Phase II Study of Durvalumab Immediately after Completion of Chemoradiotherapy in Unresectable Stage III Non–small Cell Lung Cancer: TORG1937 (DATE Study)

Shinji Nakamichi[1], Kaoru Kubota[1], Toshihiro Misumi[2], Tetsuro Kondo[3], Shuji Murakami[3], Yoshimasa Shiraishi[4], Hisao Imai[5,6], Daijiro Harada[7], Kazutoshi Isobe[8], Hidetoshi Itani[9], Saori Takata[10], Hiroshi Wakui[11], Yuki Misumi[12], Satoshi Ikeda[13], Tetsuhiko Asao[14], Naoki Furuya[15], Shinobu Hosokawa[16], Yumiko Kobayashi[17], Yuichi Takiguchi[18], and Hiroaki Okamoto[12]

ABSTRACT

Purpose: Concurrent chemoradiotherapy (CCRT) followed by durvalumab consolidation for up to 12 months is the standard of care for patients with unresectable stage III non–small cell lung cancer (NSCLC). However, exactly when to initiate durvalumab therapy after chemoradiation completion remains unknown. We evaluated the efficacy and safety of durvalumab, administered immediately after CCRT completion, for patients with unresectable stage III NSCLC.

Patients and Methods: This study was a prospective, single-arm, open-label phase II clinical trial. Patients without disease progression after definitive CCRT (two cycles of platinum-based doublet chemotherapy with 60 Gy/30 Fr radiotherapy) received durvalumab (every 2 weeks for up to 12 months) from the next day (up to 5 days) after the final radiation dose. The primary endpoint was the 1-year progression-free survival (PFS) from registration before the start of CCRT.

Results: From January 2020 to August 2020, 47 of 50 enrolled patients were evaluable for treatment efficacy and safety. The 1-year PFS from registration was 75.0% [60% confidence interval (CI), 69.0–80.0 and 95% CI, 59.4–85.3]. The objective response rate throughout the study treatment and median PFS from registration were 78.7% and 14.2 months (95% CI, 13.4 to not reached), respectively. Grade 3/4 pneumonitis and febrile neutropenia were each 4.3%.

Conclusions: Our study met the primary endpoint. The incidence of pneumonitis was similar to that of a Japanese subset in the PACIFIC study. Our data support the efficacy and safety of durvalumab administered immediately after the completion of CCRT for patients with unresectable stage III NSCLC.

Introduction

Lung cancer is a leading cause of cancer-related deaths (1). Non–small cell lung cancer (NSCLC) accounts for 85% of all lung cancer histologies (2) and about 25% of NSCLC is stage III disease (3). Concurrent chemoradiotherapy (CCRT) followed by durvalumab consolidation therapy for up to 12 months is the standard of care for patients with unresectable stage III NSCLC according to the results of the PACIFIC study (4, 5). In the study, randomization to durvalumab or placebo occurred within 1 to 42 days after completion of the last radiation dose. Although the best time for starting durvalumab after the completion of chemoradiation has not been identified, progression-free survival (PFS) and overall survival (OS) were better in the subgroup of patients administered durvalumab within 14 days after the last radiation to randomization (PFS: HR 0.39, OS: HR 0.42; refs. 4, 5).

Several preclinical studies have shown synergistic activity of radiation and immunotherapy. Deng and colleagues demonstrated radiation and anti-programmed cell death ligand 1 (PD-L1) treatment synergistically promoted antitumor immunity in mice (6). Dovedi and colleagues also showed the improved survival outcome of anti–PD-L1 antibody with fractionated radiotherapy in mice with a colon cancer cell line transplant and suggested scheduling of anti–PD-L1 antibody with radiotherapy was a significant factor for an antitumor immune response (7).

