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Original Research

Prospective analysis of factors precluding the initiation of durvalumab from an interim analysis of a phase II trial of S-1 and cisplatin with concurrent thoracic radiotherapy followed by durvalumab for unresectable, locally advanced non-small cell lung cancer in Japan (SAMURAI study)

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Abstract

Background: The standard of care for unresectable, locally advanced non-small cell lung cancer (LA-NSCLC) is chemoradiotherapy (CRT) followed by durvalumab, based on the PACIFIC trial. Disease progression and pneumonitis were reported as the main reasons to preclude the initiation of durvalumab in multiple retrospective studies. However, the transition rate and the reasons for failure to proceed to consolidation therapy with durvalumab after CRT were not evaluated prospectively. Although phase II studies in Japan have shown high efficacy and tolerability of CRT with cisplatin + S-1 (SP), no prospective study using durvalumab after SP-based CRT has yet been reported. We therefore conducted a phase II study to verify the efficacy and safety of durvalumab following SP-based CRT. In this interim analysis, we report the transition rate and the reasons for its failure.

Methods: In treatment-naïve LA-NSCLC, cisplatin (60 mg/m^2, day 1) and S-1 (80–120 mg/body, days 1–14) were administered with two 4-week cycles with concurrent thoracic radiotherapy (60 Gy) followed by durvalumab every 2 weeks for up to 12 months. The primary endpoint was 12 month progression-free survival rate.

Results: Fifty-nine patients were enrolled, of whom 86.4% (51/59) proceeded to durvalumab. All of them initiated durvalumab within 42 days after CRT [median 18 days (range: 3–38)], including 27.5% (14/51) in $<$14 days. Common reasons for failure to proceed to durvalumab were disease progression (2/59, 3.4%) and adverse events (6/59, 10.2%). Among the latter cases, four resumed treatment and proceeded to durvalumab within 42 days on off-protocol. The objective response rate and the disease control rate were 62.7% and 93.2%, respectively. The incidences of $\geqslant$grade 3 pneumonitis, febrile neutropenia, and esophagitis were 0%, 8.5%, and 3.4%, respectively.

Conclusion: Regarding durvalumab after CRT, this interim analysis of the SAMURAI study clarified the high transition rate, early introduction, and reasons for failure to proceed to consolidation therapy, which were not determined in the PACIFIC trial.

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Background

Chemoradiotherapy (CRT), traditionally consisting of concurrent platinum-based combination chemotherapy and thoracic radiotherapy (TRT), has been established as the standard of care for patients with unresectable, locally advanced non-small cell lung cancer (LA-NSCLC) in good general condition.[1] However, although CRT is intended to be curative, it often results in recurrence, with 5-year survival rates of 15–20%.[2,3]

Investigations into treatment strategies to increase the cure rate included the international randomized phase III PACIFIC trial, the results of which were published in 2017, leading to a revolution in the treatment of LA-NSCLC. In the PACIFIC trial, the patients with unresectable LA-NSCLC who had no disease progression after platinum-based CRT were randomized at a ratio of 2:1 to receive consolidation therapy with the anti-programmed death ligand 1 (PD-L1) antibody durvalumab or placebo every 2 weeks for up to 12 months. The co-primary end points of progression-free survival (PFS) and overall survival (OS) were both significantly prolonged in the durvalumab group compared with the placebo group.[4,5] The updated OS and PFS at 5 years after enrollment of the last patient have since been reported, showing 5-year OS rates of 42.9% and 33.4%, and 5-year PFS rates of 33.1% and 19.0% in the durvalumab and placebo groups, respectively.[6] Since the publication of the results of the PACIFIC trial, platinum-based CRT followed by 12 month of durvalumab has thus been proposed as the standard of care for LA-NSCLC. The major advantages of consolidation therapy with durvalumab in patients with unresectable LA-NSCLC are high PFS rates and OS rates. It is therefore important that as many patients as possible with unresectable LA-NSCLC proceed to consolidation therapy with durvalumab, which requires high antitumor efficacy and good tolerability of the concurrent CRT phase.

