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Rationale and Design for a Multicenter, Phase II Study of Durvalumab Plus Concurrent Radiation Therapy in Locally Advanced Non-Small Cell Lung Cancer: The DOLPHIN Study (WJOG11619L)

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Abstract: Durvalumab (anti-programmed cell death ligand-1) administration after concurrent chemoradiotherapy (cCRT) has improved the survival of patients with unresectable, locally advanced (LA) stage III non-small cell lung cancer (NSCLC). Some patients are unable to complete cCRT and cannot receive immunotherapy due to poor performance status based on adverse events after cCRT. Immunotherapy plays an important role in anti-programmed cell death ligand-1 (PD-L1)-positive advanced NSCLC and is replacing chemotherapy. In addition, radiotherapy and immunotherapy have been reported to have a synergistic effect. This Phase II, multicenter study (DOLPHIN, WJOG11619L, JapicCTI-194840) is designed to assess the efficacy and safety of durvalumab plus concurrent curative radiation therapy for PD-L1-positive unresectable LA-NSCLC without chemotherapy. Unresectable LA stage III NSCLC patients aged 20 years or older with a World Health Organization/Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and PD-L1 positivity are enrolled. The patients will receive curative radiation therapy (60 Gy) plus durvalumab 10 mg/kg every 2 weeks (q2w) for up to 12 months until there is evidence of disease progression (PD) or unacceptable toxicity. The primary endpoint is the 12-month progression-free survival rate as assessed by an independent central review. The secondary endpoints are progression-free survival, overall survival, objective response rate, treatment completion rate, and safety. Recruitment began in September 2019.

Keywords: clinical study, locally advanced non-small cell lung cancer, immunotherapy, programmed cell death ligand-1, durvalumab, radiation

Introduction

Approximately one-third of non-small-cell lung cancers (NSCLCs) are found in locally advanced (LA) disease, stage III at diagnosis. LA-NSCLC is considered potentially curable, but The 5-year survival rate was reported to be approximately 20%.¹⁻³ The former standard care for patients with LA-NSCLC was concurrent chemoradiotherapy (cCRT). However, the median progression-free survival (PFS) was approximately 9 months.²

The PACIFIC study has demonstrated significant PFS prolongation by consolidation with the anti-programmed cell death ligand-1 (PD-L1) agent durvalumab compared to placebo after cCRT (median PFS: 16.8 months, HR: 0.52).⁴ cCRT followed by durvalumab consolidation is now the standard of care, but only patients with good performance status (PS) can move on to consolidation therapy after cCRT. There are



no clear data on how many patients could receive durvalumab consolidation. The data on consolidation therapy using chemotherapy show that only approximately 70% of patients receive consolidation therapy.^{2,5,6} In the exploratory analysis from PACIFIC, administration of durvalumab immediately after completion of cCRT (≤ 14 days) has been shown to provide increased benefit. Basic research has established that radiation enhances the antitumour immune response and that the combination of immune checkpoint inhibitors (ICIs) and radiation has a synergistic effect.⁷ In addition, the concurrent administration of a PD-1 inhibitor and radiation has been shown to increase immune activation compared to other treatment timings in mouse models.⁸ Therefore, combination therapy of concurrent ICI and radiotherapy is expected to have a synergistic effect. Presently, several Phase I–II clinical trials with combined ICI and cCRT were reported (Table 1).^{9–11} The treatment strategy may be intriguing, but there are some questions and problems. Chemotherapy causes bone marrow suppression and organ damage as AEs. In particular, neutropenia (\geq grade 3) and febrile neutropenia develop in approximately 18–53% and 3–8% of cases, respectively, under cCRT.^{5,6} Radiation therapy has to be interrupted due to those AEs. Moreover, we must take into account that chemotherapeutic agents and their premedication, such as glucocorticoids, can affect the immune system and response to immunotherapy when combined with ICIs. Also, radiotherapy combined with immunotherapy may increase the incidence of pneumonitis.