[1]Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan. [2]Department of Biostatistics, Yokohama City University School of Medicine, Yokohama, Japan. [3]Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan. [4]Department of Respiratory Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan. [5]Division of Respiratory Medicine, Gunma Prefectural Cancer Center, Ota, Japan. [6]Department of Respiratory Medicine, International Medical Center, Saitama Medical University, Saitama, Japan. [7]Department of Thoracic Oncology and Medicine, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan. [8]Department of Respiratory Medicine, Toho University Omori Medical Center, Tokyo, Japan. [9]Department of Respiratory Medicine, Japanese Red Cross Ise Hospital, Ise, Japan. [10]Department of Respiratory Medicine, Kyorin University School of Medicine, Tokyo, Japan. [11]Division of Respiratory Diseases, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan. [12]Department of Respiratory Medicine and Medical Oncology, Yokohama Municipal Citizen's Hospital, Yokohama, Japan. [13]Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan. [14]Department of Respiratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan. [15]Department of Internal Medicine, Division of Respiratory Medicine, St. Marianna University School of Medicine, Kawasaki, Japan. [16]Department of Respiratory Medicine, Japanese Red Cross Okayama Hospital, Okayama, Japan. [17]Department of Pulmonary Medicine, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan. [18]Department of Medical Oncology, Graduate School of Medicine, Chiba University, Chiba, Japan.

Corresponding Author: Kaoru Kubota, Graduate School of Medicine, Nippon Medical School, 1-1-5, Sendagi, Tokyo 113-8603, Japan. E-mail: kkubota@nms.ac.jp

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Translational Relevance

Concurrent chemoradiotherapy (CCRT) followed by durvalumab consolidation for up to 12 months is the standard of care for patients with unresectable stage III non–small cell lung cancer (NSCLC) according to the PACIFIC study results. However, the best time for starting durvalumab has not been identified. We conducted the first prospective phase II study to evaluate the efficacy and safety of durvalumab immediately after concurrent CCRT completion in patients with unresectable stage III NSCLC. The 1-year progression-free survival from registration was 75.0%, which met the primary endpoint. The incidence of grade 3/4 pneumonitis (4.3%) was similar with reference to a Japanese subset in the PACIFIC study. Our data support the efficacy and safety of durvalumab administered immediately after the completion of CCRT for patients with unresectable stage III NSCLC.

The simultaneous combination of radiotherapy and immunotherapy is concerning from a safety viewpoint, although it is a promising method (8). We considered it important to administer durvalumab immediately after the last radiation for possible maximum efficacy. Therefore, we, the Thoracic Oncology Research Group (TORG), conducted a prospective, single-arm, phase II study (TORG1937/-DATE study) to evaluate the efficacy and safety of durvalumab treatment immediately after the completion of chemoradiotherapy for unresectable stage III NSCLC. Here, we report the results of the primary analysis.

Patients and Methods

Patients

Patients were eligible for this study if they had histologically or cytologically confirmed unresectable stage III NSCLC according to the Staging Manual in Thoracic Oncology, version 8 of the International Association for the Study of Lung Cancer. Other inclusion criteria were being female and male between 20 and 74 years of age, previously untreated, a measurable lesion according to RECIST version 1.1 (RECIST 1.1), the ability to receive definitive thoracic radiotherapy (TRT) with lung volume received at least 20 Gy ($V20_{Gy}$) under 35%, Eastern Cooperative Oncology Group performance status (PS) 0 or 1, and adequate organ function. Patients with definitive interstitial pneumonia, autoimmune disease, or continuous systemic administration of steroids (corticosteroids 10 mg or more) were excluded.

All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Study procedures were approved by the Institutional Review Board at each institution. This study is registered with the Japan Registry of Clinical Trials (jRCTs031190117).

Study design and treatments

This phase II, prospective, single-arm, open-label, multicenter study was conducted at 16 institutions in Japan. Enrolled patients received the protocol treatment consisting of CCRT with two cycles of platinum-based chemotherapy and TRT (60 Gy/30 Fr) followed by durvalumab consolidation therapy from the next day after the last radiation dose for up to 12 months.