The combination regimens of cisplatin + docetaxel (CD) and carboplatin + paclitaxel (CP) are listed as CRT chemotherapies for unresectable LA-NSCLC in Japanese guidelines. These regimens have been established as standard regimens based on their benefits in respective phase III studies, using the combination regimen of mitomycin + vindesine + cisplatin (MVP) as the control arm.[7,8] Recently, cisplatin + S-1 (SP) regimen has also been evaluated for efficacy and safety and shown to have high antitumor efficacy and good tolerability in a variety of phase II clinical trials in Japan. The PFS, median survival time, progressive disease (PD) rate, and incidences of ⩾grade 3 pneumonitis ranged from 9.3 to 20.0 months, 29.7 to 55.2 months, 0 to 5.8%, and 0 to 9.3%, respectively.[9–14] Accordingly, more patients may be expected to proceed to durvalumab if they receive CRT with the SP regimen. However, no patients treated with SP regimen were enrolled in the PACIFIC trial. It is therefore necessary to verify the efficacy and safety of consolidation therapy with durvalumab following SP-based CRT prospectively.

We are therefore conducting a multicenter, phase II study of consolidation therapy with durvalumab following SP-based CRT. All the enrolled patients have currently completed CRT and are being followed up to determine the 12-month PFS rate, as the primary end point. We conducted an interim analysis to report the proportion of patients who proceeded to durvalumab after CRT, the occurrence of events that complicated the initiation of durvalumab, the proportion of patients who responded to CRT [objective response rate (ORR)], the proportions of patients who completed TRT, the proportions of patients who completed CRT, and also adverse events in the concurrent CRT phase, which are all secondary end points.

Methods

Trial oversight

The study protocol was approved by the Yokohama City University Certified Institutional Review Board on September 17, 2019 (CRB19-002), and

was registered by the Japan Registry on Clinical Trials on November 1, 2019 (registration number: jRCTs031190127). All patients provided written informed consent. The study was funded by AstraZeneca Co., Ltd. The study design, subjects, treatment plan, and evaluation methods were in line with those of the PACIFIC trial.

Patients

This study involved a two-step registration procedure: the first registration was performed before the initiation of CRT and the second registration was performed after the completion of CRT and before the initiation of consolidation therapy with durvalumab.

The main inclusion criteria for the first registration were as follows: aged 20 years or older; histological or cytological diagnosis of NSCLC (NSCLC including a component of small cell lung cancer was not eligible); unresectable LA-NSCLC [stage IIIA/IIIB/IIIC according to the International Association for the Study of Lung Cancer (IASLC) Staging Manual in Thoracic Oncology, 8th edition]; presence of measurable lesion(s) defined in the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1; no prior chemotherapy (including molecularly targeted agents and immune checkpoint inhibitors) or TRT, including that for other cancers; expected survival $\geqslant$12 weeks; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; preserved bone marrow and organ functions [neutrophils $>1500/mm^3$, platelets $>100{,}000/mm^3$, hemoglobin $\geqslant$9.0 g/dL, serum creatinine $\leqslant$1.5 mg/dL or creatinine clearance $>$50 mL/min (by the Cockcroft Gault formula), total bilirubin $\leqslant 1.5\times$ upper limit of normal (ULN), and aspartate aminotransferase and alanine aminotransferase $\leqslant 2.5\times$ ULN]; $SpO_2 \geqslant$92% or $PaO_2 \geqslant$70 Torr (room air); and the volume of lung parenchyma that receiving $\geqslant$20 Gy (V20) $\leqslant$35%.

The inclusion criteria for the second registration were as follows: stable disease (SD), partial response (PR), or complete response (CR) to SP-based CRT; ECOG PS of 0 or 1; preserved bone marrow and organ functions (same as the criteria for the first registration); and $SpO_2 \geqslant$92% or $PaO_2 \geqslant$70 Torr (room air).

The main exclusion criteria for the first registration were as follows: interstitial pneumonia or pulmonary fibrosis determined by chest computed tomography (CT); active or previous autoimmune disease; active inflammatory disease; active infection or uncontrolled disease; a history of allogeneic transplantation; immunotherapy or any investigational product within 4 weeks prior to the initiation of study treatment; immunosuppressant medication within 28 days prior to the initiation of study treatment (excluding nasal or inhaled steroids and systemic steroid therapy $\leqslant$10 mg/day prednisolone); surgery within 4 weeks prior to registration; hepatitis B surface antigen positive or hepatitis C antibody positive; history of malignancy (excluding basal cell skin cancer and carcinoma in situ of the cervix) within 5 years prior to the initiation of study treatment; and receipt of a live attenuated vaccine within 30 days prior to registration.

