West Japan Oncology Group

# [WJOG11619L]

# Phase II study of Durvalumab (MEDI4736) Plus Concurrent Radiation Therapy in Advanced Localized NSCLC Patients (Dolphin study)


[Director of WJOG]

Kazuhiko Nakagawa

Medical Oncology, Kinki University School of Medicine

[Group representative]

Nobuyuki Yamamoto

Department of Pulmonary Medicine and Oncology, Wakayama Medical University

[Coordinating investigator/ Study secretariat]

Name: Motoko Tachihara

Name of institution: Kobe University Graduate School of Medicine

7-5-1, Kusunoki-Cho, Chuo-Ku, Kobe-city, Hyogo 650-0017, Japan

[Study secretariat]

Name: Kayoko Tsujino

Name of institution: Hyogo Cancer Center

13-70 Kiaoji-cho, Akashi-city, Hyogo, JAPAN



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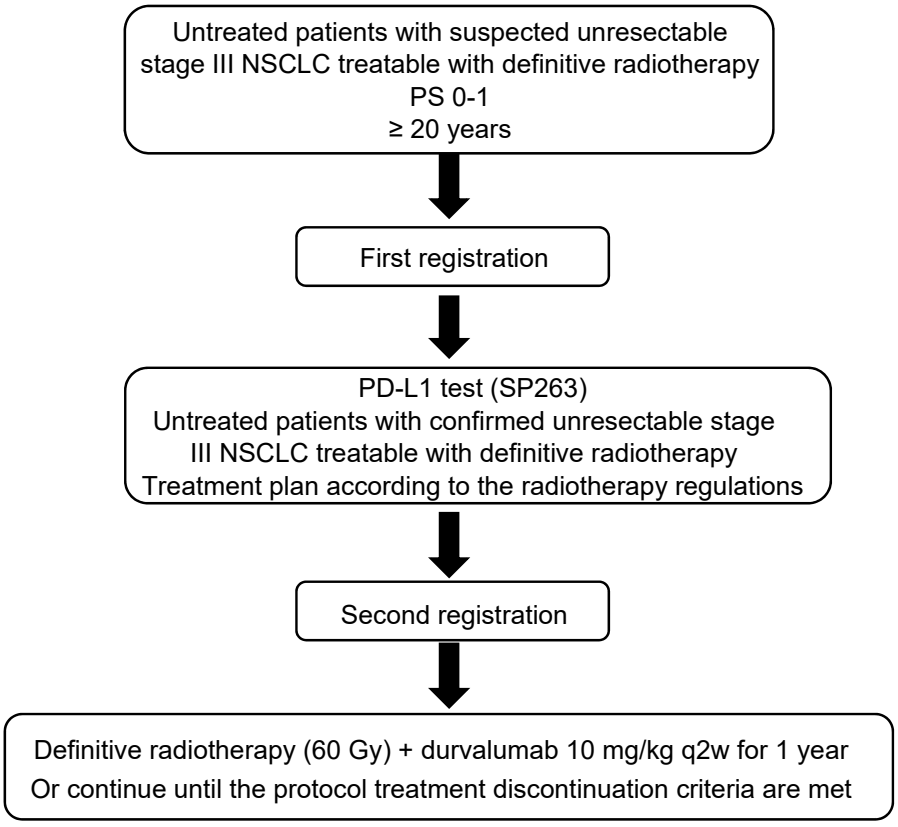
# 0. Summary

## 0.1. Schema




## 0.2. Objectives

The objective of this study is to assess the efficacy and safety of the combination therapy of durvalumab and definitive radiotherapy in untreated patients with unresectable stage III NSCLC treatable with definitive radiotherapy.

- **Primary endpoint:** 12-month proportion progression-free
- **Secondary endpoints:** Progression-free survival, 18-month proportion progression-free, overall survival, 2-year survival rate, treatment completion rate, duration of treatment response, response rate, disease control rate, time to death or distant metastasis, safety, differences in effect depending on patient background / PD-L1 expression

## 0.3. Subjects

### 0.3.1. Eligibility criteria for the first registration

All the following must be satisfied:

[IC]

1) Patients aged 20 years or older when the informed consent is obtained
2) Patients providing a written informed consent and willing to comply with the protocol after he / she receives full explanation of the study details prior to the registration in this study.

[Histologic type]

3) NSCLC diagnosed by histology

[Spread of lesions]

4) Patients presumed to be treatable with definitive radiotherapy at the stage IIIA/IIIB/IIIC based on the General Rule for Clinical and Pathological Record of Lung Cancer, 8th Edition or postoperative recurrent disease that is curable by thoracic radiotherapy.
5) Patients with measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver1.1.

[Prior therapy for lung cancer]

6) Untreated with chemotherapy
7) Postoperative recurrent patients can be registered if there were no adjuvant therapy or 24 weeks (168 days) have passed since the last date of administration of the postoperative chemotherapy. Patients who received the postoperative radiotherapy are excluded.

[Physical findings and examination]

8) 0-1 in ECOG performance status (PS)
9) There are no severe disorders in major organs (bone marrow, heart, lung, liver, kidney, etc.), and the following criteria are satisfied:
   (Use the latest data for registration among those obtained within 14 days from the registration date. Based on the registration date, the same day of the week as two weeks before is allowed.)
   - Neutrophil count $\geq 1500/mm^3$
   - Hemoglobin $\geq 9.0$ g/dL
   - Platelet count $\geq 10 \times 10^4/mm^3$
   - AST, ALT $\leq 100$ IU/L
   - Total bilirubin $\leq 2.0$ mg/dL
   - Creatinine $\leq 2.0$ mg/dL
   - Creatinine clearance $\geq 40$ mL/min (estimated value by the Cockcroft-Gault formula[*1])
   - SpO2 $\geq 93\%$ (room air)
10) Patients must weigh 30 kg or more.

*[1] When the estimated value of creatinine clearance is less than 40 mL/min, an actual measurement value is essential by the second registration.

[Others]

11) Patients expected to survive for at least 12 weeks from the start of treatment.

0.3.2. Eligibility criteria for the second registration

[Stage]

1) Patients at stage IIIA/IIIB/IIIC treatable with definitive radiotherapy based on the Classification of Lung Cancer, 8th Edition or postoperative thoracic recurrence that is curable by radiotherapy.

[PD-L1 expression]

2) PD-L1 expression of tumor cells accounts for 1% or more (SP263)

[Radiotherapy]

3) A radiation oncologist confirms that the irradiation specified in the WJOG 11619L Radiotherapy Regulations (Addendum) is possible.

[Others]

4) Patients can be confirmed to be post-menopausal or have a negative urine or serum pregnancy test result.

- Women ≤ 50 years of age: Pregnancy test negative. (However, pregnancy test will be omitted if the patient has undergone bilateral oophorectomy, bilateral salpingectomy, or hysterectomy.)
- Women ≥ 50 years of age: Have been amenorrheic for ≥ 12 months following cessation of all exogenous hormonal treatments. If not amenorrheic, a pregnancy test will be performed. (However, pregnancy test will be omitted if the patient has undergone bilateral oophorectomy, bilateral salpingectomy, or hysterectomy.)

## 0.4. Exclusion criteria for the second registration

[Multiple cancers]

1) Active multiple cancers*[1]

*[1] Multiple cancers refer to homochronous multiple cancers or heterochronous multiple cancers with a cancer-free period of no more than 3 years. Carcinoma in situ (intraepithelial carcinoma)

or lesions equivalent to intramucosal carcinoma that are deemed to have been cured by local treatment are not included in active multiple cancers.

[Complications/infection]

2) Patients with active systemic infection. (Including tuberculosis)

3) Patients with active hepatitis B or active hepatitis C (even if HBs antibody is positive, they are eligible if the viral load is below sensitivity and hepatitis is not active).

[Complications/interstitial pneumonia/autoimmune disease]

4) Patients with interstitial lung disease evident on CT.

5) Patients with complicating active autoimmune disease or history of autoimmune disease requiring steroid therapy or immunosuppressants*[2]

*[2] Note that the following patients are eligible:

(1) Patients using a stable dose of thyroid supplement hormone for autoimmune-related hypothyroidism

(2) Patients receiving a stable dose of insulin regimen for well-controlled type I diabetes mellitus

(3) Patients are eligible when patients with eczema, psoriasis, lichen simplex chronicus or only dermatologic symptoms of vitiligo satisfy the following:

The rash area accounts for less than 10% of the body surface area (BSA); only topical-steroid treatment is required; and no acute exacerbation of underlying condition observed within the past 12 months. Patients are eligible in this study when the dose of steroids is equivalent to prednisolone 10 mg/day or less.

6) Patients who need continued systemic (oral or intravenous) administration of steroids equivalent to prednisolone > 10 mg/day, or who used immunosuppressants within 14 days before registration for indications other than autoimmune disease*[3]

*[3] However, patients receiving steroids 10 mg/day or less for the following reasons are eligible:

(1) Patients taking oral steroid equivalent to prednisolone 10 mg/day or less as replacement therapy for adrenal failure, etc.

(2) Patients who acutely received steroid equivalent to prednisolone 10 mg/day or less for COPD

(3) Patients receiving mineralocorticoid for orthostatic hypotension

(4) Patients treated with steroids as premedication for hypersensitivity reactions (e.g. premedication before CT scan) or topical steroids (e.g. nasal cavity, eye, skin)

[Complications/circulatory organ]

7) Patients with a history of symptomatic congestive heart failure, unstable angina, or myocardial infarction within 1 year prior to registration.

8) Patients with clinically serious arrhythmia detected by ECG (complete left bundle branch block,

third-degree atrioventricular block, second-degree atrioventricular block).

[Others]

9) Patients with a history of immunotherapy including immune antibody therapy.

10) Patients showing morphological differentiation in the nervous system or histologic type combined with small cell lung cancer and NSCLC.

11) Patients with a history of serious drug allergy.

12) Patients with uncontrolled diabetes mellitus despite appropriate treatment.

13) Pregnant females, lactating females, females who may be pregnant at the moment, or males or females with reproductive capacities who have no intention of using effective contraception from screening to 90 days after the last dose of durvalumab monotherapy.

- Women ≤ 50 years of age: Pregnancy test negative. (However, pregnancy test will be omitted if the patient has undergone bilateral oophorectomy, bilateral salpingectomy, or hysterectomy.)
- Women ≥ 50 years of age: Have been amenorrheic for ≥ 12 months following cessation of all exogenous hormonal treatments. If not amenorrheic, a pregnancy test will be performed. (However, pregnancy test will be omitted if the patient has undergone bilateral oophorectomy, bilateral salpingectomy, or hysterectomy.)

14) Patients judged to be difficult to be registered for this study due to clinically important mental illness.

15) Patients who may become a blood donor during the study and within 90 days from the last administration.

16) Patients who received a live vaccine within 30 days before registration. Patients who may receive a live vaccine during the study and within 30 days from the last administration.

17) Other patients judged by the investigator, etc. to be ineligible.

## 0.5. Treatment

Durvalumab will be combined with radiotherapy(60Gy). Durvalumab 10 mg/kg will be administered on Day 1 and as 2-week (14-day) cycles for 1 year. Definitive thoracic radiotherapy will begin on Day 1, Durvalumab be administered up to 1 year or until the protocol discontinuation criteria are met.