Chemotherapy consisted of one of the following regimens chosen by investigators: (i) cisplatin (CDDP; 60 mg/m^2 i.v. on day 1) and twice-daily oral S-1 [according to body surface area (BSA) as follows: BSA <1.25 m^2, 80 mg per day; BSA 1.25 m^2 to <1.50 m^2, 100 mg per day; and BSA 1.5 m^2 or higher, 120 mg per day on days 1–14] of each 4-week cycle, (ii) CDDP (80 mg/m^2 i.v. on day 1) and vinorelbine (VNR; 20 mg/m^2 i.v. on days 1 and 8) of each 3- or 4-week cycle, (iii) CDDP (40 mg/m^2 i.v. on days 1 and 8) and docetaxel (DTX; 40 mg/m^2 i.v. on days 1 and 8) of each 3- or 4-week cycle, (iv) CDDP (80 mg/m^2 i.v. on day 1) and DTX (50 mg/m^2 i.v. on day 1) of each 3- or 4-week cycle, or (v) carboplatin (CBDCA) [area under the concentration–time curve (AUC) 2 mg/mL·min i.v. on days 1, 8, and 15] and paclitaxel (PTX; 40 mg/m^2 on days 1, 8, and 15) of each 3-week cycle (9, 10, 11, 12).

A total of 60 Gy TRT was given 5 days per week in 2-Gy fractions daily over 6 weeks by use of 6–10 MV X-rays from day 1. It was recommended to utilize image-guided radiotherapy. Volume definition and procedures in the radiotherapy plan are shown in Supplementary Table S1. Three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) were allowed. Prophylactic mediastinal irradiation was not necessary in this protocol.

When the efficacy of CCRT was evaluated as a complete response (CR), partial response (PR), or stable disease (SD), in accordance with RECIST 1.1, durvalumab consolidation therapy at a dose of 10 mg per kilogram of body weight via intravenous route every 2 weeks for up to 12 months was administered from the next day (up to 5 days) of the last radiation dose.

The protocol treatment was continued until the completion of durvalumab consolidation therapy for 12 months, confirmed progressive disease (PD), adverse events (AE) that make it difficult to continue treatment, withdrawal of consent, or death. The follow-up period from registration closure was determined as 1 year.

Assessments

All patients who were eligible according to the protocol were evaluated for efficacy and safety. Chest X-rays, blood counts, and blood biochemical tests were performed regularly over every course during the treatment period. Chest CT was performed at the end of CCRT before the start of durvalumab therapy to evaluate the efficacy and pneumonitis. Subsequent chest CT was performed every 8 weeks until PD. Tumor responses were evaluated per RECIST 1.1. by the Independent Review Committee (IRC) and investigators until PD. The PFS was defined as the time from registration or start of durvalumab therapy until disease progression, death, or last known follow-up. The OS was defined as the time from registration or start of durvalumab therapy until death from any cause. AEs were graded according to the NCI Common Terminology Criteria for Adverse Events (version 5.0).

Statistical analysis

Patients who violated eligibility or conformance were removed from the full analysis set (FAS). The efficacy and safety analysis set included all patients who received one or more protocol treatments in the FAS. The primary endpoint was the IRC-assessed 1-year PFS rate from registration before the start of CCRT.

The proportion of patients alive and progression-free at 1 year in the durvalumab group of the PACIFIC trial was 55.9% from the randomization of durvalumab or placebo therapy. To consider the 2-month period from primary registration to the start of durvalumab, the 1-year PFS rate is assumed to be 50%. The expected value of a 1-year PFS rate was chosen to be 63% in this study. Under conditions of one-sided α 20%, power 80%, the 1.5-year accrual period and a year follow-up from registration closure, the Southwest Oncology Group (SWOG) statistical tools (13) would require

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42 patients. The sample size was set at 47 patients, considering inappropriate and dropout cases.

We also evaluated safety, the objective response rate (ORR), 1-year PFS from the start of durvalumab therapy, PFS, 2-year PFS rate, 1-year and 2-year OS, and OS from registration and the start of durvalumab as secondary endpoints. Exploratory analysis was the efficacy by PD-L1 expression (IHC, 22C3) using a tumor proportion score, especially in patients with less than 1% PD-L1–positive tumor cells. Survival curves for PFS and OS were estimated by using the Kaplan–Meier method. The confidence interval (CI) was calculated using the Greenwood formula and a Brookmeyer–Crowley method. All statistical analyses were performed using SAS version 9.4.

Data availability statement

The data generated in this study are not publicly available due to information that could compromise patient privacy or consent but are available upon reasonable request from the corresponding author.