The main exclusion criteria for the second registration were $\geqslant$grade 2 pneumonitis prior to registration and uncontrolled disease or active infection.

Trial design and interventions

This was a single-arm, multicenter, phase II study designed to evaluate the efficacy and safety of consolidation therapy with durvalumab following SP-based CRT for treatment-naïve unresectable LA-NSCLC. Chemotherapy with intravenous cisplatin (60 mg/m^2, day 1) and oral S-1 (80–120 mg/body, days 1–14) was initiated within 14 days after the first registration. The protocol specified that two cycles of chemotherapy with a duration of 4 weeks per cycle should be administered before the completion of radiotherapy. Furthermore, it was specified that the second cycle of chemotherapy should be initiated within 42 days after day 1 of the first cycle. If this was not possible, the patients were terminated from the trial. The dose of S-1 was determined based on the body surface area as follows: 80 mg/day for $<$1.25 m^2, 100 mg/day for 1.25–1.49 m^2, and 120 mg/day for $\geqslant$1.5 m^2. TRT was initiated on day 1 of chemotherapy and administered at a dose of 2 Gy once daily for 5 days per week for a total dose of 60 Gy using an X-ray generator (6–10 MV). In addition to three-dimensional conformal radiotherapy, intensity-modulated radiation therapies were also permitted. It was specified that only the involved field should be irradiated, and no uninvolved ipsilateral hilar, mediastinal, or supraclavicular lymph nodes were irradiated prophylactically. The extent and method of radiation have been detailed in a previous report.[15]

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Chemotherapy was terminated when TRT was completed, as in the PACIFIC trial.

Patients with SD, PR, or CR to SP-based CRT initiated to receive durvalumab (10 mg/kg) via intravenous infusion within 14 days after the second registration. Durvalumab was administered every 2 weeks for up to 12 months. It was specified that durvalumab should be initiated within 42 days after completion of CRT, as in the PACIFIC trial.

Assessment

The following were carried out prior to the study-related procedures: medical history review, electrocardiography, chest X-ray, thoracoabdominal CT, head CT or magnetic resonance imaging (MRI), and bone scintigraphy or positron emission tomography CT. To evaluate the response, it was specified that thoracoabdominal CT and head CT or MRI should be performed from the end of CRT to the time of the second registration, and thoracoabdominal CT should be performed every four cycles after the initiation of durvalumab. Patients who completed 12 months of durvalumab were required to be monitored for disease progression by thoracoabdominal CT every 3 months until PD. Any head or bone lesions were examined closely after the initiation of study treatment if symptoms suggestive of metastases occurred. The response was evaluated by the investigator according to RECIST version 1.1. All adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 5.0. We measured tumor PD-L1 expression levels in tissue samples collected prior to the initiation of CRT in some cases. We also assessed the presence of epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) fusion-positive NSCLC.

Statistical analysis

The primary end point was 12-month PFS rate after the first registration. The secondary end points were PFS after the first registration, PFS after the second registration, the 18-month OS rate after the first registration, ORR for CRT, ORR in the study period including consolidation therapy with durvalumab, the proportions of patients who proceeded to durvalumab, patients who completed TRT, patients who completed CRT, and adverse events not only in the concurrent CRT phase but also in the consolidation phase. In addition, we are evaluating the relationship between the proportion of patients expressing PD-L1 and efficacy in an exploratory manner. PFS is defined as the time from each registration to confirmation of disease progression or any cause of death. OS is defined as the time from the first registration to any cause of death. Patients who completed TRT were defined as those who completed TRT at the protocol-specified dose of 60 Gy, and patients who completed CRT were defined as those who completed TRT and had two cycles of chemotherapy during TRT.

