

# A phase II study 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:** Based on the results of the PACIFIC study, chemoradiotherapy followed by 1-year consolidation therapy with durvalumab was established as the standard of care for unresectable, locally advanced non-small-cell lung cancer (LA-NSCLC). However, some topics not foreseen in that design can be explored, including progression-free survival (PFS) and overall survival (OS) after the start of chemoradiotherapy, the proportion of patients who proceeded to consolidation therapy with durvalumab, and the optimal chemotherapeutic regimens. In Japan, the combination regimen of S-1 + cisplatin (SP), for which the results of multiple clinical studies have suggested a good balance of efficacy and tolerability, is frequently selected in clinical settings. However, the efficacy and safety of consolidation therapy with durvalumab following this SP regimen have not been evaluated. We therefore planned a multicenter, prospective, single-arm, phase II study.

**Methods:** In treatment-naïve LA-NSCLC, two cycles of combination chemotherapy with S-1 (80–120 mg/body, Days 1–14) + cisplatin (60 mg/m<sup>2</sup>, Day 1) will be administered at an interval of 4 weeks, with concurrent thoracic radiotherapy (60 Gy). Responders will then receive durvalumab every 2 weeks for up to 1 year. The primary endpoint is 1-year PFS rate.

**Discussion:** Compared with the conventional standard regimen in Japan, the SP regimen is expected to be associated with lower incidences of pneumonitis, esophagitis, and febrile neutropenia, which complicate the initiation of consolidation therapy with durvalumab, and have higher antitumor efficacy during chemoradiotherapy. Therefore, SP-based chemoradiotherapy is expected to be successfully followed by consolidation therapy with durvalumab in more patients, resulting in prolonged PFS and OS. Toxicity and efficacy results of the SP regimen in this study will also provide information important to the future establishment of the concurrent combination of chemoradiotherapy and durvalumab.

**Trial registration:** Japan Registry of Clinical Trials, jRCTs031190127, registered 1 November 2019, <https://jrct.niph.go.jp/latest-detail/jRCTs031190127>

**Keywords:** chemoradiotherapy, cisplatin, durvalumab, non-small-cell lung cancer, S-1

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**Background**

Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer patients, and locally advanced lung cancer accounts for 30% of NSCLC cases.<sup>1</sup> Conventionally, concurrent chemoradiotherapy with platinum and a cytotoxic anticancer drug has been recommended as the standard of care for patients with unresectable, locally advanced NSCLC (LA-NSCLC) in good general condition.<sup>2</sup> In this population, the 5-year survival rates are disappointing (15–20%),<sup>3,4</sup> although complete cure is possible.

Amidst enthusiasm for a new treatment, the results of the PACIFIC, an international phase III study, was published in 2017. Among responders to chemoradiotherapy for unresectable LA-NSCLC, those who received consolidation therapy with the anti-PD-L1 antibody durvalumab for 1 year had significantly longer progression-free survival (PFS) (median: 16.8 months *versus* 5.6 months) and overall survival (OS) (median: not reach *versus* 29.1 months) after chemoradiotherapy, which were co-primary endpoints, than those who did not receive it.<sup>5,6</sup> Based on these results of the PACIFIC study, 1-year consolidation therapy with durvalumab was established as the standard of care for responders to chemoradiotherapy for unresectable LA-NSCLC. However, caution should be taken with regard to the following three issues when interpreting the results of the PACIFIC study: First, PFS and OS after the start of chemoradiotherapy were unclear. Since PFS and OS were assessed after chemoradiotherapy in the PACIFIC study, the results cannot be directly applied to patients at diagnosis. If PFS and OS after the start of chemoradiotherapy were available, the significance of consolidation therapy with durvalumab could be more clearly shown in contrast to conventional chemoradiotherapy. Second, 28% of responders to chemoradiotherapy were excluded from the trial between registration and randomization, but no details were reported.<sup>5</sup> Therefore, it is important to determine what proportion of patients can proceed to consolidation therapy with durvalumab after initial chemoradiotherapy and to identify reasons for failure to proceed to consolidation therapy. Third, the optimal chemotherapeutic regimens were not explored. It is important to explore a chemotherapeutic regimen that provides good balance of efficacy and tolerability so that many patients can proceed to consolidation therapy with durvalumab. In Japan, the combination regimen of S-1 + cisplatin (SP) in concurrent chemoradiotherapy for unresectable

LA-NSCLC, which was suggested in multiple phase II studies to be superior in efficacy and tolerability, seems promising.<sup>7–12</sup> However, this SP regimen was not included in the PACIFIC study, and the efficacy and safety of the regimen followed by consolidation therapy with durvalumab have not been evaluated. Therefore, there is urgent need to evaluate the efficacy and safety of consolidation therapy with durvalumab following SP-based chemoradiotherapy, which is expected to be more commonly used in Japan.