Results

Patients' characteristics

From January 2020 to August 2020, 50 patients were enrolled from 16 institutions as shown in Supplementary Fig. S1. The treatment of 47 patients was evaluable for efficacy and safety. A patient became ineligible because of the violation of eligibility. Two patients were also excluded because of non-conformance due to a change in treatment to surgical therapy. Forty-two patients (89%) received durvalumab consolidation therapy. Five patients did not receive durvalumab consolidation because of severe COVID-19 pneumonia, grade 2 pneumonitis with grade 3 febrile neutropenia (FN), a decrease in the unrecovered platelet count, a radiation pause over 14 days due to unrecovered grade 2 pneumonitis, and unrecovered myelosuppression with suspected multiple myeloma. Patients' characteristics are shown in **Table 1** and the representativeness of study participants is shown in Supplementary Table S2. Supplementary Table S3 is also shown to compare the background between this study and the PACIFIC study.

Table 1. Patients' characteristics.

	***n* = 47**	**(%)**
Sex		
Male	41	(87.2)
Female	6	(12.8)
Age (years)		
Median (range)	65	(42–74)
cStage		
IIIA	19	(40.4)
IIIB	21	(44.7)
IIIC	7	(14.9)
Smoking		
Current	24	(51.1)
Past	17	(36.2)
Never	6	(12.8)
PS		
0	28	(59.6)
1	19	(40.4)
Histology		
Adenocarcinoma	27	(57.4)
Squamous cell carcinoma	15	(31.9)
Adenosquamous carcinoma	1	(2.1)
Others	4	(8.5)
PD-L1 (22C3) expression		
≥50%	19	(40.4)
1%–49%	11	(23.4)
<1%	10	(21.3)
Unknown	7	(14.9)
EGFR mutation		
Negative	29	(61.7)
Positive	3	(6.4)
Unknown	15	(31.9)
ALK fusion		
Negative	25	(53.2)
Positive	5	(10.6)
Unknown	17	(36.2)

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; PS, performance status.

Treatment delivery and efficacy

The details of treatment delivery are summarized in Supplementary Table S4. The median time from registration to the start of CCRT was 1 day (0–13 days). Regarding the chemotherapy regimen, 44.7%, 27.7%, 19.1%, and 8.5% of patients received CDDP+VNR, CBDCA+PTX, CDDP+DTX, and CDDP+S-1, respectively. A total of 60 Gy radiotherapy was completed in 93.7% of patients. The radiotherapy techniques used were 68.1% 3D-CRT, 23.4% IMRT, and 8.5% a combination of both. One case of pneumonia and two cases of pneumonitis were the reasons for uncompleted radiation treatments. The start date for durvalumab after the completion of CRT was mostly the next day (71.4%). One patient (2.4%) who started durvalumab after 8 days because of waiting for the recovery of PS after the completion of radiotherapy was included because it was clinically appropriate for the patient's safety and consistent with the subject of our study.

The 1-year PFS rate from registration by IRC, a primary endpoint, was 75% (60% CI, 69.0–80.0 and 95% CI, 59.4–85.3) as shown in **Table 2**, as the lower limit level of the 60% CI and 95% CI exceeded the threshold of 50%. The 1-year PFS rate from registration by the investigator (INV) was 77.8% (60% CI, 72.0–82.5 and 95% CI, 62.6–87.4). The median PFS (mPFS) from registration by IRC was 14.2 months [95% CI, 13.2—not reached (NR)] and the mPFS from the start of durvalumab therapy by IRC was 12.7 months (95% CI, 12.7–NR) with 14.0 months of a median follow-up period (**Fig. 1**). The 1-year OS rate from registration was 97.7% (95% CI, 84.6–99.7) and the 1-year OS rate from the start of durvalumab was 97.4% (95% CI, 82.8–99.6). Two of 42 patients who received durvalumab could not be evaluated for 1-year PFS and PFS from the start of durvalumab due to withdrawal of consent and interruption of visiting the hospital by the patient's will prior to CT evaluation.

The tumor response and waterfall plot of assessment throughout the study treatment from registration before the start of CCRT are shown in **Table 2** and Supplementary Fig. S2. The CR, PR, SD, and ORR were 4.3%, 74.5%, 19.1%, and 78.7%, respectively. In patients with a CR, the lymph nodes were selected as target measurable lesions; their short diameters were less than 10 mm after treatment. No patient had a response rate of PD.