The sample size design and statistical methods have been described previously.[15] Assuming that the duration of CRT was 6 weeks and that up to 6 weeks were required from the end of CRT to the initiation of consolidation therapy with durvalumab, it was estimated that up to 3 months were required from the initiation of CRT to that of consolidation therapy with durvalumab. We accordingly used the 9-month PFS rate (64%) in the PACIFIC trial for reference to calculate the expected 12-month PFS rate in this SAMURAI study. However, the PFS rate of 64% was based on the assumption that all patients treated with CRT could proceed to durvalumab. A randomized phase II study of SP-based CRT versus CD-based CRT in Japan (TORG1018) found PD and mortality rates during SP-based CRT of 2% and 0%, respectively.[14] Accordingly, the expected 12-month PFS rate in this SAMURAI study was calculated as 64% of 98% of all patients after excluding patients with PD (2% of all patients), that is, approximately 63% ($0.98 \times 0.64 = 0.63$). Patients who failed to proceed to durvalumab due to adverse events were included to calculate the expected 12-month PFS rate based on the assumption that they would not experience disease progression or die thereafter. The threshold 12-month PFS rate was assumed to be 47% based on the results of TORG1018.[14] The necessary sample size was calculated to be 52 patients at $\alpha = 0.10$ (one-sided) and $\beta = 0.8$, and the planned sample size of 58 patients was determined to allow for a dropout rate of approximately 10% (withdrawal of consent and ineligibility).

The 95% confidence intervals (CIs) for the proportions of patients who proceeded to durvalumab, the ORR, and disease control rate (DCR) for CRT were calculated using the Clopper–Pearson method. The analysis was carried out using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 1. Baseline characteristics of the intention-to-treat population*.

		***N*=59**	
Age, years	Median (range)	68	(42–81)
Sex, *n* (%)	Male/female	51/8	(86.4/13.6)
Disease stage, *n* (%)	IIIA/IIIB/IIIC	26/29/4	(44.1/49.1/6.8)
ECOG performance-status score, *n* (%)[$]	0/1	27/32	(45.8/54.2)
Tumor histologic type, *n* (%)	Squamous/nonsquamous	23/36	(39.0/61.0)
Smoking history, *n* (%)	Yes/no	54/5	(91.5/8.5)
PD-L1 status, *n* (%)	⩽50%/1–49%/<1%/unknown	20/17/12/10	(33.9/28.8/20.3/17.0)
EGFR mutation, *n* (%)	Positive/negative/unknown	3/36/20	(5.1/61.0/33.9)
ALK fusion, *n* (%)	Positive/negative/unknown	4/30/25	(6.8/50.8/42.4)

*Including all patients who underwent first registration.
[$]ECOG performance status range 0–4, with 0 indicating no symptoms and higher scores indicating increased disability.
ALK, anaplastic lymphoma kinase; ECOG, eastern cooperative oncology group; EGFR, epidermal growth factor receptor; PD-L1, programmed death ligand 1.

Results

Patients and treatment

Fifty-nine patients from 22 centers in Japan were enrolled at the first registration between December 16, 2019, and August 18, 2020. This interim analysis was set out after the last patient initiated consolidation therapy with durvalumab. The median follow-up time was 9.0 months (range: 5.0–13.8).

The baseline characteristics of the patients are presented in Table 1. The median age of all patients was 68 years, and the majority were men (86.4%) and current or former smokers (91.5%); 61.0% had a nonsquamous histologic type of tumor. The tumor PD-L1 expression level, which was measured in tissue samples collected prior to the initiation of CRT, was ⩾50% in 33.9%, 1–49% in 28.8%, <1% in 20.3%, and unknown in 17.0%. The proportion of patients with EGFR mutation-positive NSCLC was 5.1% and with ALK fusion-positive NSCLC was 6.8%.

All patients initiated SP-based CRT within 14 days after the first registration. The proportions of patients who completed induction therapy are presented in Table 2. The proportion of patients who completed TRT was 96.6% (57/59), with a median total radiation dose of 60 Gy (range: 12–60 Gy). The proportion of patients who completed CRT was 91.5% (54/59).

Efficacy

The antitumor efficacy of CRT is presented in Table 3. The ORR was 62.7% (95% CI: 49.1–75.0), the DCR was 93.2% (95% CI: 83.5–98.1), and the PD rate was 3.4%.

The proportion of patients who proceeded to durvalumab was 86.4% (51/59) (95% CI: 75.0–94.0) as shown in Table 4. The median time from the end of CRT to the initiation of durvalumab was 18 days (range: 3–38 days). Among them, 27.5% (14/51) of patients initiated durvalumab in <14 days after completion of CRT.