We therefore planned a multicenter, prospective, single-arm, phase II study of consolidation therapy with durvalumab following SP-based chemoradiotherapy for unresectable LA-NSCLC. This study is abbreviated as the SAMURAI study (A phase II study of **S-1** and cisplatin with concurrent thoracic radiotherapy followed by durvalumab for **unresectable**, locally **advanced** non-small-cell lung cancer in Japan).

**Methods/design**

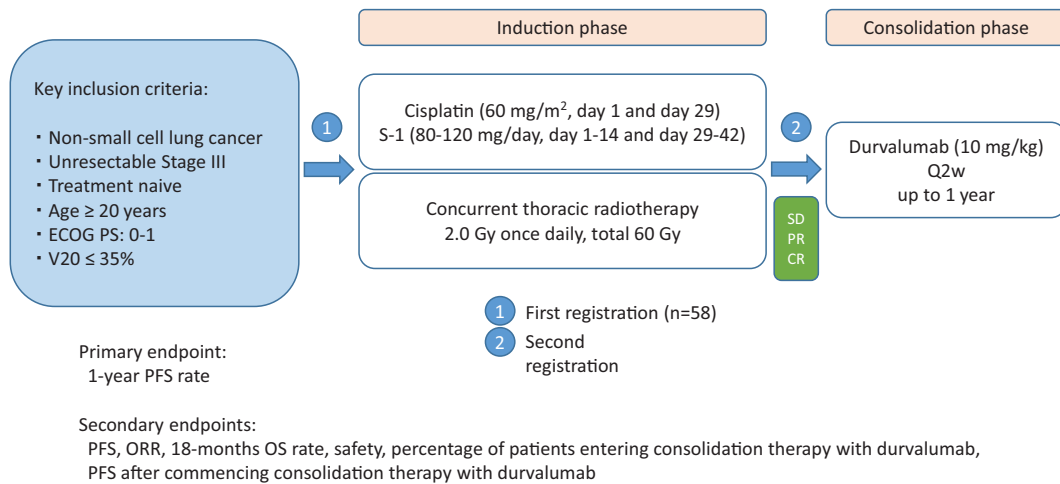
The study will be conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Yokohama City University Certified Institutional Review Board (CRB19-002) (registration number: jRCTs031190127). All patients will provide written informed consent before enrollment. The study is funded by AstraZeneca Co., Ltd. The subjects, treatment plan, and evaluation methods are in line with those of the PACIFIC trial.

*Study design and patients*

This study is designed as a single-arm, multicenter, phase II study to evaluate the efficacy and safety of consolidation therapy with durvalumab following SP-based chemoradiotherapy for treatment-naïve unresectable LA-NSCLC. Accrual began in December 2019 and the study will continue for 3 years. The study schema is presented in Figure 1.

A first registration will be performed before chemoradiotherapy to select patients who receive SP-based chemoradiotherapy. Later, a second registration will be performed for patients with stable disease (SD), partial response (PR), or complete response (CR) to chemoradiotherapy to select patients who receive consolidation therapy with durvalumab for 1 year.

The inclusion criteria for the first registration are 20 years of age or older; histological or cytological



**Figure 1.** Treatment schema for the SAMURAI study: phase II trial of S-1 plus cisplatin concurrent thoracic radiotherapy for locally advanced non-small-cell lung cancer.

ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; V20, percentage of lung volume exceeding 20 Gy.

diagnosis of NSCLC (NSCLC including the component of small cell lung cancer is not eligible); unresectable, locally advanced lung cancer [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.; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; preserved bone marrow and organ functions; SpO<sub>2</sub>  $\geq$  92% or PaO<sub>2</sub>  $\geq$  70 Torr (room air); and volume of lung parenchyma that received 20 Gy or more (V20)  $\leq$  35%. The inclusion criteria for the second registration are SD, PR, or CR to chemoradiotherapy; ECOG PS of 0 or 1; preserved bone marrow and organ functions; and SpO<sub>2</sub>  $\geq$  92% or PaO<sub>2</sub>  $\geq$  70 Torr (room air). The exclusion criteria for the first registration are patients with interstitial pneumonia or pulmonary fibrosis; patients with active or previous autoimmune disease; and patients with active inflammatory disease. The exclusion criteria for the second registration is patients with grade 2 or higher radiation pneumonitis prior to registration.

### Assessment

Prior to study-related procedures, the following will be performed: review of medical history; physical examination; hematology and blood chemistry; screening for infection with hepatitis B virus, hepatitis C virus, and human immunodeficiency virus; electrocardiography; chest X-ray;

thoracoabdominal computed tomography (CT); head CT or magnetic resonance imaging (MRI); and bone scintigraphy or positron emission tomography (PET)-CT. To evaluate the response, thoracoabdominal CT and head CT or MRI will be performed before the second registration, and thoracoabdominal CT will be performed every four cycles after the start of consolidation therapy with durvalumab. The response will be evaluated according to RECIST version 1.1. All adverse events will be graded according to the Common Terminology Criteria for Adverse Events, version 5.0. The prescribed clinical informations are input to an electric data capturing system.

### Treatment

Chemoradiotherapy with oral S-1 (80–120 mg/body, Days 1–14) and intravenous cisplatin (60 mg/m<sup>2</sup>, Day 1) will be started within 14 days after the first registration, with two cycles administered at an interval of 4 weeks. The dose of S-1 will be determined based on the body surface area as follows: 80 mg/day for  $<1.25$  m<sup>2</sup>; 100 mg/day for 1.25–1.49 m<sup>2</sup>; and 120 mg/day for  $\geq 1.5$  m<sup>2</sup>. Radiation will be started 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. An X-ray generator (6–10 MV) will be used. In addition to three-dimensional conformal radiotherapy, intensity-modulated radiation therapies (IMRTs), including volumetric modulated arc therapy (VMAT), image-guided radiotherapy, and four-dimensional conformal radiotherapy,

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are also permitted. Before radiotherapy starts, a CT scan of the tumor in the chest will be performed in order to determine tumor volume. The gross tumor volume (GTV) will be delineated according to the primary tumor, and the nodal involvement will be determined from contrast-enhanced CT, or PET with FDG, or both. A CT without contrast is only permitted if the patient has a contrast allergy. The clinical target volume 1 (CTV1) will be contoured with 5 mm around the GTV and regional lymph node regions. The clinical target volume 2 (CTV2) will be contoured with 5 mm around the GTV after the initial 40 Gy/20 fr. The planning target volume 1 (PTV1) includes the CTV1 plus a 5–10 mm margin, and PTV2 includes the CTV2 plus a 5 mm margin after the initial 40 Gy/20 fr. The initial 40 Gy/20 fr will be delivered to CTV1 and the final 20 Gy/10 fr will be delivered to a reduced volume defined as CTV2. This modification of margins around 40 Gy are applied to three-dimensional conformal radiotherapy and not to IMRT or VMAT. To define the target volumes in accordance with International Commission on Radiation Units and Measurements (ICRU) Report #50 and #62 will be recommended. Only the involved field will be irradiated, and no ipsilateral hilar, mediastinal, or supraclavicular lymph nodes will be prophylactically irradiated if not involved. The normal tissue constraints shall be prioritized in the following order for treatment planning. The mean lung dose should optimally be <20 Gy, V20 must be  $\leq 35\%$ , the mean dose to the esophagus is optimally kept below 34 Gy, and the limits to heart must be  $V45 < 35\%$  or  $V30 < 30\%$ . These are based on the PACIFIC study protocol. Although, the size of the target volumes are not limited, IMRT or VMAT are recommended if the volumes exceed a dose of V20 over 35%. Chemotherapy will be terminated when radiotherapy is completed, as in the PACIFIC study. The second registration will be performed for responders within 42 days after completion of radiotherapy, and enrolled patients will receive consolidation therapy with durvalumab (10 mg/kg) *via* intravenous infusion every 2 weeks for up to 1 year.