## 0.6. Planned number of registered subjects and research period

Target number of subjects to be registered: 35

Study period: From August 15, 2019 to 31 May

Subject registration period: From August 15, 2019 to December 15, 2020

Follow-up period: 1.5 years from the date of last subject's registration

Note that early analysis will be performed according to the procedure separately specified to determine whether or not treatment should be discontinued when 20 subjects complete a simultaneous combination therapy of radiotherapy and durvalumab. When progressive disease (PD) rate at the end of radiotherapy is observed in 6 subjects (30%) or more, the study will be terminated early. Registration will not be suspended during the early analysis.

## 0.7. Contact


Clinical Study Coordinating Secretariat

EPS Corporation

2-23 Shimomiyabicho, Shinjuku-ku, Tokyo 162-0822

<Contact>

7th floor KingOsaka Biru 1-7 Toyotsucho, Suita. Osaka 564-0051

TEL : [redacted] / FAX: [redacted]

E-mai; prj-dolphin-jimu@eps.cojp

●Contact for inclusion/exclusion criteria in patient registration

Motoko Tachihara

Kobe University Graduate School of Medicine

7-5-1, Kusunoki-Cho, Chuo-Ku, Kobe-city, Hyogo 650-0017

FAX: [redacted]

TEL: [redacted]

e-mail: mt0318@med.kobe-u.ac.jp

●Contact for radiation therapy

Kayoko Tsujino

Hyogo Cancer Center

13-70 Kiaoji-cho, Akashi-city, Hyogo, JAPAN 673-8558

TEL : [redacted] / FAX : [redacted]

e-mail:tsujinok@gmail.com

## 0.8. Study Operation Cost

The cost for operation of this study will be supported by AstraZeneca K.K..

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# 1. Objective

The objective of this study is to assess the efficacy and safety of the combination therapy of durvalumab and definitive radiotherapy in untreated patients with unresectable stage III NSCLC treatable with definitive radiotherapy.

- **Primary endpoint:** 12-month proportion progression-free
- **Secondary endpoints:** Progression-free survival, 18-month proportion progression-free, overall survival, 2-year survival rate, treatment completion rate, duration of treatment response, response rate, disease control rate, time to death or distant metastasis, safety, difference in effect depending on patient background/PD-L1 expression

# 2. Background and rationale for the study plan

## 2.1. Background

### 2.1.1. Epidemiology of lung cancer

Lung cancer is a common malignancy in the world. According to data from the Global Burden of Cancer Study (GLOBOCAN) 2012 reported by the WHO European Region, the annual number of patients with lung cancer is estimated to be approximately 1.825 million and the annual number of deaths is estimated to be approximately 1.59 million in the world[1)]. According to "Cancer Registries/Statistics" by the Center for Cancer Control and Information Services of the National Cancer Center in Japan, the estimated number of patients with lung cancer in 2017 was 86,700 men and 42,000 women, totaling 128,700, and the numbers of patients with cancer by site show that lung cancer ranked the third after stomach and large intestine[2)]. The number of deaths from lung cancer in 2017 was estimated to be the highest (55,600 men, 22,400 women, totaling 78,000)[2)]. Lung cancer is classified into adenocarcinoma, squamous cell carcinoma, large cell carcinoma, small cell carcinoma, etc. according to the histologic type[3)], and is broadly divided into small cell lung cancer and non-small cell lung cancer according to the pathology and treatment policy. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers, and is classified into squamous cell carcinoma, adenocarcinoma, large cell carcinoma, etc. according to the histologic type. Adenocarcinoma accounts for more than half of all NSCLC[4)]. Treatment of lung cancer is selected based on staging by the TNM classification. According to the Clinical Practice Guideline for Lung Cancer 2018 by the Japan Lung Cancer Society[5)], surgical resection is the standard treatment for clinical stage I and II NSCLC. For locally advanced clinical stage III cancer, therapeutic strategy is subdivided based on T and N factors. For clinical stage IIIA, either surgical resection,

chemoradiotherapy, or radiotherapy alone is selected according to the TNM classification, resectability, and feasibility of definitive radiotherapy. For clinical stage IIIB, chemoradiotherapy is the standard therapy. Among unresectable clinical stage IIIA, IIIB, and IIIC cancers, chemotherapy is the standard therapy for patients untreatable with definitive radiotherapy and patients with clinical stage IV cancer.

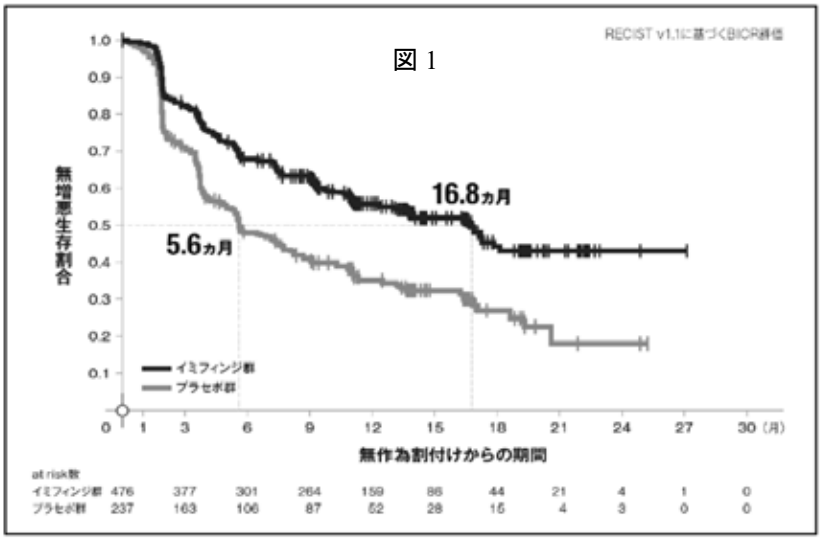
#### 2.1.2. Selection of study population and its rationale

According to a nationwide survey of lung cancer patients treated in Japan in 2002, of patients in whom NSCLC was diagnosed, 11.8% had clinical stage IIIA and 16.3% had clinical stage IIIB cancer at the time of diagnosis, and the 5-year survival rate of these patients was reported to be 30.9% and 16.7%, respectively[6]. For these stage III NSCLCs, the result of a meta-analysis summarizing studies comparing radiation monotherapy and chemoradiotherapy showed that the survival rate in patients treated with chemoradiotherapy was significantly higher than that in patients treated with radiation monotherapy (HR 0.87, P=0. 0052, 15-30% reduction in the risk of death at 2 years)[7)-8)], indicating that chemoradiotherapy has long been the main treatment approach. However, the 5-year survival rate is as poor as approximately 15-20%[7)-9)], which is by no means satisfactory. Therefore, in this study, patients with unresectable NSCLC treatable with definitive radiotherapy were selected as the target population.

## 2.2. Standard of care for the subjects

In recent years, PD-1/PD-L1 inhibitors, immuno-checkpoint inhibitors, were clinically used as standard therapy for advanced/recurrent NSCLC, and their effects were also considered promising in stage III. PACIFIC Study (an international phase III study) comparing durvalumab consolidation therapy (the durvalumab group) with the placebo group in patients with stage III NSCLC who achieved disease control after simultaneous chemoradiotherapy was conducted. Primary endpoints were set as both progression-free survival (PFS) and overall survival (OS), and the result of an intermediate analysis showed that the hazard ratio (HR) for PFS was 0.52 (16.8 months vs 5.6 months, 95% CI: 0.42-0.65, P < 0.001), indicating that PFS was significantly extended in the durvalumab group as compared to the placebo group (Figure 1)[10)]. Then, it was reported that OS was also significantly extended in the durvalumab group with HR of 0.68 (NR vs 28.7 months, 95% CI: 0.47-0.997, P=0.00251)[11)]. Based on this study result, durvalumab was approved in Japan in July 2018 as maintenance therapy after definitive chemoradiation therapy for unresectable locally advanced NSCLC and became a new standard therapy.

図 1




無増悪生存期間のKaplan-Meier曲線（最大解析対象集団）

## 2.3. Protocol treatment

2.3.1. Study treatment regimen in this study

Definitive thoracic radiotherapy (60 Gy) and durvalumab 10 mg/kg are used in combination. Durvalumab will be administered on Day 1 and will be administered in 2-week cycles. Radiotherapy will begin on Day 1. Durvalumab will be continued for up to 1 year or until the protocol treatment discontinuation criteria are met.

2.3.2. Rationale for study plan

2.3.2.1. Rationale for concurrent use of radiotherapy and PD-L1 antibody

Detailed examinations of PACIFIC Study revealed that patients who received durvalumab early (less than 14 days) after chemoradiotherapy showed better results on PFS than those who received after 14 days[10]. In patients who received durvalumab less than 14 days after radiotherapy, the PFS was HR 0.33 (95% CI: 0.20-0.55), and HR 0.70 (95% CI: 0.51-0.95 ) after 14 days. The efficacy of the combination use of radiotherapy and immune antibody therapy has been shown in many basic studies[12)-19)]. Irradiation causes an inflammatory response in the cancer microenvironment through destruction of cancer cells, matures dendritic cells that present antigens by causing immunogenic cell death (ICD), and induces more anti-tumor T cells. This causes not only direct action of T cells but also increases in memory cells and abscopal effects. Abscopal effect is a phenomenon in which tumor response is observed in a distant lesion outside the radiation field by the enhancement of the systemic tumor immunity due to radiotherapy. Although the tumor response

is not observed frequently in radiation monotherapy, it may be enhanced by combining immuno-checkpoint inhibitors with radiotherapy[15]. Radiation and PD-L1 expression have also been investigated, and radiotherapy has been shown to increase PD-L1 expression[15] while PD-L1 expression decreases over time[20]. In addition, it has been reported that the combination of radiotherapy and PD-L1 antibody is most effective not when sequentially administered but when concurrently used[21]. These phenomena are consistent with the fact that administration of durvalumab early after radiotherapy was more effective in PACIFIC. Moreover, in a clinical research, there was a report on a phase II comparative study in patients with oligometastatic advanced NSCLC, in which the group receiving pembrolizumab after radiotherapy on a metastatic site was compared with the group receiving pembrolizumab without radiotherapy. It was suggested that the group receiving pembrolizumab after radiotherapy had a prolonged OS effect as well as a better response rate[22]. This shows the abscopal effect, a high systemic effect induced by the combination of radiotherapy and immuno-checkpoint inhibitors. Based on the above, it is hypothesized that the concurrent use of radiotherapy and PD-L1 inhibitors may have synergistic effects and may be most effective.