Toxicities

Any AEs from registration are summarized in **Table 3**. Grade 4 neutropenia, grade 3–4 anemia, and grade 3 FN occurred in 12.8%, 8.5%, and 4.3% of patients, respectively. Pneumonitis occurred in 78.7% with any grade and 4.3% with grade 3 or more. Supplementary Figure S3 shows the grade and onset date for pneumonitis. No treatment-related deaths occurred up to the data cutoff.

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Table 2. Survival and tumor response outcomes.

Survival outcomes		***n* = 47 ([a]*n* = 40, [b]*n* = 42)**
1-year PFS rate		
From registration by IRC, % [60% CI], [95% CI]	75.0	[69.0–80.0], [59.4–85.3]
From registration by INV, % [60% CI], [95% CI]	77.8	[72.0–82.5], [62.6–87.4]
From start of durvalumab by INV, % [95% CI][a]	71.5	[54.2–83.2]
mPFS		
From registration by IRC, months [95% CI]	14.2	[13.4–NR]
From registration by INV, months [95% CI]	14.2	[13.4–17.5]
From start of durvalumab by IRC, months [95% CI][a]	12.7	[12.7–NR]
From start of durvalumab by INV, months [95% CI][a]	12.6	[12.3–16.1]
1-year OS rate		
From registration by INV, % [95% CI]	97.7	[84.6–99.7]
From start of durvalumab by INV, % [95% CI][b]	97.4	[82.8–99.6]
Tumor response outcomes		***n* = 47**
Best overall response, *n* (%)		
CR	2	(4.3)
PR	35	(74.5)
SD	9	(19.1)
PD	0	(0)
NE	1	(2.1)
ORR		
n (%) [95% CI]	37	(78.7) [64.3–89.3]
DCR		
n (%) [95% CI]	46	(97.9) [88.7–99.9]

Abbreviations: CI, confidence interval by Greenwood formula; CR, complete response; DCR, disease control rate; INV, investigator; IRC, Independent Review Committee; mPFS, median progression-free survival; NE, not evaluated; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Forty of 42 patients receiving durvalumab consolidation were available for efficacy analysis. Two patients could not be evaluated for 1-year PFS and PFS from the start of durvalumab due to withdrawal of consent and self-interruption prior to CT evaluation.

[b]Forty-two patients receiving durvalumab consolidation were available for efficacy analysis.