Regarding the reasons for failure to proceed to durvalumab, eight patients (8/59, 13.6%) failed because of disease progression (2/59, 3.4%) and discontinuation due to adverse events (6/59, 10.2%). Adverse events led to discontinuation of treatment in two patients who met the protocol discontinuation criteria (grade 4 hypokalemia in one patient and grade 2 pneumonitis during CRT in one patient), three patients who failed to meet the criteria for initiating the second cycle of chemotherapy (grade 2 decreased white blood cell count in one patient and grade 1 increased

Table 2. Proportions of patients who completed induction therapy.

Variable	*N* = 59
Patients who completed TRT, *n* (%)	57 (96.6)
Radiation total dose, median (range), Gy	60 (12–60)
Reasons for not continuing TRT, *n*	
Met the study withdrawal criteria due to grade 4 hypokalemia	1
Met the study withdrawal criteria due to grade 2 pneumonitis during TRT	1
Patients who completed CRT, *n* (%)	54 (91.5)
Reasons for not continuing CRT, *n*	
Met the study withdrawal criteria due to grade 4 hypokalemia	1
Met the study withdrawal criteria due to grade 2 pneumonitis during TRT	1
Failed to meet criteria for second cycle of treatment due to grade 2 decreased white blood cells	1
Failed to meet criteria for starting second cycle due to grade 1 increased creatinine	2

CRT, chemoradiotherapy; TRT, thoracic radiotherapy.

Table 3. Antitumor efficacy*.

Variable	*N* = 59
Objective response rate	
No. of patients with response	37
% of patients (95% CI)	62.7 (49.1–75.0)
Disease control rate	
No. of patients with response	55
% of patients (95% CI)	93.2 (83.5–98.1)
Best overall response, *n* (%)	
Complete response	0
Partial response	37 (62.7)
Stable disease	18 (30.5)
Progressive disease	2 (3.4)
Could not be evaluated	2 (3.4)

*Tumor response assessed by clinical investigators.
CI, confidence interval.

serum creatinine in two patients), and one patient who failed to meet the criteria for initiating durvalumab (grade 2 anemia).

The subsequent clinical courses of patients who failed to proceed to consolidation therapy are presented in Table 5. Of the six patients who withdrew from treatment due to adverse events, four recovered from SP-based CRT toxicity and received durvalumab on an off-protocol basis within 42 days after the completion of CRT.

Safety

Adverse events with an incidence of ⩾5% during the CRT phase are presented in Table 6. The most common adverse events of ⩾grade 3 were decreased neutrophil count (20.3%) and anorexia (10.2%). Regarding the most common adverse events during CRT which complicate the early initiation of durvalumab, the incidences of pneumonitis, febrile neutropenia, and esophagitis were 6.8%, 8.5%, and 47.5% across all grades, respectively, and 0%, 8.5%, and 3.4% at grade 3 or higher, respectively. No grade 5 adverse events were reported during the CRT phase.

Discussion

To the best of our knowledge, this is the first prospective study to investigate the proportion of patients with treatment-naïve unresectable LA-NSCLC who proceeded to consolidation therapy with durvalumab after SP-based CRT.

In this study, the transition rate to consolidation therapy after CRT was 86.4%, and the reasons for failure to proceed to durvalumab were adverse events (10.2%) and disease progression after CRT (3.4%). Multiple retrospective studies have evaluated the proportion of patients who could proceed to durvalumab after CRT in LA-NSCLC,[16–20] and the results of five retrospective studies and the SAMURAI study are summarized in Table 7.

According to the results of these five retrospective studies, approximately 50–75% of patients with LA-NSCLC are expected to proceed to durvalumab after CRT, with disease progression after CRT and ⩾grade 2 pneumonitis being the most common reasons for failure. However, all the previous studies were retrospective and thus subject to selection bias. Furthermore, the SP-based regimen was selected for chemotherapy in only 0–11% of all the patients. In contrast, the current SAMURAI study was conducted prospectively and showed

Table 4. Transition rate to consolidation therapy with durvalumab.