On the other hand, in advanced NSCLC, the PD-1 inhibitor pembrolizumab significantly prolongs overall survival (OS) in PD-L1-positive patients compared to

platinum-based chemotherapy.¹² Therefore, it is no exaggeration to say that ICIs are replacing chemotherapy in PD-L1 positive lung cancer.

From the above background, the key drug used in combination with radiotherapy seems to be ICIs. It is unclear whether chemotherapy is essential for the treatment of LA-NSCLC. Thus, we designed this phase II study to assess the efficacy and safety of durvalumab plus concurrent curative radiation therapy for LA-NSCLC without chemotherapy.

Materials and Methods

Study Design and Objective

DOLPHIN is a prospective, multicenter, single-arm, phase II study that is designed to evaluate the efficacy and safety of durvalumab plus concurrent curative radiation therapy for PD-L1-positive unresectable LA-NSCLC.

Endpoints

The primary endpoint is the 12-month PFS rate assessed by independent central review.

The secondary endpoints are PFS, OS, the objective response rate, the disease control rate, time to death or distant metastasis, the treatment completion rate, and safety.

Treatment

Patients receive durvalumab 10 mg/kg every 2 weeks (q2w) for up to 12 months until evidence of disease progression (PD) or unacceptable toxicity, whichever comes first. Radiation is started on day 1 of durvalumab

Table 1 Reported Studies of Combination Immune Checkpoint Inhibitors with CRT for Locally Advanced NSCLC

Trial	Phase	n	Type of Radiation	Treatment	Median PFS (Months)	1-Year PFS Rate (%)	Median OS (Months)	Gr \geq 3 Pneumonitis (%)
NICOLAS (ETOP) ⁹	II	79	Conventional	Three cycles of cCRT with nivolumab then nivolumab up to 1 year	12.7	53.7	38.8	11.7
DETERRED ¹⁰ Part I	II	10	IMRT, Proton	cCRT \rightarrow chemo-atezolizumab X2 \rightarrow atezolizumab up to 1 year	18.6	–	22.7	0.0
DETERRED ¹⁰ Part II	II	30	IMRT, Proton	cCRT with atezolizumab \rightarrow chemo-atezolizumab X2 \rightarrow atezolizumab up to 1 year	13.2	–	Not reached	3.0
Rutgers ¹¹	I	30	Conventional, IMRT, Proton	Pembrolizumab added in 3+3 cohort from consolidation to cCRT	18.7	69.7	29.4	10.0

Abbreviations: IMRT, intensity modulated radiation therapy; cCRT, concurrent chemoradiotherapy; PFS, progression free survival; OS, overall survival.

treatment. Planned radiation is performed by 3-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT), either of which can be selected for each case. Patients will be scheduled to receive 60 Gy in 30 fractions 5 days per week (prescribed to D95% of the planning target volume [PTV]) administered to involved fields (without elective nodal irradiation).

Key Eligibility Criteria

This study consists of two stages of registration (Figure 1). The main eligibility criteria for the primary registration include 1) age of 20 years or older; 2) Eastern Cooperative Oncology Group PS 0 or 1; 3) histologic evidence of NSCLC; and 4) suspected unresectable stage III disease or postoperative recurrent disease that was curable by radiation (Table 2). The main eligibility criteria for the secondary registration include 5) confirmed unresectable stage III disease or postoperative recurrent disease that is curable by the radiation protocol; 6) PD-L1 \geq 1% (SP263 antibody); and 7) adequate organ function, including hematologic, lung, hepatic and renal function.

Study Assessments

Objective tumour assessments are performed by independent central review and investigators in accordance with RECIST v1.1. The assessments are conducted at baseline and every 8 weeks until PD. Safety variables include symptoms, vital signs, physical examinations, evaluation of changes to concomitant medications, clinical laboratory parameters (hematology, serum chemistry), and the incidence, timing and severity of AE. AEs will be graded using the Common Terminology

Criteria for Adverse Events (CTCAE), version 5.0. An independent external data safety monitoring committee will review progress of study treatment, the radiation treatment delivered, and safety data throughout the study. All data will be collected by an electronic data capture (EDC) system.