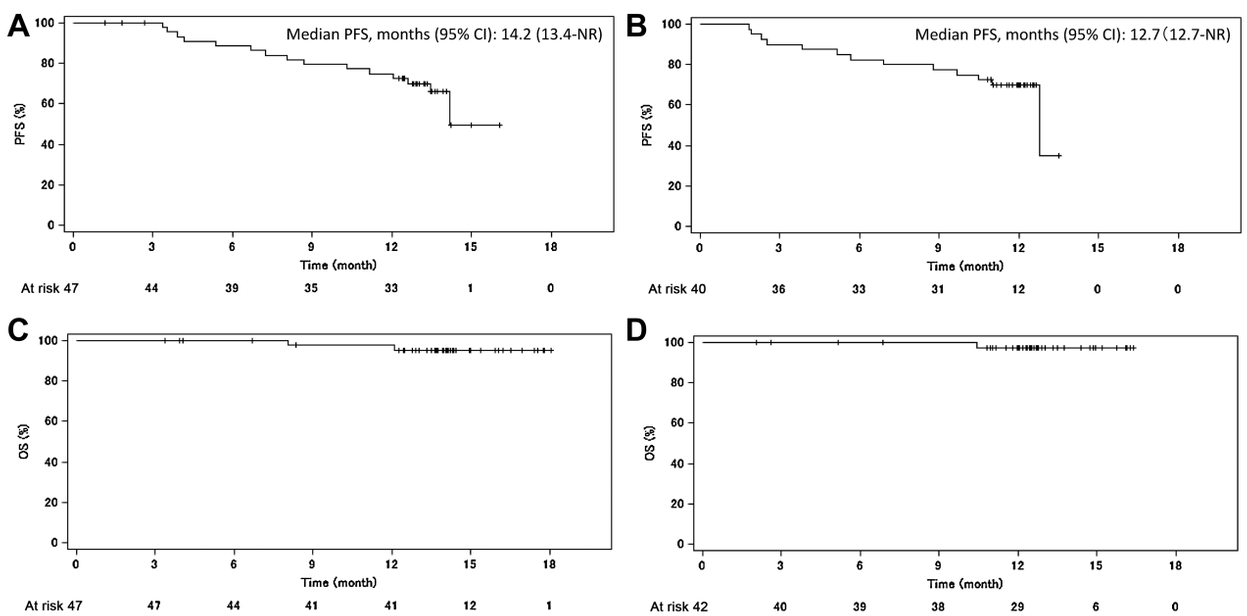

Figure 1.

PFS and OS. PFS from registration (**A**), PFS from the start of durvalumab (**B**), OS from registration (**C**), OS from the start of durvalumab (**D**). CI, confidence interval; NR, not reached.

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Table 3. AEs.

	n = 47			
Adverse event	**Any grade, *n* (%)**		**G3 or more, *n* (%)**	
Leukopenia	42	(89.4)	26	(55.3)
Neutropenia	37	(78.7)	21	(44.7)
Anemia	45	(95.7)	4	(8.5)
Thrombocytopenia	28	(59.6)	2	(4.3)
Febrile neutropenia	2	(4.3)	2	(4.3)
AST increased	20	(42.6)	1	(2.1)
ALT increased	22	(46.8)	1	(2.1)
Creatinine increased	15	(31.9)	0	(0)
Pneumonitis	37	(78.7)	2	(4.3)
Lung infection	10	(21.3)	7	(14.9)
Diarrhea	11	(23.4)	2	(4.3)
Nausea	21	(44.7)	0	(0)
Vomiting	6	(12.8)	0	(0)
Anorexia	25	(53.2)	4	(8.5)
Esophagitis	26	(55.3)	0	(0)
Hyperthyroidism	1	(2.1)	0	(0)
Hypothyroidism	1	(2.1)	0	(0)
Allergic reaction	2	(4.3)	2	(4.3)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; G3, grade 3.

Discussion

To the best of our knowledge, this study is the first prospective study to evaluate the efficacy and safety of durvalumab administered immediately after the completion of chemoradiation. The 1-year PFS rate from registration by IRC was 75%, which met the primary endpoint. Despite the limited follow-up period, the PFS and OS results were also encouraging. The PFS from the start of durvalumab was 12.7 months, which was not notably different from the mPFS of the PACIFIC study (16.8 months; ref. 4) and PACIFIC-R study (21.7 months; ref. 14). The numerically shorter mPFS in our study might be due to the short follow-up duration.

Few reports exist concerning the timing of durvalumab therapy after radiotherapy completion. A retrospective study reported on the efficacy and start date for durvalumab therapy using a U.S. Veterans Health Administration database ($n = 728$; ref. 15). The authors concluded that the initiation of durvalumab treatment up to 120 days after radiotherapy completion was not associated with PFS or OS. In contrast, PFS with ≤42 days of durvalumab initiation from the last radiotherapy ($n = 411$, mPFS: 25.7 months) was relatively better compared with PFS with >42 days ($n = 954$, mPFS: 20.8 months) in findings from the PACIFIC-R study (14). Supplementary Table S5 summarizes the efficacy and safety of this study compared with the previous studies. Long-term survival outcomes are significantly important for immunotherapy, such as the 5-year survival results of the PACIFIC study (16). We should consider carefully the PFS and OS results of the final analysis in our study.

Radiotherapy and chemotherapy are considered to induce immunogenic changes in cancer cells and improve the efficacy of immunotherapy. Many clinical trials, shown in Supplementary Table S6, are reported and ongoing (17). While combining radiotherapy and immunotherapy may increase the efficacy, it may also increase AEs (especially pneumonitis). We should also confirm carefully the safety as well as the efficacy.