2.3.2.2. Rationale for omission of chemotherapy

For stage III NSCLC, the roles of chemotherapy are a systemic anticancer effect and a radiosensitization effect (local effect to enhance the antitumor effect). As first-line treatment for patients with locally advanced or metastatic NSCLC which express PD-L1 in at least 1% of tumor cells, the anti-PD-1 antibody pembrolizumab significantly prolonged overall survival in patients treated with pembrolizumab monotherapy[23], demonstrating the superiority of PD-1 antibody therapy to chemotherapy in terms of systemic antitumor effect (KEYNOTE-042 Study). Although these results were obtained in patients with advanced NSCLC, it has been reported that immuno-checkpoint inhibitors exert their effects at a lower tumor burden[24], and therefore immuno-checkpoint inhibitors are expected to be more effective than chemotherapy also in stage III lung cancer. On the other hand, the sensitizing effect of immunotherapy has been suggested in basic studies as shown in 2.3.2.1. In addition, immune antibody therapy also has a potent local antitumor effect as well as a systemic anticancer effect. In a study investigating the effect of preoperative chemotherapy with nivolumab, it has been reported that the response rate by RECIST was 10% and the major pathological response (MPR) was 43% after 2 cycles of preoperative nivolumab[25], and a high local antitumor effect is expected when immuno-checkpoint inhibitors are combined with radiotherapy.

Adverse events caused by chemotherapy include bone marrow depression and organ disorder. Particularly in chemoradiotherapy, approximately 10% of patients experience febrile neutropenia, which may require suspension of radiotherapy. Another report says that there is a correlation between decreased lymphocyte count and prognosis in chemoradiotherapy[26]. Therefore, the

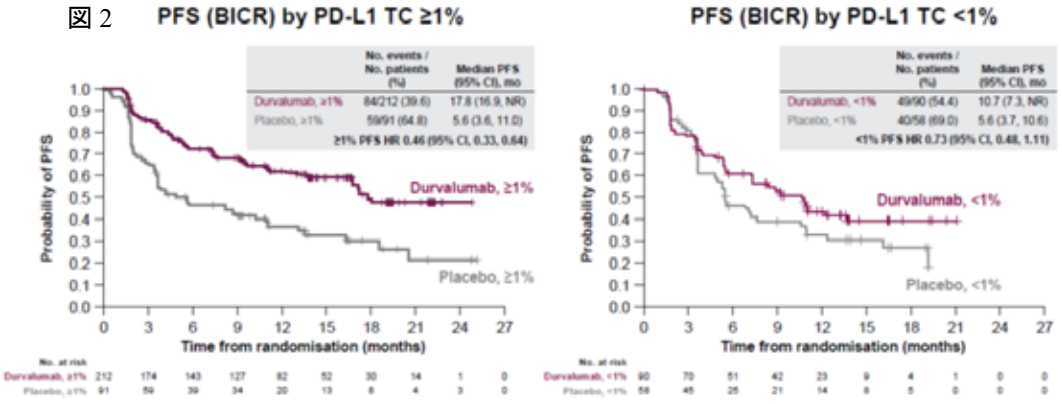
possibility that suppressing bone marrow and decreasing lymphocyte count by chemotherapy may decrease immune function cannot be ruled out. In addition, steroids are generally administered to prevent adverse events such as nausea and allergy associated with chemotherapy. However, early concomitant use of steroids has been reported to be a poor prognostic factor in immune antibody therapy[27]. Therefore, steroids may weaken the effects of immune antibody therapy.

Based on the above, it is considered that if chemotherapy can be replaced with immuno-checkpoint inhibitors in conventional chemoradiotherapy for stage III NSCLC, the treatment may be effective with fewer adverse events.

2.3.2.3. Rationale for including patients with PD-L1 (SP263) ≥1%

Maintenance therapy effect of durvalumab was not shown in patients with negative PD-L1 (SP263) expression prior to treatment even in an post-hoc analysis of PACIFIC Study[28]. Therefore, PD-L1 negative was excluded from the target population.

図 2




2.3.2.4. Other treatment regimens under development

Currently, a triple therapy regimen is tested in which chemoradiotherapy and immunotherapy are concomitantly used and immunotherapy is conducted as maintenance therapy (NICOLAS-ETOP, PACIFIC II). In NICOLAS-ETOP, the safety of 3-drug combination therapy with nivolumab is being examined. The incidence of grade 3 or higher radiation pneumonitis reached 10.3%, approximately 3-fold than that of the durvalumab group in PACIFIC. PACIFIC II is a study on triple therapy with durvalumab, which is currently ongoing and no result has been reported. Although the results of PACIFIC II are unknown, the triple therapy with chemoradiotherapy and immunotherapy poses safety concerns including pneumonitis[17]. Even if the safety of PACIFIC II is confirmed, it will not be possible to perform the triple therapy in all patients, and there will also be many patients who cannot use the triple therapy in daily clinical practice. This study is designed to examine the efficacy and safety of radiotherapy and immunotherapy that cannot be confirmed in PACIFIC and

PACIFIC II, and it will be of sufficient value to evaluate the results. In addition, if the study yields promising results, it may be a candidate for a new treatment with less toxicity and a high therapeutic effect.

Based on the results of these clinical and basic studies, durvalumab in combination with definitive radiotherapy may be a new treatment regimen with fewer adverse events and a high therapeutic effect for untreated patients with unresectable stage III NSCLC treatable with definitive radiotherapy. Therefore, we believed that it is beneficial to identify its efficacy and safety, and planned a Phase II Multicenter Single-Arm Study (an investigator-initiated clinical study).

## 2.4. Study design

### 2.4.1. Clinical hypothesis and phase setting for this study

This is a phase II study to explore the efficacy and safety of the combination therapy with durvalumab and definitive radiotherapy in untreated patients with unresectable stage III NSCLC treatable with definitive radiotherapy.

### 2.4.2. Rationale for endpoints

· Primary endpoint: 12-month progression-free survival rate

PFS curve shows The difference between the two groups (placebo and durvalumab) has widen at approximately 6 months, which is one of the primary endpoints in the PACIFIC Study, and the difference is almost parallel since after 6monts. In immunotherapy, durable response can be expected in responders, and it is considered clinically significant in patients treatable with definitive radiotherapy to be progression-free for 1 year or longer than the median progression-free survival. Thus, proportion progression-free at 12 months was adopted as the primary endpoint in this study.

· Secondary endpoints: Progression-free survival, 18-month proportion progression-free, overall survival, 2-year survival rate, treatment completion rate, duration of treatment response, response rate, disease control rate, time to death or distant metastasis, safety, difference in effect depending on patient background/PD-L1 expression

As the efficacy endpoints in this study, the above items, which are the same as those in PACIFIC Study, will be assessed in addition to the 12-month proportion progression-free. The incidence of adverse events will also be assessed as there are no safety data on the combination use of radiotherapy and durvalumab.

### 2.4.3. Rationale for the number of registered subjects

In PACIFIC Study, the 12-month progression-free survival rate was 35.3% (95%CI: 29.0 to 41.7) in the placebo group and 55.9% (95%CI: 51.0 to 60.4) in the durvalumab group. The 12-month progression-free survival rate in patients with PD-1 ≥1% was 35% in the placebo group and 62% in the durvalumab group, although exact statistical values were not shown. Differently from PACIFIC Study, it should also be considered in this study that patients who cannot transit to durvalumab maintenance therapy due to enlarged tumors developed after immunoradiotherapy and patients who cannot transit to maintenance therapy due to decreased PS or adverse events account for 20% to 30% of all. Taking into account that inferiority to the conventional chemoradiotherapy is not allowed and based on the above, 32 patients are required when calculated on the assumption of the 12-month progression-free survival rate threshold of 28%, one-sided significance level of 5% with the expected value of 50%, the power of 80%, the registration period of 12 months and the follow-up period of 18 months. It was planned to registratet 35 patients considering some deviations and dropouts.

In addition, as this study does not require chemotherapy and the possibility of undertreatment cannot be ruled out, an early analysis will be carried out from an ethical point of view. Based on the facts that the disewase control rate of PROCLAIM Study[20] was 70% to 80% and the proportion of PDof 3 groups in WJTOG0105[21] was 10% to 13%, etc., the study will be terminated early if the proportion of PD at the time of immunoradiotherapy completion exceeds 30% (6 subjects or more) of the 20 analyzed subjects.

## 2.5. Planned number of registered subjects and research period

Target number of subjects to be registered: 35
Study period: From August 15, 2019 to February 28, 2022 (for 2.5 years)
Subject registration period: From August 15, 2019 to September 15, 2020 (for 1 year)
Follow-up period: 1.5 years from the date of last subject's registration

Note that early analysis will be performed according to the procedure separately specified to determine whether or not treatment should be discontinued when 20 subjects complete a simultaneous combination therapy of radiotherapy and durvalumab. When the proportion of PD at the end of radiotherapy is observed in 6 subjects (30%) or more, the study will be terminated early. Registration will not be suspended during the early analysis.

# 3. Outline of the study drug

## 3.1. Name

1) Investigational Drug

Durvalumab

2) Nonproprietary name

Durvalumab (Genetical Recombination)（JAN）durvalumab（INN）

3) Structural formula

Glycoprotein is composed of 3 H chains ( $\gamma$ 1 chain) which consist of 451 amino acid residues and 2 L chains ( $\kappa$ chain) which consist of 215 amino acid residues.

4) Formula and molecular weight

Formula: $C_{6502}H_{10018}N_{1742}O_{2024}S_{42}$（protein portion, 4 chains）

H-chain: $C_{2212}H_{3401}N_{589}O_{677}S_{16}$

L-chain: $C_{1039}H_{1612}N_{282}O_{335}S_{5}$

Molecular weight: approximate 149,000 Da

5) Dosage form/strength

Nonproprietary name: Durvalumab

Dosage form/strength: 500mg injection (1 vial 10mL containing 500mg)

## 3.2. Study drug labeling

The packaging and labeling of the investigational drug is described in the separately established "Procedure for Control of the Investigational Drug."

## 3.3. Storage of the study drug

The investigational drug is stored in a safe place under appropriate storage conditions. Appropriate storage conditions and transportation conditions are described in the label attached to the container of the investigational drug, the Investigator's Brochure, and the Procedure for Control of the Investigational Drug.

## 3.4. Procedures for storage and control of the study drug

The investigational drug is provided by the investigational drug supplier for the sponsor-investigator at each study center at a specified time after submission of a clinical study plan notification. A specific procedure for providing the investigational drug is stipulated in the separately established "Procedure for Control of the Investigational Drug." The sponsor-investigator explains the contents of the study to the investigational drug controller at the study center, submits the "Procedure for Control of the Investigational Drug" to the investigational drug controller, and

requests for the storage and control of the investigational drug. The investigational drug controller appropriately stores and controls tablets of the investigational drug and their outer containers during the study period whether tablets of the investigational drug are used or not and prepares an investigational drug accountability log to know the usage of the investigational drug. The sponsor-investigator checks investigational drug control records, remaining tablets, and entries in the case report forms (CRFs) for consistency, investigates the cause of any inconsistency, and makes necessary corrections immediately.

After completion of the study, the investigational drug controller returns unused tablets of the investigational drug and empty containers to the sponsor-investigator. When returning them, the investigational drug controller should make the privacy information of each subject such as subject name (initials) and medical record ID illegible. If losing unused tablets of the investigational drug or their empty containers, the investigational drug controller should document what has been lost and reasons. The sponsor-investigator discards all of the unused tablets of the investigational drug according to "Procedure for Control of the Investigational Drug" and their empty containers returned by the investigational drug controller.

# 4. Diagnostic criteria and staging

## 4.1. Diagnostic criteria

Follow the "Classification of Lung Cancer, 8th Edition" for diagnosis of lung cancer.