Early analysis was conducted to examine whether the study could be continued when 20 patients had completed the combination therapy of radiotherapy and durvalumab.

If patients with PD assessed by the investigator were found in 6 cases (30%) or more, the study was discontinued early.

Statistical Analysis

The 12-month PFS rate in the PACIFIC trial was 35.3% (95% confidence interval (CI), 29.0 to 41.7) in the placebo group and 55.9% (95% CI, 51.0 to 60.4) in the durvalumab group.⁴ We assumed the threshold of the 12-month PFS rate to be 28% and the expected rate to be 50%. The number of patients needed to provide 80% power for a one-sided 0.05 level of type I error was calculated to be 32. Considering ineligible patients after enrolment, the sample size was set at 35. PFS and OS will be analysed using the Kaplan-Meier method to estimate the median points with 95% CIs.

Ethical Considerations

This study is being conducted in accordance with the principles of the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. Written informed consent will be obtained from all patients before study enrolment. Moreover, it has been approved by the institutional review

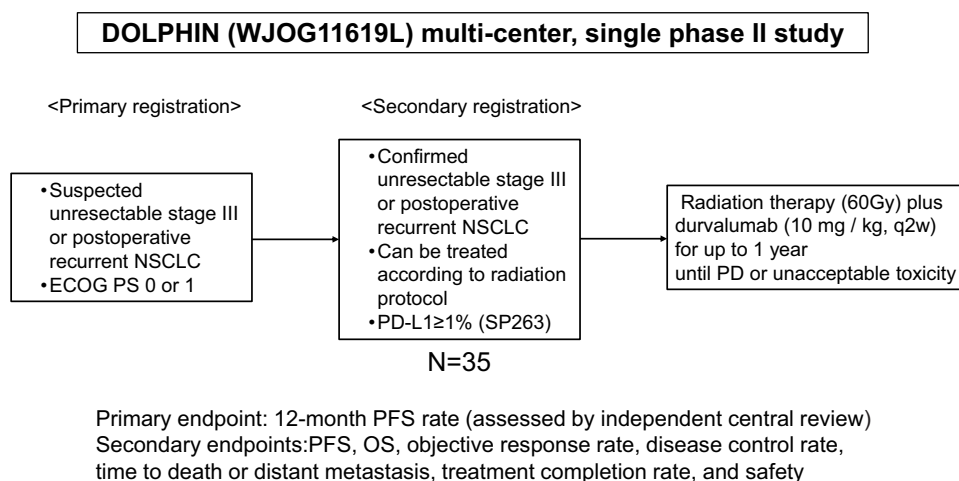


Figure 1 Design of the DOLPHIN study.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; PFS, progression free survival; OS, overall survival.

Table 2 Inclusion and Key Exclusion Criteria

Inclusion Criteria
<p><The primary inclusion criteria></p> <p>Written informed consent</p> <p>Age ≥20 years old</p> <p>Histologic evidence of NSCLC</p> <p>Suspected locally advanced NSCLC (stage IIIA, B, C) or postoperative recurrence</p> <p>ECOG performance status of 0 or 1</p> <p>With measurable lesions</p> <p>Availability of tumor tissue for IHC</p> <p>Adequate organ and bone marrow function</p> <p>SpO₂ ≥93%</p> <p>No past history of thoracic radiation therapy and chemotherapy</p> <p>24 weeks have passed since adjuvant chemotherapy</p> <p>Life expectancy of ≥12 weeks</p> <p>Body weight ≥30kg</p> <p><The secondary inclusion criteria></p> <p>Confirmed unresectable locally advanced NSCLC is curable by the radiation protocol</p> <p>PD-L1 positive of tumor cells (SP263)</p> <p>Irradiation is possible (60 Gy in 30 fractions prescribed to D95% of PTV to involved fields)</p>
Key Exclusion criteria
<p>Active double cancer</p> <p>Active infection, including tuberculosis, hepatitis B and C</p> <p>Interstitial lung disease detected by chest-CT</p> <p>Complication of active autoimmune disease</p> <p>Prescription of more than 10mg PSL continuously</p>