### Statistical design

The primary endpoint is 1-year PFS rate which is calculated from the first registration until disease progression or any cause of death. The secondary endpoints are PFS, response rate, 18-month OS rate, safety and adverse event profiles, proportion of patients who complete chemotherapy, proportion

of patients who complete radiotherapy, proportion of patients who complete chemoradiotherapy, proportion of patients who proceed to consolidation therapy with durvalumab, and PFS after the second registration. In addition, the relationship between the proportion of patients expressing PD-L1 and the efficacy will be evaluated for an exploratory data analysis. In the PACIFIC study, the 1-year PFS rate was 56%.<sup>5</sup> However, the PFS was calculated from randomization of patients to receive consolidation therapy with durvalumab after completion of chemoradiotherapy. To estimate the 1-year PFS rate after the start of chemoradiotherapy in the PACIFIC study, therefore, it is necessary to estimate the time from the start of chemoradiotherapy to randomization upon completion of chemoradiotherapy. Assuming that 6 weeks of chemoradiotherapy are usually required from the start to the end, and that up to 6 weeks were required from the end of chemoradiotherapy to the start of consolidation therapy with durvalumab as specified in the protocol of the PACIFIC study, it is estimated that up to 3 months are required from the start of chemoradiotherapy to the start of consolidation therapy with durvalumab. Accordingly, we used the 9-month PFS rate (approximately 64% based on the Kaplan–Meier curve) in the PACIFIC study for reference to calculate the expected 1-year PFS rate in the SAMURAI study.

However, the PFS rate of 64% is based on the assumption that all patients treated with chemoradiotherapy can proceed to consolidation therapy. In actuality, patients who cannot proceed to consolidation therapy due to PD despite chemoradiotherapy and patients who die during chemoradiotherapy should be taken into account. In the only randomized phase II study (TORIG1018) showing higher utility of the SP regimen than the combination regimen of cisplatin + docetaxel (CD), the PD and mortality rates during chemoradiotherapy using the SP regimen were 2% and 0%, respectively, although this regimen differed in mode of administration (full *versus* divided administration) from the CD regimen (OLCSG0007) established as the standard of care in Japan.<sup>12</sup> Accordingly, the expected 1-year PFS rate in the SAMURAI study was calculated as 64% in 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 fail to proceed to consolidation therapy with durvalumab due to an adverse event were included to calculate the expected 1-year PFS rate based on the

assumption that they would not experience disease progression or die thereafter. On the other hand, the threshold 1-year PFS rate was assumed to be 47% based on the results of TORG1018. The necessary sample size was calculated to be 52 patients at  $\alpha=0.10$  and  $\beta=0.8$ . To allow for a dropout rate of approximately 10% (withdrawal of consent and ineligibility), the planned sample size of 58 patients was determined.

## Discussion

S-1 is an oral anticancer drug developed in Japan by combining tegafur, a prodrug of 5-fluorouracil (5-FU), with gimeracil (CDHP), a strong DPD inhibitor, and oteracil potassium for reducing gastrointestinal toxicity, and is widely used in clinical settings. S-1 has good tolerability and antitumor efficacy not only in advanced or recurrent NSCLC, but also in various other cancers, including gastric cancer, colorectal cancer, breast cancer, pancreatic cancer, and gallbladder cancer.<sup>13-17</sup> In addition, S-1, which is orally administered and much needed by patients, is often selected as the standard of care for many of these cancers in Japan. Furthermore, since CDHP was suggested by a basic experiment to be a radiation sensitizer, S-1 seems promising as a chemoradiotherapy regimen as well.<sup>18,19</sup>