## 4.2. Staging

TNM Classification (UICC 8th edition) is used for the staging of NSCLC at the first diagnosis.

# 5. Eligibility criteria

## 5.1. Eligibility criteria for the first registration

All the following must be satisfied:

[IC]

1) Patients aged 20 years or older when the informed consent is obtained
2) Patients providing a written informed consent and willing to comply with the protocol after he/she receives full explanation of the study details prior to the registration in this study.

[Histologic type]

3) NSCLC diagnosed by histology

[Spread of lesions]

4) Patients presumed to be treatable with definitive radiotherapy at the stage IIIA/IIIB/IIIC based

on the Classification of Lung Cancer, 8th Edition or postoperative recurrent disease that is curable by thoracic radiotherapy.

5) Patients with measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver1.1.

[Prior therapy for lung cancer]

6) Untreated with chemotherapy

7) Postoperative recurrent patients can be registered if there were no adjuvant therapy or 24 weeks (168 days) have passed since the last date of administration of the postoperative chemotherapy. Patients who received the postoperative radiotherapy are not excluded.

[Physical findings and examination]

8) 0-1 in ECOG performance status (PS)

9) There are no severe disorders in major organs (bone marrow, heart, lung, liver, kidney, etc.), and the following criteria are satisfied:
(Use the latest data for registration among those obtained within 14 days from the registration date. Based on the registration date, the same day of the week as two weeks before is allowed.)

- Neutrophil count $\geq 1500/mm^3$
- Hemoglobin $\geq 9.0$ g/dL
- Platelet count $\geq 10 \times 10^4/mm^3$
- AST, ALT $\leq 100$ IU/L
- Total bilirubin $\leq 2.0$ mg/dL
- Creatinine $\leq 2.0$ mg/dL
- Creatinine clearance $\geq 40$ mL/min (estimated value by the Cockcroft-Gault formula[*1])
- SpO2 $\geq 93\%$ (room air)

10) Patients must weigh 30 kg or more.

*[1] When the estimated value of creatinine clearance is less than 40 mL/min, an actual measurement value is essential and is necessary to confirm by the second registration.

[Others]

11) Patients expected to survive for at least 12 weeks from the start of treatment.

## 5.2. Eligibility criteria for the second registration

[Stage]

1) Patients at stage IIIA/IIIB/IIIC treatable with definitive radiotherapy based on the Classification of Lung Cancer, 8th Edition or postoperative thoracic recurrence that is curable by radiotherapy.

[PD-L1 expression]

2) PD-L1 expression of tumor cells accounts for 1% or more (SP263)

[Radiotherapy]

3) A radiation oncologist confirms that the irradiation specified in the WJOG 11619L Radiotherapy Regulations (Addendum) is possible.

[Others]

4) Patients can be confirmed to be post-menopausal or have a negative urine or serum pregnancy test result.

- Women ≤ 50 years of age: Pregnancy test negative. (However, pregnancy test will be omitted if the patient has undergone bilateral oophorectomy, bilateral salpingectomy, or hysterectomy.)
- Women ≥ 50 years of age: Have been amenorrheic for ≥ 12 months following cessation of all exogenous hormonal treatments. If not amenorrheic, a pregnancy test will be performed. (However, pregnancy test will be omitted if the patient has undergone bilateral oophorectomy, bilateral salpingectomy, or hysterectomy.)

### 5.3. Exclusion criteria for the second registration

[Multiple cancers]

1) Active multiple cancers*[1]

*[1] Multiple cancers refer to homochronous multiple cancers or heterochronous multiple cancers with a cancer-free period of no more than 3 years. Carcinoma in situ (intraepithelial carcinoma) or lesions equivalent to intramucosal carcinoma that are deemed to have been cured by local treatment are not included in active multiple cancers.

[Complications/infection]

2) Patients with active systemic infection. (Including tuberculosis)

3) Patients with active hepatitis B or active hepatitis C (even if HBs antibody/HCV antibody are positive, they are eligible if the viral load is below sensitivity and hepatitis not active).

[Complications/interstitial pneumonia/autoimmune disease]

4) Patients with interstitial lung disease evident in CT.

5) Patients with complicating active autoimmune disease or history of autoimmune disease requiring steroid therapy or immunosuppressants*[2]

*[2] Note that the following patients are eligible:

(1) Patients using a stable dose of thyroid supplement hormone for autoimmune-related hypothyroidism

(2) Patients receiving a stable dose of insulin regimen for well-controlled type I diabetes mellitus

(3) Patients are eligible when patients with eczema, psoriasis, lichen simplex chronicus or only dermatologic symptoms of vitiligo satisfy the following:

The rash area accounts for less than 10% of the body surface area (BSA); only topical-steroid treatment is required; and no acute exacerbation of underlying condition observed within the past 12 months. Patients are eligible in this study when the dose of steroids is equivalent to prednisolone 10 mg/day or less.

6) Patients who need continued systemic (oral or intravenous) administration of steroids equivalent to prednisolone > 10 mg/day, or who used immunosuppressants within 14 days before registration for indications other than autoimmune disease[*3]

[*3] However, patients receiving steroids 10 mg/day or less for the following reasons are eligible:

(1) Patients taking oral steroid equivalent to prednisolone 10 mg/day or less as replacement therapy for adrenal failure, etc.

(2) Patients who acutely received steroid equivalent to prednisolone 10 mg/day or less for COPD

(3) Patients receiving mineralocorticoid for orthostatic hypotension

(4) Patients treated with steroids as premedication for hypersensitivity reactions (e.g. premedication before CT scan) or topical steroids (e.g. nasal cavity, eye, skin)

[Complications/circulatory organ]

7) Patients with a history of symptomatic congestive heart failure, unstable angina, or myocardial infarction within 1 year prior to registration.

8) Patients with clinically serious arrhythmia detected by ECG (complete left bundle branch block, third-degree atrioventricular block, second-degree atrioventricular block).

[Others]

9) Patients with a history of immunotherapy including immune antibody therapy.

10) Patients showing morphological differentiation in the nervous system or histologic type combined with small cell lung cancer and NSCLC.

11) Patients with a history of serious drug allergy.

12) Patients with uncontrolled diabetes mellitus despite appropriate treatment.

13) Pregnant females, lactating females, females who may be pregnant at the moment, or males or females with reproductive capacities who have no intention of using effective contraception from screening to 90 days after the last dose of durvalumab monotherapy.

· Women ≤ 50 years of age: Pregnancy test negative. (However, pregnancy test will be omitted if the patient has undergone bilateral oophorectomy, bilateral salpingectomy, or hysterectomy.)

· Women ≥ 50 years of age: Have been amenorrheic for ≥ 12 months following cessation of all exogenous hormonal treatments. If not amenorrheic, a pregnancy test will be

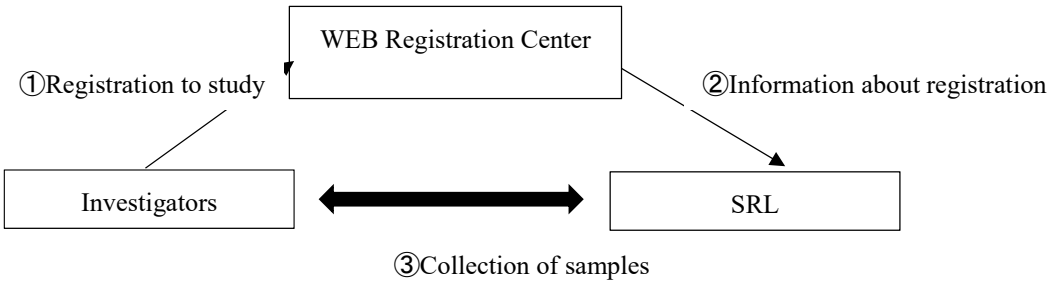
performed. (However, pregnancy test will be omitted if the patient has undergone bilateral oophorectomy, bilateral salpingectomy, or hysterectomy.)

14) Patients judged to be difficult to be registered for this study due to clinically important mental illness.
15) Patients who may become a blood donor during the study and within 90 days from the last administration.
16) Patients who received a live vaccine within 30 days before registration. Patients who may receive a live vaccine during the study and within 30 days from the last administration.
17) Other patients judged by the investigator, etc. to be ineligible.

### 5.4. PD-L1 test (SP263)

As a test kit for immunostaining to measure PD-L1 protein expressed in cancer tissue and cells in this study, "VENTANA PD-L1 (SP263) Assay" should be used. This assay is based on the immunohistochemistry (IHC) method as the measurement principle, and detection is carried out using an automated immunostaining apparatus from Ventana BenchMark series. This SP263 has been used for examination of the efficacy of durvalumab by PD-L1, including PACIFIC Study. For specimens involving a PD-L1 test, the following points should be noted:

- Specimens collected immediately before the first registration should be used wherever possible.
- Specimens collected from examination performed within a clinical setting, such as bronchoscopy and CT-guided examination, are acceptable. Note that the collected tissue must contain at least 100 tumor cells.
- In patients with postoperative recurrence, specimens collected within 5 years should be used.
- With the use of formalin-fixed paraffin-embedded tumor tissue samples, 4 coated slides sliced into 4-5 μm should be submitted to SRL (SRL, Inc.).




## 6. Registration

### 6.1. Registration procedures

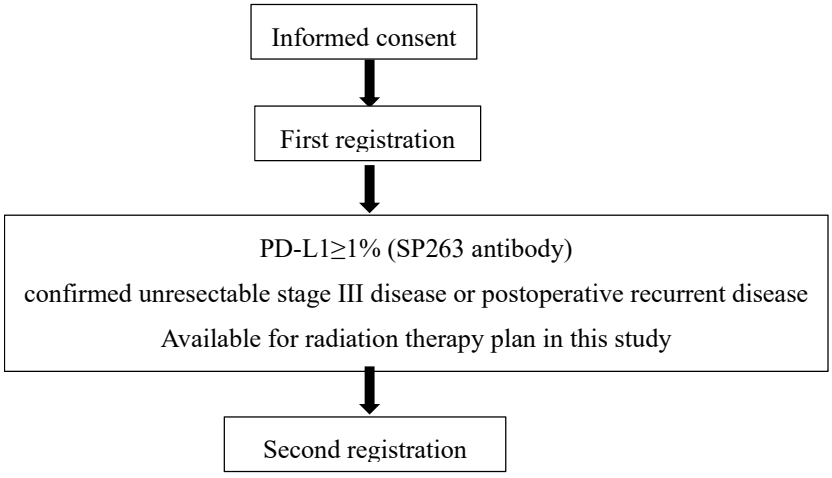
1) The investigator or other personnel explains the present study to each candidate subject and

obtains written consent from the subject.

2) The investigator or other personnel will log in to the web system for the patient registration. After confirming that each subject meets all of the inclusion criteria in "5.1 Eligibility criteria for the first registration", the investigator or other personnel inputs data for the first registration and registers the subject via the electronic data capture (EDC) system.
3) The investigator or other personnel will send the specimens of the first registration to the central lab of PD-L1(SP263).
4) The investigator or other personnel will log in to the Web system. After confirming that each subject meets all of the inclusion criteria in "5.2 Eligibility criteria for the second registration" and does not conflict with any of the exclusion criteria in "5.3 Exclusion criteria for the second registration", the investigator or other personnel inputs data for the second registration and registers the subject.
5) The investigator or other personnel will confirm the enrollment number in EDC.
6) The investigator or other personnel will start the protocol treatment.

