.), https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40.

9. R. A. Soo, M. Loh, T. S. Mok, et al., "Ethnic Differences in Survival Outcome in Patients With Advanced Stage Non-Small Cell Lung Cancer: Results of a Meta-Analysis of Randomized Controlled Trials," *Journal of Thoracic Oncology* 6 (2011): 1030–1038, https://doi.org/10.1097/JTO.0b013e3182199c03.

10. M. Nishio, H. Saito, K. Goto, et al., "IMpower132: Atezolizumab Plus Platinum-Based Chemotherapy vs Chemotherapy for Advanced NSCLC in Japanese Patients," *Cancer Science* 112 (2021): 1534–1544, https://doi.org/10.1111/cas.14817.

11. T. John, H. Sakai, S. Ikeda, et al., "First-Line Nivolumab Plus Ipilimumab Combined With Two Cycles of Chemotherapy in Advanced Non-Small Cell Lung Cancer: A Subanalysis of Asian Patients in CheckMate 9LA," *International Journal of Clinical Oncology* 27 (2022): 695–706, https://doi.org/10.1007/s10147-022-02120-0.

12. M. A. Socinski, R. M. Jotte, F. Cappuzzo, et al., "Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC," *New England Journal of Medicine* 378 (2018): 2288–2301, https://doi.org/10.1056/NEJMoa1716948.

13. S. P. Hack, A. X. Zhu, and Y. Wang, "Augmenting Anticancer Immunity Through Combined Targeting of Angiogenic and PD-1/PD-L1 Pathways: Challenges and Opportunities," *Frontiers in Immunology* 11 (2020): 598877, https://doi.org/10.3389/fimmu.2020.598877.

14. S. A. Patel, M. B. Nilsson, X. Le, T. Cascone, R. K. Jain, and J. V. Heymach, "Molecular Mechanisms and Future Implications of VEGF/VEGFR in Cancer Therapy," *Clinical Cancer Research* 29 (2023): 30–39, https://doi.org/10.1158/1078-0432.CCR-22-1366.

15. Q. X. Lin, W. W. Song, W. X. Xie, et al., "Sequential Treatment of Anti-PD-L1 Therapy Prior to Anti-VEGFR2 Therapy Contributes to More Significant Clinical Benefits in Non-Small Cell Lung Cancer," *Neoplasia* 59 (2025): 101077, https://doi.org/10.1016/j.neo.2024.101077.

16. Y. Zhao, S. Guo, J. Deng, et al., "VEGF/VEGFR-Targeted Therapy and Immunotherapy in Non-Small Cell Lung Cancer: Targeting the Tumor Microenvironment," *International Journal of Biological Sciences* 18 (2022): 3845–3858, https://doi.org/10.7150/ijbs.70958.

17. R. J. Motzer, T. Powles, M. Burotto, et al., "Nivolumab Plus Cabozantinib Versus Sunitinib in First-Line Treatment for Advanced Renal Cell Carcinoma (CheckMate 9ER): Long-Term Follow-Up Results From an Open-Label, Randomised, Phase 3 Trial," *Lancet Oncology* 23 (2022): 888–898, https://doi.org/10.1016/S1470-2045(22)00290-X.

18. N. Boku, T. Omori, K. Shitara, et al., "Nivolumab Plus Chemotherapy in Patients With HER2-Negative, Previously Untreated, Unresectable, Advanced, or Recurrent Gastric/Gastroesophageal Junction Cancer: 3-Year Follow-Up of the ATTRACTION-4 Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial," *Gastric Cancer* 27 (2024): 1287–1301, https://doi.org/10.1007/s10120-024-01535-0.

19. K. Kato, Y. Doki, I. Chau, et al., "Nivolumab Plus Chemotherapy or Ipilimumab Versus Chemotherapy in Patients With Advanced Esophageal Squamous Cell Carcinoma (CheckMate 648): 29-Month Follow-Up From a Randomized, Open-Label, Phase III Trial," *Cancer Medicine* 13 (2024): e7235, https://doi.org/10.1002/cam4.7235.

20. M. Riihimäki, A. Hemminki, M. Fallah, et al., "Metastatic Sites and Survival in Lung Cancer," *Lung Cancer* 86 (2014): 78–84, https://doi.org/10.1016/j.lungcan.2014.07.020.

21. S. Vicent, N. Perurena, R. Govindan, and F. Lecanda, "Bone Metastases in Lung Cancer. Potential Novel Approaches to Therapy," *American Journal of Respiratory and Critical Care Medicine* 192 (2015): 799–809, https://doi.org/10.1164/rccm.201503-0440SO.

22. A. Del Conte, E. De Carlo, E. Bertoli, et al., "Bone Metastasis and Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer (NSCLC): Microenvironment and Possible Clinical Implications," *International Journal of Molecular Sciences* 23 (2022): 6832, https://doi.org/10.3390/ijms23126832.

23. X. Xie, M. Zhou, L. Wang, et al., "Effects of Combining Immune Checkpoint Inhibitors and Anti-Angiogenic Agents on Bone Metastasis in Non-Small Cell Lung Cancer Patients," *Human Vaccines & Immunotherapeutics* 19 (2023): 2241310, https://doi.org/10.1080/21645515.2023.2241310.

24. Y. Asano, N. Yamamoto, S. Demura, et al., "Combination Therapy With Immune Checkpoint Inhibitors and Denosumab Improves Clinical Outcomes in Non-Small Cell Lung Cancer With Bone Metastases," *Lung Cancer* 193 (2024): 107858, https://doi.org/10.1016/j.lungcan.2024.107858.

25. J. Zhang, L. Zhao, H. Li, Y. Jia, and F. Kong, "Immunosenescence and Immunotherapy in Older NSCLC Patients," *Journal of Cancer Research and Therapeutics* 20 (2024): 9–16, https://doi.org/10.4103/jcrt.jcrt_1523_23.

26. K. Okishio, R. Morita, J. Shimizu, et al., "Nivolumab Treatment of Elderly Japanese Patients With Non-Small Cell Lung Cancer: Subanalysis of a Real-World Retrospective Observational Study (CA209-9CR)," *ESMO Open* 5 (2020): e000656, https://doi.org/10.1136/esmoopen-2019-000656.

27. Y. Uehara, T. Hakozaki, R. Kitadai, et al., "Association Between the Baseline Tumor Size and Outcomes of Patients With Non-Small Cell Lung Cancer Treated With First-Line Immune Checkpoint Inhibitor Monotherapy or in Combination With Chemotherapy," *Translational Lung Cancer Research* 11 (2022): 135–149, https://doi.org/10.21037/tlcr-21-815.

28. S. Gadgeel, J. E. Gray, M. T. Rizzo, P. Peterson, J. S. Kim, and D. Rodríguez-Abreu, "Pemetrexed and Platinum Plus Pembrolizumab in Patients With Metastatic Nonsquamous NSCLC by Tumor Burden at Baseline: A Post Hoc Efficacy Analysis of KEYNOTE-189," *JTO Clinical and Research Reports* 3 (2022): 100389, https://doi.org/10.1016/j.jtocrr.2022.100389.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Overall survival (OS) according to the PD-L1 expression status. **Figure S2:** Progression free survival (PFS) according to the PD-L1 expression status. **Figure S3:** Swimmer plot of 4-year survivors who received local treatment, representing treatment-free period, discontinuations, BOR, and subsequent therapy. **Table S1:** Subsequent therapies. **Table S2:** Treatment-related adverse events (TRAEs). **Table S3:** Types of subsequent therapies administered to 4-year survivors.