In Japan, the CD (OLCSG0007) and CP (WJTOG0105: carboplatin + paclitaxel) regimens were compared with the combination regimen of mitomycin + vindesine + cisplatin as the chemotherapeutic regimen in chemoradiotherapy for unresectable LA-NSCLC in the respective phase III studies.<sup>20,21</sup> The CD regimen was not demonstrated to be superior in OS, which was the primary endpoint, but was superior in 2-year OS rate. The CP regimen was not demonstrated to be non-inferior in OS, which was the primary endpoint, but was associated with less toxicity and closely overlapping survival curves. Given these findings, the guidelines in Japan recommend these two regimens. More recently, a randomized phase II study of SP regimen *versus* CD regimen (TORG1018) was conducted. The 2-year OS rate, which was the primary endpoint, was 69% in the CD combination group and 79% in the SP combination group, and the median survival time was 50.8 months in the CD combination group and 55.2 months in the SP combination group, suggesting good outcomes with the SP regimen.<sup>12</sup>

To prolong OS in the treatment of unresectable LA-NSCLC, many patients may have to proceed to consolidation therapy with durvalumab. For that purpose, the adverse event profile and antitumor efficacy of chemoradiotherapy are important. The advantages of the SP regimen with regard to these two points are described below. First, an advantage of the SP regimen is discussed from an adverse event perspective. The most common adverse events that complicate the initiation of consolidation therapy may be radiation pneumonitis, followed by radiation esophagitis and febrile neutropenia.<sup>22,23</sup> Based on the results of OLCSG0007, WJTOG0105, and TORG1018, the incidence of grade 3 or higher radiation pneumonitis was reported to be 10%, 1%, and 0% with the CD, CP, and SP regimens, respectively.<sup>12,20,21</sup> As indicated by the fact that patients with grade 2 or higher radiation pneumonitis were excluded from the PACIFIC study, the incidence of radiation pneumonitis is important in selecting a regimen. The incidence of grade 3 or higher radiation esophagitis was 14%, 8%, and 4% with the CD, CP, and SP regimens, respectively, and the incidence of grade 3 or higher febrile neutropenia was 22%, 3%, and 6%, respectively.<sup>12,20,21</sup> On the other hand, subgroup analyses of PFS and OS in the PACIFIC study showed that the time from last radiotherapy to randomization <14 days tended to have lower hazard ratios than the time  $\geq 14$  days (PFS: 0.39 *versus* 0.63, OS: 0.42 *versus* 0.81).<sup>5,6</sup> Taken together, the SP and CP regimens seem promising from an adverse event perspective. Next, advantages of the SP regimen are discussed from an antitumor perspective. Based on the results of OLCSG0007, WJTOG0105, and TORG1018, the response rate was 79%, 63%, and 72% with the CD, CP, and SP regimens, respectively, with preferable differences in the cisplatin-based combination regimen.<sup>12,20,21</sup> Similarly, the PD rate was 3%, 11%, and 2% with the CD, CP, and SP regimens, respectively.<sup>12,20,21</sup> On the other hand, chemotherapeutic regimen-based subgroup analyses of PFS and OS in the PACIFIC study showed that the cisplatin-based combination regimen tended to have lower hazard ratios than the carboplatin-based combination regimen (PFS: 0.51 *versus* 0.61, OS: 0.64 *versus* 0.75).<sup>5,6</sup> Accordingly, the SP and CD regimens seem promising from an antitumor perspective.

Thus, the SP regimen is considered to be one of the best regimens available in Japan in terms of balance of toxicity and efficacy. Therefore,

SP-based chemoradiotherapy is expected to be successfully followed by consolidation therapy with durvalumab in many patients, resulting in prolonged PFS and OS.

At present, the international PACIFIC2 study (NCT03519971) and the ECOG-ACRIN5181 study (NCT04092283) in the US are ongoing to evaluate the efficacy of concurrent combination of chemoradiotherapy and durvalumab. From the perspective that the concurrent combination of chemoradiotherapy and durvalumab may be established as the standard of care in the future, the balance of toxicity and efficacy in chemotherapeutic regimens must be improved more than ever. It may therefore be highly significant to produce such evidence through the SAMURAI study.

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### Authors' contributions

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### Conflict of interest statement

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### Consent for publication

Consent for publication must be obtained from all patients.

### Ethics approval and consent to participate

Yokohama City University Certified Institutional Review Board approved this protocol on 17 September 2019 (approval number: CRB3180007). This clinical trial was registered in the Japan Registry on Clinical Trials on 1 November 2019 (registry number: jRCTs031190127). Written informed consent must be obtained from all patients.

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### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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