Registration using the EDC system:

- The investigator or other personnel should access to the web registration system for the study via the Internet.
- To enter necessary information in accordance with instructions in the enrollment system to make registration.
- To obtain an enrollment number as a registration result.
- Registration may be accepted 24 hours excluding time of maintenance.




## 6.2. Precautions

1) Once subjects are registered, their registration will not be cancelled (They will not be deleted

from the database.).

2) In the case of double registration, the first registration information (enrollment number) will be adopted as a rule.

3) Error or double registration should be promptly notified if identified.

4) In principle, safety should be confirmed within 14 days from the day of enrollment (The same day of a week is acceptable.), and then the protocol treatment should be initiated.

## 6.3. Contact information regarding registration

Clinical Study Coordinating Secretariat
EPS Corporation
2-23 Shimomiyabicho, Shinjuku-ku, Tokyo 162-0822
<Contact>
7th floor KingOsaka Biru 1-7 Toyotsucho, Suita. Osaka 564-0051
TEL : [redacted] / FAX: [redacted]
e-mai; prj-dolphin-jimu@eps.cojp

●Contact how to register and reception time
EDC Data Center
EPS Corporation
1-17-6 Esakacho, Suita. Osaka 564-006
TEL : [redacted] / FAX: [redacted]
Reception Time: Monday to Friday, 9:00am to 5:00pm (Excluding Saturdays, Sundays, and holidays, and designated days for the year-end and New Year holiday)

●Contact for inclusion/exclusion criteria in patient registration
Motoko Tachihara
Kobe University Hospital
7-5-2, Kusunoki-Cho, Chuo-Ku, Kobe-city, Hyogo 650-0017
FAX: [redacted]
TEL: [redacted]
e-mail: mt0318@med.kobe-u.ac.jp

●Contact for radiation therapy
Kayoko Tsujino
Hyogo Cancer Center
13-70 Kiaoji-cho, Akashi-city, Hyogo, JAPAN 673-8558
TEL : [redacted] / FAX : [redacted]

e-mail:tsujinok@gmail.com

# 7. Protocol treatment plan

## 7.1. Treatment details

### 7.1.1. Drugs used

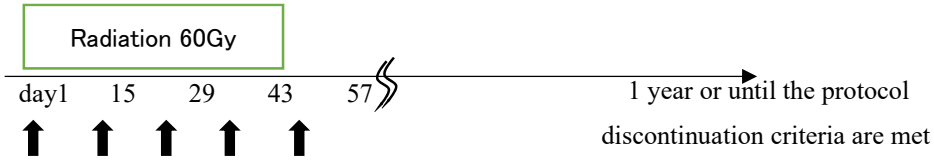
Study drug

| Non-proprietary name | Abbreviated name | Dosage form and strength | Manufacturer |
|---|---|---|---|
| Durvalumab | Durvalumab | 500 mg/10 ml | AstraZeneca K. K. |

### 7.1.2. Treatment schedule

The method of drug administration conforms to 7.4 Precautions on administration. The protocol for administration schedule shall be complied with.

Durvalumab 10 mg/kg will be administered on Day 1 and as 2-week (14-day) cycles for 1 year or until the protocol discontinuation criteria are met (figure below). Definitive thoracic radiotherapy will be started on Day 1.




・ In principle, the dose is rounded down to the nearest ten.

<Preparation method of the study drug>

(1) At preparation

1) Durvalumab is supplied in a single-use vial, and does not contain preservatives.
2) The designated pharmacist at each site should adjust the dilution of durvalumab in a clean environment using an aseptic technique.
3) Before preparation, visually ensure that there is no foreign insoluble matter or discoloration. Durvalumab is colorless to pale yellow and clear to opalescent liquid. Do not use if turbidity, discoloration or foreign insoluble matter is observed.
4) Do not shake the vials or stir them vigorously.
5) Take out the required amount from the vial and inject into a drip bag that contains isotonic sodium chloride solution or 5% glucose injection to make a final concentration of 1 to 15 mg/mL. Invert the drip bag slowly for mixing. Do not freeze or shake the diluent. The time from withdrawal from a vial to the start of administration should not exceed the

following time:

- Within 24 hours at 2-8°C
- Start administration within 4 hours if stored at room temperature.

6) Use immediately after preparation. When storing the diluent without immediately using it, start administration within 24 hours if stored at 2-8°C and within 4 hours if stored at room temperature.
7) Durvalumab is for single use. Do not reuse it.
8) Discard the residual liquid in the vial.

(2) At administration

1) Durvalumab should be intravenously infused for 60 minutes or longer using a sterile low protein-binding 0.2- or 0.22-μm inline filter (made of polyethersulfone, etc.). If there is an interruption during the infusion, the total allowable infusion time should not exceed 8 hours at room temperature.
2) Do not administer other drugs concomitantly using the same drip line.
3) At the end of the infusion of durvalumab, the IV line should be flushed or the infusion should be completed according to the site's rules.
4) Should the preparation time or infusion time exceed the time limit, a new dose should be diluted from a new vial. Durvalumab does not contain preservatives and any unused portion should be discarded.
5) Follow **7.4 Precautions on administration**.

7.1.3. Radiotherapy

The WJOG 11619L Radiotherapy Regulations (Addendum 2) should be followed. The excerpts of the key points are as follows.

1) Radiotherapy will begin on Day 1, concurrently with the start date of durvalumab. There will be no specified order or time interval between durvalumab administration and radiotherapy.
2) For radiotherapy, volume prescription three-dimensional treatment plan/volume prescription (D 95) or intensity modulated radiation therapy (IMRT) may be selected for each subject. IMRT selection is limited to sites certified by the WJOG Radiation Therapy Board.
3) Dose fractionation should be 2 Gy per dose, once daily, 5 days per week, a total of 30 doses, a total dose of 60 Gy, a total treatment period of 42 days, and an allowable total treatment period of 63 days.
4) In order to minimize the effect of dose distribution in the body due to enlargement or shrinkage of tumor during treatment on the therapeutic effect or adverse events, diagnostic CT or treatment planning CT will be performed at approximately 30-40 Gy has been administered

during treatment. If the change is large, re-planning should be done as necessary.

5) The evaluation criteria for dose limitation rules are as shown in the table below.

| | Compliance - RT | Deviation - RT |
|---|---|---|
| **Prescribed dose** | | |
| PTV D95% | 60 Gy ≤ D95% < 61 Gy | 57 Gy ≤ D95% < 60 Gy<br>or<br>61 Gy ≤ D95% ≤ 63 Gy |
| PTV D1% | D1% ≤ 72 Gy | 72 Gy< D1% ≤ 75 Gy |
| PTV D99% | 51 Gy ≤ D99% | 45 Gy ≤ D99% < 51 Gy |
| ITV(CTV) D99% | 58 Gy ≤ D99% | 54 Gy ≤ D99% < 58 Gy |
| **Normal tissue** | | |
| Spinal cord | D0.03 cc ≤ 50 Gy | 50 Gy < D0.03 cc ≤ 52 Gy<br>and<br>D1 cc ≤ 50 Gy |
| Lung (whole lung-GTV) | V20 Gy ≤ 35% and<br>MLD ≤ 20 Gy and<br>V5 Gy ≤ 60% | 35% < V20 Gy or 20 Gy < MLD,<br>or 60% < V5 Gy but V20 Gy ≤<br>40% and MLD ≤ 22 Gy V5 Gy ≤<br>65% |
| Esophagus | D0.03cc ≤ 66 Gy | 66 Gy < D0.03cc ≤ 72 Gy |
| Heart | V45 Gy ≤ 35% | 35% < V45 Gy ≤ 40% |
| Hot spots outside PTV excluding lung fields | D0.03cc ≤ 72 Gy | 72 Gy < D0.03cc ≤ 75 Gy |
| Brachial plexus | D0.03cc ≤ 66 Gy | 66 Gy < D0.03cc ≤ 70 Gy |

7.1.4. Start of treatment

Start the protocol treatment within 14 days after the second registration. If protocol treatment was started after 15 days, the reason should be reported.

"7.3.1. Administration criteria for each course" is not available for the start of Course 1.

7.1.5. Discontinuation prior to treatment

If it is determined that the protocol treatment cannot be started for some reasons (for example, progression before treatment but after registration [rapid progression prevents the start of the protocol treatment], or the treatment is changed after ineligibility is found due to a change in pathological diagnosis after registration), the case should be handled as a discontinued case prior to

the protocol treatment.

## 7.2. Discontinuation of protocol treatment

If any of the following is satisfied, discontinue the protocol treatment.

1) When the protocol treatment is judged to be ineffective

   However, a subject may continue the treatment as long as the following criteria are met based on RECIST 1.1 even after the first PD was confirmed. If further progression is noted in the subject by subsequent specified CT assessment, the treatment should be discontinued.

   - In the opinion of the investigator, clinical response is achieved and no rapid disease progression is observed.
   - Toxicity is tolerable
   - General condition is stable
   - Continuous treatment beyond progression will not delay urgent intervention required to prevent serious complications due to disease progression

2) When the protocol treatment cannot be continued due to adverse events
   (i) When grade 4 non-hematologic toxicity is observed

   Note that the following adverse reaction (hematologic toxicity) in CTCAE v5.0 is excluded:

   "Anemia"; "bone marrow hypocellular"; "lymphocyte count decreased"; "neutrophil count decreased"; "white blood cell count decreased"; and "platelet count decreased".

   Treatment discontinuation is not required in a case where biochemical tests show just temporary development of a grade 4 event which does not require any treatment or is not assessed as life-threatening.

   (ii) When grade 3 or higher interstitial lung disease/pneumonitis occurs
   (iii) When adverse events cannot be controlled even after hormone replacement therapy or insulin replacement therapy
   (iv) When subjects satisfy the provisions on discontinuation of the protocol treatment in "7.3. Administration criteria for each course and treatment change criteria"
   (v) When the principal (sub) investigator, etc. determines that subjects need to discontinue the protocol treatment in terms of safety due to reasons other than treatment change criteria

3) When subjects wish to discontinue the protocol treatment
   (i) When subjects wish to discontinue treatment because the causality with an adverse event cannot be ruled out
   (ii) When subjects wish to discontinue treatment because the causality with an adverse event

can be ruled out

* When patients reject the participation prior to the protocol treatment and after registration
* When the causality with an adverse event can be ruled out, such as subjects or their family's moving during the protocol treatment

(iii) When subjects withdraw their consent

4) When subject die during the protocol treatment
5) When ineligibility is found during the protocol treatment period and it is determined that continuing the protocol treatment will not be beneficial to subjects
6) When the subject is transferred to another hospital during the protocol treatment period and it is determined that the protocol treatment cannot be continued

* The protocol treatment discontinuation date shall be the date of death if subjects die during the protocol treatment, or otherwise be the date when the attending physician determined to discontinue the protocol treatment.