Variable	*N* = 59		
No. of patients who received consolidation therapy	51		
% of patients (95% CI)	86.4 (75.0–94.0)		
Median time from the end of CRT to the initiation of durvalumab (days)	18		
<14 days, *n* (%)	14 (27.5)		
⩽42 days, *n* (%)	51 (100)		
The reasons for failure to proceed to durvalumab, *n*	8		
Disease progression	2		
Due to adverse events	6		
Met the protocol discontinuation criteria		2	
Grade 4 hypokalemia			1
Grade 2 pneumonitis			1
Failed to meet the criteria for initiating the second cycle of chemotherapy		3	
Grade 2 decreased white blood cells			1
Grade 1 increased serum creatinine			2
Failed to meet the criteria for initiating durvalumab		1	
Grade 2 anemia			1

CI, confidence interval; CRT, chemoradiotherapy.

that 86.4% of patients proceeded to durvalumab, with the reasons for failure to proceed being disease progression after CRT in 3.4% and ⩾grade 2 pneumonitis in 1.7%. Compared with the previous five retrospective studies, the proportion of patients who proceeded to durvalumab was higher and the proportions of patients with disease progression after CRT and ⩾grade 2 pneumonitis were lower in this SAMURAI study.

Multiple explanations support the high proportion of patients that proceeded to durvalumab in this SAMURAI study.

Regarding its antitumor efficacy, the absence of disease progression after CRT is an absolute requirement for the initiation of durvalumab. Accordingly, treatment strategies in the CRT phase should be chosen with a focus on a low PD rate rather than high response rate. In Japan, the CD (OLCSG0007) and CP regimens (WJTOG0105) have been established as standard CRT regimens for LA-NSCLC based on their benefits in phase III studies with the MVP regimen as the control arm. The PD rates for the CD regimen in OLCSG0007 and the CP regimen in WJTOG0105 were 3.0% and 10.9%, respectively.[7,8] A recent randomized phase II study of CD versus SP (TORG1018) found a higher 2-year OS rate for the more tolerable SP regimen. The PD rate for the SP was 1.9% in TORG1018, and other phase II studies using the SP regimen showed PD rates of 0–5.8%.[9–14] The PD rate in the SAMURAI study was 3.4%, which was comparable to previous reports. Taken together, both the SP and CD could be promising treatment regimens in terms of their high efficacy.

Regarding its tolerability, less toxic CRT regimens are important for transition to consolidation therapy. The most common ⩾grade 3 adverse events that complicate the early initiation of durvalumab are generally considered pneumonitis, esophagitis, and febrile neutropenia.[21,22] The incidences of

Table 5. Patients who failed to proceed to protocol-specified treatment with durvalumab.

	Adverse events with discontinuation of protocol treatment	Grade (CTCAE 5.0)	TRT dose (Gy)	Chemotherapy (cycles)	Transition to durvalumab	Reasons for proceeding or not proceeding to durvalumab	Days from the end of CRT to the initiation of durvalumab
1	Hypokalemia	4	54	2	Yes	Off protocol	40
2	Decreased white blood cells	2	60	1	Yes	Off protocol	21
3	Increased creatinine	1	60	1	Yes	Off protocol	4
4	Anemia	2	60	2	Yes	Off protocol	42
5	Increased creatinine	1	60	1	No	PD after CRT	None
6	Pneumonitis	2	12	1	No	Grade 2 pneumonitis during CRT	None

CRT, chemoradiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; TRT, thoracic radiotherapy.

⩾grade 3 pneumonitis, esophagitis, and febrile neutropenia in the CD regimen from OLCSG0007 were 10.1%, 14.1%, and 22.2%, and those in the CP regimen from WJTOG0105 were 0.7%, 7.4%, and 3.4%.[7,8] In contrast, the incidences of such adverse events in TORG1018 were 0%, 3.8%, and 1.9%, and those in the other phase 2 studies were 0% to 9.3%, 0% to 10.0%, and 0% to 9.3%.[9–14] Furthermore, in the SAMURAI study, they were 0%, 3.4%, and 8.5%, respectively, which were as low as previously reported. All adverse events reported in the CRT phase of the SAMURAI study were known events. Taken together, both the SP and CP could be promising treatment regimens in terms of their high tolerability.

These results suggest that the SP regimen, with its antitumor efficacy and tolerability, could be a promising strategy allowing patients with LA-NSCLC to proceed to durvalumab soon after CRT.