Abbreviations: NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status; IHC, Immunohistochemistry; SpO₂, arterial oxygen saturation of pulse oximetry; PD-L1, programmed cell death ligand-1; CT, computed tomography; PSL, prednisolone.

board of all 12 participating institutions (Kobe University Graduate School of Medicine, Hyogo Cancer Center, Kindai University, Kobe City Medical Center General Hospital, Kansai Medical University Hospital, Sendai Kousei Hospital, Kyushu University, Wakayama Medical University, Kurume University School of Medicine, Osaka City General Hospital, National Hospital Organization Kyushu Cancer Center, and Aichi Cancer Center

Hospital). The study protocol has been registered in the JapicCTI database: JapicCTI-194840.

Discussion

New treatment options are required for patients with unresectable LA-NSCLC. The DOLPHIN study was designed to evaluate the efficacy and safety of durvalumab plus concurrent radiation therapy for unresectable LA-NSCLC without chemotherapy.

Combined ICI and cCRT are possible new treatment strategy, but the efficacy and safety concerns remain unclear. In the NICOLAS study, which is a single-arm phase II trial of cCRT along with the PD-1 antibody nivolumab, grade 3 or higher pneumonitis occurred in 11.7% (grade 5; 1) of cases, which was three times higher than that of the PACIFIC trial.⁹ It may be due to cCRT combined with immunotherapy. Notably, the treatment success rate of the protocol was 39.2%, and 43.5% of treatment cases were terminated due to adverse events (AEs). Moreover, the 1-year PFS (53.7%) and the median PFS (12.7 months) were lower than expected based on the results from the PACIFIC study.⁴ The other phase I–II studies also showed the similar results.^{10,11} Now, the Phase III study to evaluate the efficacy and safety of cCRT plus concurrent durvalumab compared with conventional cCRT is now ongoing (PACIFIC II). Even if PACIFIC II regimen results in better, we cannot know whether cCRT plus concurrent ICI or cCRT followed by ICI is better.

Although the best choices and timing of immunotherapy, radiotherapy, and systematic chemotherapy remain unclear, the essential key drug type used in combination with radiotherapy seems to be ICIs. Currently, there are limited trials of combined immunotherapy and radiation therapy without chemotherapy (Table 3). Our trial is the first prospective study for only unresectable LA-NSCLC, and which will not be confirmed by the PACIFIC and ongoing PACIFIC II. We believe we can present the new

Table 3 Ongoing Studies of Combination Immune Checkpoint Inhibitors with Radiation

Trial	Trial Number	Phase	n	Stage	Eligibility Biomarker	Type of Radiation	Systemic Treatment
ARCHON-I	NCT03801902	I	24	II–III	PD-L1 ≥50%	AHF or conventional radiotherapy	Durvalumab
SPRINT	NCT03523702	I	63	II–III	PD-L1 status	Conventional	Pembrolizumab or chemotherapy
This trial	JapicCTI-194840	II	35	III	PD-L1 ≥1%	Conventional, IMRT	Durvalumab

Abbreviation: AHF, accelerated hyperfractionated.

significance of combination therapy with concurrent ICI and radiotherapy by investigating the safety and efficacy of durvalumab plus concurrent radiotherapy in this study. If this clinical trial has promising results, the therapeutic protocol may be a candidate for a new treatment strategy with low toxicity and high therapeutic effect for patients with unresectable LA-NSCLC. Recruitment began in September 2019, all 35 patients were registered in November 2020, and treatments are now ongoing.

Conclusion

The phase II study will be able to evaluate the efficacy and safety of durvalumab plus concurrent curative radiation therapy for PD-L1-positive unresectable LA-NSCLC without chemotherapy.

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Disclosure

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