The percentage of patients with any grade, or grades 1, 2, 3, 4, and 5 pneumonitis in the safety and efficacy analysis set were 37 (78.7%), 21 (44.7%), 14 (29.8%), 2 (4.3%), 0%, and 0%, respectively. However, the percentage of patients with pneumonitis in the durvalumab group in the PACIFIC study was 33.9% with any grades, 3.4% with grades 3–4, and 0.8% with grade 5. In comparison, the frequency of pneumonitis in a subset of Japanese patients was reported as 73.6% with any grade, 5.6% with grades 3–4, and 1.4% with grade 5 in the durvalumab group (18). The incidence of pneumonitis in this study was higher than that in the PACIFIC study, but was similar to the results of the Japanese cohort in the PACIFIC study. As shown in Supplementary Fig. S3, no specific tendency was noted in the date of onset and grade of pneumonitis. In addition, $V20_{Gy}$ under 35% was set as the eligibility criteria and TRT was set without prophylactic mediastinal irradiation in this study protocol to avoid the risk of severe pneumonitis. On the basis of these results, we considered pneumonitis to be a manageable AE for our study treatment.

Our study had several limitations. First, because this was a single-arm, phase II study with a small sample size, the current data were not confirmatory. Second, the chemotherapy regimens and radiotherapy methods and techniques may have influenced the outcomes. The chemotherapy regimens and number of cycles are not fully consistent with the PACIFIC study. Furthermore, our data on good tolerance for CCRT also potentially influenced outcomes. Third, we excluded patients 75 years old and over in this study, which might have affected the results. In Japanese clinical trials for patients with stage III NSCLC, patients 75 years old and over had usually been excluded, and elderly patients' specific trials were conducted. The Japanese guidelines recommend chemoradiotherapy with daily CBDCA administration for elderly patients who are not fit for cisplatin administration based on the results of JCOG0301 (19). Fourth, our study lacked full data on PD-L1 expression levels. In *post hoc* analyses of the PACIFIC study, a PFS benefit with durvalumab was observed regardless of PD-L1 expression (SP263). In addition, an OS benefit was consistently observed in patients with tumor cell PD-L1 expression of 1% or more (20). The efficacy of treatment by PD-L1 expression level as an exploratory analysis will be investigated in our final analysis. Fifth, the PFS and OS in this article are preliminary data. We need to report further results of long-term outcomes and consider identifying the predictive factor for efficacy and safety, especially pneumonitis, in the final analysis.

Conclusion

The 1-year PFS rate was 75%, which met the primary endpoint. The incidence of pneumonitis was similar with reference to a Japanese subset in the PACIFIC study, and no unexpected AEs were observed. Our data support the efficacy and safety of durvalumab administered immediately after the completion of CCRT for patients with unresectable stage III NSCLC.

Authors' Disclosures

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Authors' Contributions

S. Nakamichi: Conceptualization, resources, data curation, investigation, visualization, methodology, writing–original draft, project administration. **K. Kubota:** Conceptualization, supervision, funding acquisition, methodology, project administration, writing–review and editing. **T. Misumi:** Data curation, formal analysis, methodology, writing–review and editing. **T. Kondo:** Resources, investigation, writing–review and editing. **S. Murakami:** Resources, investigation, writing–review and editing. **Y. Shiraishi:** Resources, investigation, writing–review and editing. **H. Imai:** Resources, investigation, writing–review and editing. **D. Harada:** Resources, investigation, writing–review and editing. **K. Isobe:** Resources, investigation, writing–review and editing. **H. Itani:** Resources, investigation, writing–review and editing. **S. Takata:** Resources, investigation, writing–review and editing. **H. Wakui:** Resources, investigation, writing–review and editing. **Y. Misumi:** Resources, investigation, writing–review and editing. **S. Ikeda:** Resources, investigation, writing–review and editing. **T. Asao:** Resources, investigation, writing–review and editing. **N. Furuya:** Resources, investigation, writing–review and editing. **S. Hosokawa:** Resources, investigation, writing–review and editing. **Y. Kobayashi:** Resources, investigation, writing–review and editing. **Y. Takiguchi:** Resources, investigation, writing–review and editing. **H. Okamoto:** Conceptualization, supervision, methodology, project administration, writing–review and editing.

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Note

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