Lastly, there are several possible clinical advantages resulting from the early introduction of durvalumab after CRT in this SAMURAI study. In our study, the median time from the end of CRT to the initiation of durvalumab was 18 days, and 27.5% (14/51) of the patients initiated durvalumab in <14 days. From this perspective, in the PACIFIC trial, the patients who could proceed to durvalumab in <14 days tends to have better OS than those in ⩾14 days (hazard ratio: 0.54 *versus* 0.79).[6] This is the result of a subset analysis and may only reflect the nature of the original lung cancer. That is, even within the same unresectable LA-NSCLC category, patients with low tumor volume and good general condition would be more tolerant of CRT and therefore proceed to durvalumab earlier, and OS might only reflect such nature of the original lung cancer. However, in patients with the same nature of the original lung cancer, the hypothesis would be valid that they would proceed to durvalumab earlier with expectations for the effects of immunotherapy that may contribute to OS if they could complete CRT in good immune status by a regimen with high tolerability. In our SAMURAI study, OS analysis will be verified in upcoming final report.

This study has several limitations.

First, in this interim analysis, the incidence of ⩾grade 3 pneumonitis was evaluated only in induction phase. Radiation pneumonitis may occur within several weeks to several months after radiotherapy.[23] Therefore, a sufficient follow-up time including consolidation phase is required to properly evaluate the incidence of pneumonitis of SP-based CRT. However, given the low incidence of ⩾grade 3 pneumonitis based on the previous phase 2 clinical trials with long follow-up, similar results will be expected in our SAMURAI study.

Second, we conducted a single-arm study with limited sample size. However, with reference to

Table 6. Hematologic and non-hematologic adverse events during the CRT phase.

	Any grade*	Grade 1	Grade 2	Grade 3	Grade 4
		Number of patients with event (%)			
Decreased neutrophil count	34 (57.6)	7 (11.9)	15 (25.4)	6 (10.2)	6 (10.2)
Decreased platelet count	12 (20.3)	5 (8.5)	3 (5.1)	3 (5.1)	1 (1.7)
Decreased white blood cells	8 (13.6)	0	5 (8.5)	3 (5.1)	0
Febrile neutropenia	5 (8.5)	–	–	5 (8.5)	0
Anorexia	28 (47.5)	15 (25.4)	7 (11.9)	6 (10.2)	0
Esophagitis	28 (47.5)	10 (16.9)	16 (27.1)	2 (3.4)	0
Rash	9 (15.3)	7 (11.9)	1 (1.7)	1 (1.7)	0
Anemia	8 (13.6)	4 (6.8)	1 (1.7)	3 (5.1)	0
Diarrhea	8 (13.6)	3 (5.1)	3 (5.1)	2 (3.4)	0
Vomiting	6 (10.2)	2 (3.4)	2 (3.4)	2 (3.4)	0
Increased creatinine	6 (10.2)	6 (10.2)	0	0	0
Malaise	5 (8.5)	3 (5.1)	2 (3.4)	0	0
Constipation	5 (8.5)	3 (5.1)	2 (3.4)	0	0
Pneumonitis	4 (6.8)	3 (5.1)	1 (1.7)	0	0
Oral mucositis	4 (6.8)	3 (5.1)	0	1 (1.7)	0
Hyponatremia	4 (6.8)	0	2 (3.4)	2 (3.4)	0
Fever	4 (6.8)	4 (6.8)	0	0	0
Hypoalbuminemia	3 (5.1)	0	2 (3.4)	1 (1.7)	0

*Included are events that were reported in at least 5% of the patients.
CRT, chemoradiotherapy.

the list of the used regimens in the PACIFIC trial, the sample size varied from 1 to 158 patients among 18 regimens. Assuming that SP-based CRT was adopted in the PACIFIC regimen, this regimen applied to 59 patients in our study would be supposed to the fourth most used regimen. In this point of view, our study could be well worth.

Third, the dose intensity of chemotherapy in SP-based CRT might be a matter. Regarding the intravenously administered chemotherapy, its dose intensity will reach almost 100% because the administration of the second course of chemotherapy can be supposed to complete with enough time before the end of 6 weeks RT. In contrast, regarding the orally administered S-1, if arranged to be discontinued at the end of RT as in the PACIFIC trial, its dose intensity will not reach 100% in some patients because that of S-1 can be supposed to complete without enough time before the end of 6 weeks RT.