#### 7.2.1. Definition of protocol treatment completion

This study is designed to continue the protocol treatment for 1 year or until the protocol treatment discontinuation criteria are met. Therefore, if the administration successfully continues for one year, it will be regarded as protocol treatment completion.

#### 7.2.2. Attention on withdrawal of consent

Data following withdrawal of consent shall not be collected. (It is impossible to collect data after withdrawal of consent.) Ensure to check patients' will to find out whether it is refusal of the protocol treatment/tests or true withdrawal of consent.

## 7.3. Administration criteria for each course and treatment change criteria

Discontinuation, interruption and suspension of administration shall be based on adverse events, and change in doses be based on adverse reactions. Terms used for administration criteria and treatment change criteria are as follows:

Discontinuation: premature termination of a part of or all treatment that is not resumed

Interruption/suspension: a temporary halt of treatment that can be resumed

#### 7.3.1. Administration criteria for each course

The start date of the second and subsequent courses can be allowed within +7 days (until the same day of the week that the administration is scheduled to be started).

Administration the second and subsequent courses shall be started after it is confirmed that the following criteria are met within 3 days before administration of the course. When administration is postponed, set the start date to day 1 of the course and administration and subsequent schedules will follow this. (Imaging schedule will no change.)

| Item | Administration criteria |
|---|---|
| PS | 0-1 |
| Pyrexia | <38°C |
| Immune-related adverse events**<br>(other than brain, skin or hyperglycemia) | ≤ Grade 1 |
| Hyperglycemia*/skin disorders*** | ≤ Grade 2 |
| Pneumonitis | ≤ Grade 1 |
| Meningoencephalitis | Grade 0 |

* Case that insulin is used due to hyperglycemia which is occurred as an adverse event. If patients have diabetes as a complication and insulin is used, this case is not available. The restart of Durvalumab is possible in case that blood sugar level is stable with an appropriate treatment even if hyperglycemia of grade 3 is observed.

** Hypothyroidism which are stable due to hormone replacement, adrenal dysfunction or pituitary insufficiency which are dosed prednisolone equivalent 10mg / day or less, and endocrine disorders which are stable with symptomatic treatmetnt such as hyperthyroidism can be administered.

*** If grade 2 of skin disorder persists for 1-2 weeks, administration should be started after recovery to grade 1.

- Other; If the attending physician considers necessary due to adverse events other than the above, the extension is allowed (the reason shall be provided in the CRF)
- Durvalumab can be suspended for up to 90 days from the last administration. Durvalumab shall be discontinued if drug suspension is needed for more than 90 days. Note that holidays that may cause a delay in this limit will not be counted.
- In this study, Addendum “Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy” (hereinafter referred to as “Toxicity Management Guidelines for Durvalumab”) should be followed for management of adverse events associated with durvalumab.
- When systemic steroid is administered for each immune-related adverse event, and when the immune-related adverse event improves/resolves under the dose equivalent to prednisolone 10 mg/day or less within 90 days after the start, of predonisolone the treatment can be resumed if the administration criteria for each course are met.

7.3.2. Dose reduction criteria of the second and subsequent courses

The dose of durvalumab should be 10 mg/kg, and the drug should be used at the same dose throughout the study.

The dose will not be recalculated due to a change in body weight, etc.

The dose of durvalumab shall not be reduced due to adverse events.

7.3.3. Discontinuation criteria of durvalumab of the second and subsequent courses

1) When the administration criteria of durvalumab for each course in section 7.3.1. are not met even for the 90-day suspension period after actions are taken according to "Toxicity Management Guidelines for Durvalumab"
2) When the following adverse events are observed:

| Item | discontinuation criteria |
|---|---|
| Immune-related adverse events<br>Lungs (pneumonia, interstitial lung disease (ILD))<br>Kidney (nephritis, renal dysfunction)<br>Heart (myocarditis, etc.) | ≥ Grade 3 |
| Immune-related adverse events<br>Diarrhea / colitis<br>Skin disorders (including rash, dermatitis, and pemphigoid)<br>Muscle disorders (myositis / polymyositis, etc.) | Grade 4 |
| Neurological disorders (including non-infectious meningitis, non-infectious encephalitis, autonomic neuropathy) | ≥ Grade 3 |
| Peripheral neuromotor syndrome (Guillain-Barré syndrome, myasthenia gravis, etc.) | Grade 4 |
| Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Other Severe Skin Disorders (SCAR) | In definitive diagnosis |
| Intestinal perforation | Any Grade |
| Liver dysfunction / hepatitis | 1) Grade 4<br>2) If any of the following is met<br>・AST>8×ULN,<br>・ALT>8×ULN<br>・T-bil>5×ULN<br><br>3) Hy's law, |

| | |
|---|---|
| | ASTor ALT >3×ULN<br>T-bil>2×ULN<br>There is no cause other than the study drug |
| Acute pancreatitis | ≥ Grade 3 |
| Transverse myelitis | Any Grade |
| Allergic reaction (Infusion-Related Reactions) | ≥ Grade 3 |

Refer and follow the latest version of "Toxicity Management Guidelines for Durvalumab" (Addendum).

3) When the investigator, etc. considers that subjects need to discontinue the study.

7.3.4. Criteria for suspension/resumption of radiotherapy

The WJOG 11619L Radiotherapy Regulations (Addendum 2) should be followed. The excerpts of the key points are as follows.

| Adverse event | Radiotherapy suspension criteria (Any of the following) | Radiotherapy Resumption criteria (All of the following) |
|---|---|---|
| Neutrophil count | < 500/mm$^3$<br>(Grade 4) | ≥ 500/mm$^3$<br>(≤ Grade 3) |
| Platelet count | < 2.5 × 10$^4$/mm$^3$<br>(Grade 4) | ≥ 2.5 × 10$^4$/mm$^3$<br>(≤ Grade 3) |
| Pyrexia | ≥ Grade 1<br>Pyrexia of ≥ 38.0°C (axillary temperature) | Temperature declined to ≤ 37.0°C |
| Pneumonitis | When signs of grade 2 or higher pneumonitis are noted.<br>When grade 1 pneumonitis spread outside the radiation field is observed, an internal medicine specialist and the physician in charge of radiotherapy should discuss and decide whether to interrupt the treatment. | Before resumption, the internal medicine specialist and the physician in charge of radiotherapy should have a careful discussion. The administration should be resumed only if it is judged possible. |
| Esophagitis | Grade 3 | ≤ Grade 2 |

| | | |
|---|---|---|
| | (Severely impaired eating/swallowing function; Tube feeding/TPN/hospitalization required) | (Symptomatic impaired eating/swallowing function; oral nutritional support required) |
| Radiation dermatitis | Grade 3<br>(Moist desquamation in areas other than folds; bleeding due to mild trauma or friction) | ≤ Grade 2<br>(Moderate to severe erythema; patchy moist desquamation. however, limited to most folds; moderate edema) |
| Febrile neutropenia | Grade 3 | Grade 0 |
| Infection* | Grade 3 | Grade 0 |

In addition to the criteria above, radiotherapy should be suspended if the investigator considers it necessary to suspension and the reason is recorded in CRFs. Radiotherapy can resume according to investigator decision..

## 7.4. Precautions on administration

· The dose of durvalumab should be 10 mg/kg, and the drug should be used at the same dose throughout the study.

First administration

· Dissolve durvalumab in isotonic sodium chloride solution or 5% glucose injection 100-250 mL and administer over 60 minutes.
· Even if there is an interruption during the infusion, the total allowable infusion time should not exceed 8 hours at room temperature.
· The first administration should be conducted with full attention paid to infusion reaction.
· At the first administration, premedication of antihistamine is not provided.
· Monitor the subject for signs and symptoms of infusion reactions (chills, rash, flushing, shortness of breath, dizziness, pyrexia, etc.) and signs and symptoms of anaphylaxis (generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.) during infusion.
· If any sign of grade 2 or lower infusion reactions or anaphylaxis is observed, reduce the infusion rate by about half or interrupt the infusion until the symptoms improve. If the symptoms improve, resume the infusion at 50% and complete the infusion.
· When infusion reaction is noted, symptomatic therapy with acetaminophen, ibuprofen, diphenhydramine, famotidine or other H2-receptor antagonists, etc. may be performed according to the standard medical procedure.
· The study treatment should be discontinued in case of grade 3 or higher infusion reaction.

Symptomatic therapy with epinephrine, diphenhydramine, steroid, etc. should be performed according to the standard medical procedure.

Second administration and thereafter

- Subjects who experienced infusion reaction at the first administration will receive premedication of antihistamine at the discretion of the principal (sub) investigator at the second administration and thereafter.
- Subjects who did not experience infusion reaction shall not receive premedication.
- In the same manner as the first dose, dissolve durvalumab in isotonic sodium chloride solution or 5% glucose injection 100-250 mL and 0.9% saline, and administer over 60 minutes. If there is an interruption during the infusion for some reason, the total allowable infusion time should not exceed 8 hours at room temperature.

## 7.5. Adverse events and management

For adverse events caused by durvalumab and their management, follow "Toxicity Management Guidelines for Durvalumab" (Addendum).

## 7.6. Combination therapy/supportive therapy

A CRF shall include the names of every combination drug/therapy provided to the subject during the period specified in "7.6.1. Observation period of combination therapy" with the reasons for concomitant use.

### 7.6.1. Observation period of combination therapy

The observation period of combination drug/therapy shall be from the first administration date to 14 days after the last administration of the study drug. It shall be until the first administration date of post treatment if the post treatment for NSCLC is started within 14 days after the last administration of the study drug.

### 7.6.2. Prohibited combination drugs

The following drugs and therapy are prohibited from the registration date to the end or discontinuation of the protocol treatment:

1) Anti-tumor treatment
   (1) Chemotherapy (including molecular target drugs)
   (2) Other immunotherapy
   (3) Surgical treatment
   (4) Others (including hormone therapy)

2) Prophylactic administration to prevent the occurrence of adverse events (the prophylactic administration to prevent recurrence of observed adverse events is acceptable)
3) Other study drugs and unapproved drugs
4) Live vaccine

* Consult with coordinating investigator whether or not it is use herbs and drugs that may have immunomodulatory activity in natural remedies.

7.6.3. Acceptable supportive therapies

Concomitant use of the drugs or therapy that does not affect the efficacy assessment including the drugs or therapy below is allowed.

1) G-CSF drug
Administer each G-CSF drug according to the indications, dosage and administration, and precautions in the package insert of the drug.
2) Antibiotics
If grade 3 or higher leukopenia or neutropenia is accompanied with pyrexia of 38.0°C or higher, or if some sort of infection is suspected, administer an appropriate antibiotic.
3) Transfusion
If grade 3 or higher hemoglobin decreased or grade 4 platelets decreased is observed, transfusion is allowed.
4) Steroids
Steroids may be used for adverse events, etc. as needed.
5) Tests and supportive therapy for subjects with HBs-antigen negative and HBc-antibody positive and/or HBs-antibody positive
6) Hormones
Hormone replacement therapy (e.g. hypothyroidism)
7) Inactivated vaccine
8) Symptomatic therapy or other drugs considered to be necessary to improve subjects' conditions should be administered according to the instruction by the investigator, etc.

Symptomatic therapy with acetaminophen, ibuprofen, diphenhydramine, famotidine and other H2-receptor antagonists, etc. may be administered to subjects who experienced infusion reaction according to the standard medical procedure. Clinically-indicated supportive therapies (supplemental oxygen, β2 adrenergic agonists, etc.) should be used to treat serious infusion reactions (dyspnea, hypotension, wheezing, bronchospasm, tachycardia, oxygen saturation decreased, respiratory distress, etc.).

7.6.4. Prohibited actions

The following actions are prohibited during treatment and within 90 days after the last dose.

1) Transfusion donor
2) Sexual intercourse without contraception

* Highly effective methods of contraception (failure rate < 1%) used in Japan are as follows:

- OC (low-dose oral contraceptives)
- IUS (intrauterine system)
- Copper IUD (intrauterine device)
- Surgical sterilization

## 7.7. Post treatment

In principle, after the completion of the protocol treatment, treatment for the underlying disease should not be performed until worsening of the underlying disease is confirmed. Progression after completion of the protocol treatment and post-treatment after discontinuation of the protocol treatment are not specified.

# 8. Endpoints and laboratory tests

8.1.1. Tests and endpoints before the first registration

1) Patient basic information
   a) Patient identification code
   b) Initials (can be substituted by "* [asterisk]")
   c) Date of birth (can be substituted by "* [asterisk]")/age
   d) Informed consent acquisition date
   e) Sex
   f) PS
   g) Height/body weight
   h) Histologic type (adenocarcinoma, squamous carcinoma, large cell carcinoma, other)
   i) Diagnosis method (histology, confirmed diagnosis date)
2) Tests to be conducted within 14 days before the first registration
   (1) Hematology: white blood cells, neutrophils, lymphocytes, hemoglobin, platelets
   (2) Blood biochemistry: Alb, T-bil, AST, ALT, γGTP, ALP, BUN, Cr, Na, K, Cl
   (3) Urinalysis: urine protein, urine sugar
   (4) Percutaneous oxygen saturation ($SpO_2$)

8.1.2. Tests and endpoints before the second registration

Tests and evaluations from 1) to 6) will take place before the second registration. Of note, if a subject has the results of tests carried out within the specified period, the test results prior to informed consent are allowed to be used, if the subject agrees to it. The same tests do not have to be carried out after the informed consent is obtained.

1) Patient basic information
    a) Main medical history (If there is a history of malignant tumor, provide the last treatment date and the treatment details)
    b) Major complications
    c) Stage (including primary or recurrence)
    d) Target lesion, non-target lesion
    e) Smoking history (none [100 cigarettes or less in lifetime], ex-smoker [100 cigarettes or more in lifetime but quit smoking at least 1 year before registration], current smoker [currently smoking 100 cigarettes or more in lifetime (including cessation of smoking within 1 year before registration)])
    f) Presence or absence of gene mutation (EGFR gene test)
        * Although ALK gene test, ROS1 gene test, and BRAF (V600E) mutation test are not essential, it is desirable to have them conducted as much as possible in routine medical practices.
2) Tests to be conducted before the second registration (at any time period)
    HBs antigen, HBc antibody, HBs antibody, HCV antibody
3) Tests to be conducted within 3 months (within 92 days at a maximum) before the second registration
    a) 12-lead electrocardiogram at rest
    b) Diabetes test, thyroid function test, adrenal gland/pituitary gland function test: (fasting blood glucose, HbA1c, TSH, FT3 or FT4, ACTH)
    c) Anti-nuclear antibody, rheumatoid factor (RA), KL-6
4) Tests to be conducted within 4 weeks before the second registration (the same day of the week as the registration day is acceptable)
    a) Chest x-ray (front)
    b) Thoracic and abdominal CT (slice thickness of 5 mm or less): Plain CT is allowed when contrast agents cannot be used due to contrast-agent allergy, renal disorder, etc.
    c) Brain CT or brain MRI (slice thickness of 5 mm or less): Plain MRI or CT is allowed when contrast agents cannot be used due to contrast-agent allergy, renal disorder, etc.
    d) Laboratory tests

(i) Alb, AMY, lipase, CRP

(ii) Urinalysis: urine protein, urine sugar

(iii) Urine or serum pregnancy test result (premenopausal women; see "5.2. Eligibility criteria for the second registration")

(iv) Blood pressure

5) Tests to be conducted within 6 weeks before the second registration (the same day of the week as the registration day is acceptable)

PET-CT test

6) Observation and tests to be conducted within 14 days before the second registration

a) Subjective/objective symptoms

Nausea, vomiting, allergic reaction

General disorders: pyrexia, fatigue

Skin and subcutaneous tissue disorders: pruritus, leukoderma, alopecia

Gastrointestinal disorders: constipation, diarrhea, nausea, vomiting, mucositis oral

Metabolism and nutrition disorders: inappetence

Vascular disorders: hypertension, thromboembolism

Respiratory, thoracic and mediastinal disorders: bronchopulmonary hemorrhage, epistaxis, pneumonitis

## 8.2. Tests and endpoints during protocol treatment period

Test results and clinical findings after treatment start should be reported 14 days after the last day of the protocol treatment. If post treatment is started within 14 days, information before the start of post treatment should be reported.

However, with regard to the efficacy endpoints, as an increased frequency may cause a bias in the efficacy evaluation, the evaluation should be made at the specified frequency except when progression is suspected.

### 8.2.1. Safety endpoints

Evaluate the following items at the start of the course or within 3 days before the start. Tests will be performed according to routine clinical practice while dosing is delayed because the administration criteria for durvalumab are not met.

a) PS

b) Subjective/objective symptoms and physical findings (described in CTCAE v5.0 -JCOG)

· Blood and lymphatic system disorders: febrile neutropenia

· General disorders and administration site conditions: pyrexia, fatigue, edema extremities

· Skin and subcutaneous tissue disorders: alopecia, other (skin eruption)

· Gastrointestinal disorders: diarrhea, nausea, vomiting, mucositis oral
· Metabolism and nutrition disorders: inappetence
· Nervous system disorders: peripheral sensory neuropathy
· Respiratory, thoracic and mediastinal disorders: pneumonitis, epistaxis, bronchopulmonary hemorrhage
· Infections and infestations: bronchial infection, lung infection, upper respiratory tract infection, bladder infection, mediastinal infection, pleural infection, wound infection, urinary tract infection

c) Laboratory tests

Hematology: white blood cells, neutrophils, lymphocytes, hemoglobin, platelets

Blood biochemistry: Alb, T-bil, AST, ALT, γGTP, BUN, Cr, Na, K, Cl, CRP, AMY, lipase

Urinalysis: urine protein, urine sugar

Blood pressure

Percutaneous oxygen saturation (SpO2)

#### 8.2.2. Efficacy endpoint

The following image tests are performed in the same way as baseline evaluation. For evaluation, thoracic and abdominal CT is conducted once every 8 weeks (±1 week) with the second registration date as the starting point. Plain CT evaluation is allowed when contrast agents cannot be used. Of note, for bone lesions, bone scintigraphy and PET, etc. are performed only when progression is suspected. Bone scintigraphy and PET as image test for efficacy evaluation are not performed except when progression is suspected. If the protocol treatment is discontinued for some reasons other than disease progression, the efficacy evaluation will be performed in the above period as much as possible.

1) Thoracic-upper abdominal CT (slice thickness of 5 mm or less): contrast CT is desirable
2) Brain contrast MRI or brain contrast CT (to be conducted when metastasis is suspected; otherwise in accordance with routine medical practice)
3) Bone scintigraphy or PET (only when progression is suspected)

### 8.3. Tests and endpoints after completion of study treatment

#### 8.3.1. Safety assessment after treatment completion

1) Laboratory tests

They are not particularly specified, and are conducted based on routine medical practice.

#### 8.3.2. Efficacy assessment after treatment completion

1) Progression information (thoracic and abdominal CT assessments to be performed every 8

weeks)

- Date of progression, site of progression, diagnosis method
- For subjects who completed the protocol treatment without progression of the underlying disease (PD), the presence or absence of progression (date and site of exacerbation) should be investigated.
- If a subject meets the criteria in 7.2.1) and continues to receive the treatment after the first PD has been confirmed, the date of the second PD diagnosis should be investigated.

2) Survival information

The last confirmation date, survival status, date and cause of death (in case of death)

3) Presence/absence of post treatment (surgery/radiotherapy/drug name/treatment start date/PS at treatment start)

Subjects who received post treatment will continue the subsequent treatment course as much as possible.

## 8.4. Study calendar

| | Before the first registration | Before the second registration | Each course (Once every 2 weeks) | At discontinuation/ progression | Follow-up |
|---|---|---|---|---|---|
| Informed consent acquisition | ● | | | | |
| Patient characteristics | ● | | | | |
| General laboratory tests | ●[14] | ● | ● | ○ | ○ |
| Test for diabetes/ thyroid/adrenal functions | | ●[92] | ○ | | |
| Anti-nuclear antibody/RA/KL-6 | | ●[92] | | | |
| PS | ● | | ● | ● | ○ |
| Physical findings (Medical examination)/PS | | ●[14] | ● | ● | |
| Subjective symptoms | | ●[14] | ● | ● | ○ |
| Chest X-P | | ●[28] | ○ | ○ | |
| Thoracic and abdominal CT | | ●[28] | ● Every 8 weeks | | ○* |
| FDG-PET | | ●[42] | ○ | | |
| Bone scintigraphy | | ○ | ○ | | |
| Brain MRI or CT | | ●[28] | ○ | | ○* |
| SpO2 measurement | ●[14] | | ● | ○ | ○ |
| Blood pressure | | ●[28] | ● | ○ | ○ |

| | | | | | |
|---|---|---|---|---|---|
| Electrocardiogram | | ●[92] | | | |
| SP263 | | ● | | | |
| Treatment plan according to the radiotherapy regulations | | ● | | | |

●: Required

●[XX]: Implemented within XX days before registration

○: Based on routine medical practice

* If subjects discontinue for some reasons other than cancer progression, continue on the same schedule even after the study drug is discontinued.

# 9. Data collection

## 9.1. Enrollment number

Enrollment numbers assigned at the time of enrollment should be used for identifying the subjects.

## 9.2. CRF

### 9.2.1. Types of CRFSs

In this study, a system (EDC) to electronically prepare CRFs will be used, and CRFs will be electronically recorded.

1) Enrollment and baseline records
2) Treatment records
3) Laboratory tests
4) Clinical findings
5) Concomitant therapies and supportive therapies
6) Report of treatment completion
7) Imaging test records
8) Follow-up investigation

### 9.2.2. Completion of CRFs

Preparation of the CRF using the EDC system

1) The sponsor-investigator (investigator) and other relevant persons should use the EDC system and enter data in the CRF.
2) The investigator should ensure that CRFs to be submitted are accurate, complete and sent in a timely manner, and that enrollment numbers are utilized for identifying the subjects.

3) Data contained in the CRF, which are based on source documents, shall be consistent with the source documents. If there is any inconsistency with source documents, the investigator/subinvestigator should prepare a record describing its reason, submit it to the coordinating investigator and keep its copy. If there is any change or modification in the record on the CRF, the investigator/subinvestigator should make the change or modification in accordance with a manual. Changes or modifications shall be made in such a way to keep the originally documented information legible.