Fourth, it is difficult to extrapolate the results of this Samurai study to treatment with other standard regimens. As indicated in this interim analysis report, high rates of transition to durvalumab after CRT, failure to initiate durvalumab, and low PD rates are observed with SP-based CRT regimens, and whether the same results can be extrapolated to other standard regimens should be carefully considered. In the future, it is expected that the durvalumab transition rate and reason for transition failure will be clarified, even for the standard treatment regimens.

Table 7. Selected data from studies of durvalumab after CRT.

	Study design	Survey period	*N*	Eligible to consolidation therapy with durvalumab, *n*		Possibility of proceeding to durvalumab (%)	Ineligible reasons to receive durvalumab	(*n*)	(%)
Hosoya *et al.*[16]	Retrospective	2009–2017	82	Yes	63	76.8	Progressive disease after CRT	7	8.5
							Grade 2 or worse pneumonitis	6	7.3
							Only one cycle of chemotherapy due to adverse event	4	4.9
				No	19		Poor PS (⩾2)	1	1.2
							Residual toxicity from CRT	1	1.2
Sakaguchi *et al.*[17]	Retrospective	2011–2018	73	Yes	51	69.9	Grade 2 or worse pneumonitis	14	19.2
							Poor PS (⩾2)	7	9.6
							Progressive disease after CRT	3	4.1
				No	22				
Eichkorn *et al.*[18]	Retrospective	2009–2019	437	Yes	220	50.3	Progressive disease after CRT	138	31.6
							Grade 2 or worse pneumonitis	62	14.2
							Autoimmune disease	30	6.9
				No	217		Poor PS (⩾2)	4	0.9
							Only one cycle of chemotherapy due to adverse event	2	0.5
							Others (PD-L1 expression 0%)	43	9.8
Kuang *et al.*[19]	Retrospective	2018–2019	196	Yes	97	49.5	Progressive disease after CRT	19	9.7
							Poor PS (⩾2)	8	4.1
							Residual toxicity from CRT	4	2.0
				No	99		Mutation status	3	1.5
							Autoimmune disease	1	0.5

(Continued)

Table 7. (Continued)

	Study design	Survey period	*N*	Eligible to consolidation therapy with durvalumab, *n*		Possibility of proceeding to durvalumab (%)	Ineligible reasons to receive durvalumab	(*n*)	(%)
							Others (including patients/physicians preference)	64	32.7
Saito *et al.*[20]	Retrospective	2018–2019	302	Yes	225	74.5	Grade 2 or worse pneumonitis	20	6.6
							Progressive disease after CRT	10	3.3
							Poor PS (⩾2)	7	2.3
				No	77		Mutation status	3	1.0
							Insufficient CRT	3	1.0
							Others (including patients preference)	34	11.3
Current study (SAMURAI)	Prospective	2019–2020	59	Yes	51	86.4	Only one cycle of chemotherapy due to adverse event	3	5.1
							Progressive disease after CRT	2	3.4
							Grade 2 or worse pneumonitis	1	1.7
				No	8		Residual toxicity from CRT	1	1.7
							Others (hypokalemia while in CRT phase)	1	1.7

CRT, chemoradiotherapy; PD-L1, programmed death ligand 1; PS, performance score.

Fifth, patients with unresectable LA-NSCLC represent a heterogeneous population. Therefore, the interpretation of the study results, including the number of dropouts due to progressive disease during the CRT phase, in this patient population requires caution according to the differences in the ratio of stage IIIA, IIIB, and IIIC. Actually, substage imbalance was observed in the SAMURAI study, with 44.1% classified as stage IIIA, 49.1% as stage IIIB, and 6.8% as stage IIIC, indicating the high percentage of stage IIIA and the minimal percentage of stage IIIC.

Conclusion

Regarding durvalumab after CRT, this interim analysis of the SAMURAI study clarified the high transition rate, early introduction, and reasons for failure to proceed to the consolidation therapy, which were not determined in the PACIFIC trial. These results could be explained by the antitumor efficacy and tolerability of the SP-based CRT regimen. Further results of the SAMURAI study will be reported, including the primary end point.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Yokohama City University Certified Institutional Review Board on September 17, 2019 (CRB19-002). All patients provided written informed consent.

Consent for publication

All authors have read the manuscript and approve its submission to Therapeutic Advances in Medical Oncology.

Author contributions

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Availability of data and materials

Not applicable.

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