### 9.3. Collection method of CRF

CRFs will be collected by sending them through the EDC system. Timing for their submission will be in accordance with separately specified "EDC input guidelines."

## 10. Handling regarding safety

### 10.1. Definition of adverse events

An adverse event is an unfavorable medical event occurring during and after administration of a pharmaceutical product or deterioration of symptoms and signs from before administration, and refers to any event, irrespective of having a causal relationship with administration of the pharmaceutical product or not. Unfavorable medical events refer to abnormalities of symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, hepatomegaly) or test results (e.g., laboratory values, electrocardiogram). In this study, adverse events refer to unfavorable medical events that occur during the study including observation or wash-out period after the start of the study treatment.

### 10.2. Definition of serious adverse events

A serious adverse event meets one or more of the following criteria regardless of the administered dose of an investigational drug.

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- May have caused a congenital anomaly/birth defect, spontaneous abortion
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Important medical events that do not result in immediate life-threatening or death, hospitalization, disability, or dysfunction but may endanger the patient, or the events which medical treatment has

been taken to avoid reaching the condition defined as "serious adverse event" their outcomes are "serious adverse events" are necessary to judge whether to make them serious based on medical and scientific grounds. Examples of medically significant events are allergic bronchospasm requiring intensive care in the emergency room or at home, non-hospitalization of blood disorders or convulsions, drug addiction or substance abuse.

Adverse Events (AEs) for new malignant tumours reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history, and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy

The above explanation applies only if the malignant tumor event observed is a new malignant tumor (ie, it is not a tumor treated with the study and not metastasis. Malignant tumors undergoing transformation (such as Richter's syndrome, in which B-cell chronic lymphocytic leukemia transforms into diffuse large B-cell lymphoma), rarely part of normal progression, are not considered as new malignant tumor.

Progression of the cancer targeted in this study, including signs and symptoms, is not considered a serious adverse event. Hospitalization due to signs and symptoms of disease progression should not be reported as a serious adverse event. These events will be documented in the medical chart as disease progression events (e.g. hospitalization for aggravation of the underlying disease).

### 10.3. Adverse events assessed as other medically important conditions

Other significant adverse events will be classified as "adverse events of special interest (AESIs)" if they are of particular clinical significance, other than serious adverse events and adverse events resulting in subjects' discontinuation from the study treatment. This AESI includes both serious and non-serious events.

"Adverse events of special interest (AESIs)" caused by durvalumab include the following adverse events:

- Diarrhea / colitis, intestinal perforation

- Pneumonitis / ILD
- Hepatitis / transaminase elevation
- Endocrine disorders (ie, hypophysitis / hypopituitarism, adrenal insufficiency, hyperthyroidism, hypothyroidism, and type 1 diabetes)
- Rash / dermatitis
- Nephritis / increased blood creatinine
- Pancreatitis / serum lipase and amylase increase
- Myocarditis
- Myositis / polymyositis
- Immune thrombocytopenia
- Neuropathy / neuromuscular toxicity (Guillain-Barré syndrome, myasthenia gravis, etc.)
- There are other rare / infrequently occurring inflammatory reactions (pericarditis, sarcoidosis, uveitis, and eye, skin, blood system, and rheumatism-related events, etc. that may be immune-mediated causes, etc. Not limited to these).
- Reactions associated with infusion due to various pharmacological causes and hypersensitivity / anaphylactic reactions are also considered to be particularly noteworthy adverse events.

For details of adverse events caused by durvalumab and their management, refer to and follow attached “Toxicity Management Guidelines for Durvalumab” (Addendum).

## 10.4. Assessment of adverse events

Adverse events should be assessed according to “NCI-CTCAE version 5.0, Common Terminology Criteria for Adverse Events V5.0, Japanese translation JCOG version (CTCAE v5.0 -JCOG)”. For laboratory test values, the common reference range of JCOG should be used. In grading an adverse event, select the grade closest to the definition contents of each grade. For consideration of the causal relationship between adverse events seen regarding treatment-related deaths and deaths, report on the adverse events and input into EDC.

## 10.5. Determination of causality

The investigator, etc. must assess the causal relationship between the study drug and an adverse event and answer “Yes” or “No” to the question, “Do you think there is a reasonable possibility that the adverse event may have been caused by the study drug?”

In case of a serious adverse event, causal relationship to other treatments should also be assessed. If a serious adverse event is considered related to study procedures, the relationship should be "Related".

## 10.6. Measures taken when an adverse event occurs and follow-up survey

The investigator, etc. should monitor each subject for adverse events during the study treatment period and for 90 days after the last dose of the study drug, and take appropriate measures and follow up the subject if any adverse event has occurred.

All adverse events that occurred within 90 days after the last dose should be followed up to resolution unless, in the opinion of the investigator, etc., they will not resolve due to the subject's underlying disease (pre-existing disease such as a complication), or there is a reasonable reason such as subsequent therapy, missed visit, or death. If follow-up cannot be performed, this should be recorded in the medical chart.

## 10.7. Adverse events that must be reported (report of serious adverse events)

If the investigator, etc. or a study coordinator became aware of the occurrence of a serious adverse event during the clinical study, he/she must immediately (within 24 hours) report the adverse event to the coordinating investigator using a detailed report (“[Medical] Form 12 and Form for detailed description (or Form 12-1, 2) Serious Adverse Event Report”) in accordance with the separately specified "Procedures for Handling of Safety Information" and also report it to the head of the site according to the rules of the site.

The information essential for the investigator, etc. to report a serious adverse event for the first time is the registration number or subject identification code, adverse event term, seriousness, and onset date. The following detailed information should also be reported immediately after it is obtained.

- Severity
- Outcome (date of disappearance, if possible)
- Causal relationship (causal relationship to the study drug and, if applicable, concomitant medications)
- Date on which it became serious
- Whether or not the study drug was discontinued
- Treatment for the adverse event
- Concomitant therapy (excluding treatment for the adverse event)
- Concomitant medications (If the causal relationship with the adverse event cannot be evaluated, prior medications should also be included)
- Date of birth and sex
- History of present illness (complications)
- Relevant medical history
- Date of death and course until death, if applicable

Multiple adverse events may be recorded as adverse events leading to discontinuation or death. If the cause of death is unknown, it should be handled as “death of unknown cause”. If an autopsy was performed, a copy of the autopsy report should be submitted as necessary.

The coordinating investigator should report serious adverse events reported by the investigator, etc. or the study drug provider to investigators of other sites, sponsor-investigators, and the study drug provider. Investigators of other sites, sponsor-investigators, and the study drug provider should notify the coordinating investigator that the information has been received.

The investigator, etc. must also immediately (within 24 hours) report any additional information on a serious adverse event or a non-serious adverse event that later became serious according to the above procedure.

## 10.8. Report to Minister of Health, Labour and Welfare

If it is necessary to report adverse events obtained in “10.7 Adverse events that must be reported (report of serious adverse events)” to the Minister of Health, Labour and Welfare, the coordinating investigator should prepare a report in accordance with the separately specified “Procedures for Handling of Safety Information” in coordination with the investigator and submit it to the Pharmaceuticals and Medical Devices Agency within the specified period.

## 10.9. Report to study drug provider

When the coordinating investigator obtained information on “10.7 Adverse events that must be reported (report of serious adverse events)”, abnormal liver function values as defined by Hy's law, overdose, or pregnancy, the coordinating investigator should report it to the study drug provider in accordance with the separately specified “Procedures for Handling of Safety Information”.

If a report was submitted to the Pharmaceuticals and Medical Devices Agency in “10.8 Report to Minister of Health, Labour and Welfare”, a copy of the report should be submitted to the study drug provider.

## 10.10. Measures taken at the time of pregnancy

**Female Exposure**

If a female subject becomes pregnant during study treatment, the protocol treatment must be discontinued immediately.

Pregnancy itself is not considered an adverse event unless there is a suspicion that the study drug may have reduced the effect of the contraceptive medication. Congenital anomaly and spontaneous abortion should be reported as a serious adverse event. Elective abortion unaccompanied by complications should not be handled as an adverse event. However, outcomes of

all pregnancies (spontaneous abortion, elective abortion, extra-uterine pregnancy, normal birth, congenital anomaly) should be followed up and documented even if the subject was withdrawn from the study. If the investigator, etc. became aware of pregnancy within 90 days after the last dose of durvalumab, the investigator, etc. should immediately (within 24 hours of awareness) report the event to the coordinating investigator. The coordinating investigator should report the information to the study drug provider in accordance with "10.9 Report to study drug provider".

**Male Exposure**

Pregnancy in a partner of a male subject is not considered an adverse event. Where possible, outcomes of all pregnancies (spontaneous abortion, elective abortion, extra-uterine pregnancy, normal birth, or congenital anomaly) should be followed up and documented. If information on pregnancy is obtained from a partner of a male subject, consent must be obtained from the partner of the male subject for collection of information related to pregnancy and outcome. The outcome of any pregnancy in a partner of a subject occurring from the start of study treatment until 90 days after the end of study treatment should be followed up and documented.

### 10.11. New cancers

The development of a new primary cancer should be regarded as a serious AE. New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. Metastasis should not be reported as an AE/SAE, as they are considered to be disease progression.

## 11. Response assessment and endpoints

### 11.1. Definition of endpoints

11.1.1. 12-month progression-free survival rate

Regard the second enrollment date as the starting date, and check the presence/absence of either all-cause death or progression based on image tests or diagnosis of an evident progression in the clinical setting as of when 12 months (1 year) have passed. The survey for patients whose death or progression has not been confirmed as of Month 12 or patients for whom it is unknown when these events were achieved will be censored at the most recent medical consultation date as outpatient/inpatient before loss to follow-up.

Progression based on image tests should be assessed according to "New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1)-Japanese translation JCOG version-".

#### 11.1.2. Progression-free survival

With the registration date as the starting date, the shortest period until either the date of all-cause death, the date the image test revealed progression, or the date when progression was diagnosed in the clinical setting.

The survey for patients whose death or progression has not been confirmed at the time of analysis or patients for whom it is unknown when these events were achieved will be censored at the most recent medical consultation date as outpatient/inpatient before loss to follow-up.

#### 11.1.3. Overall survival

With the registration date as the starting date, the period until the date of all-cause death. Patients who survive or are lost to follow-up at the time of analysis will be censored on the last survival confirmation date.

#### 11.1.4. Response rate

Follow “New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1)-Japanese translation JCOG version-” for evaluation of tumor response.

The assessment at baseline should be performed using image tests prior to treatment start.

To determine CR and PR of best overall response, at least 4-week response continuing period is required for confirmation. To determine SD of best overall response, overall SD of a 8-week period from registration is required. Response rate is the percentage of subjects with CR or PR in the analysis population.

The response at each time point should be assessed according to Tables 1-3 of RECIST version 1.1 “4.4.1. Response at each time point”. (Note that tumor marker should not be used for assessment of CR for non-target lesions.)

#### 11.1.5. Duration of response

The shortest period until either the date the image test revealed progression, the date when progression was diagnosed in the clinical setting, or the date of death (by all causes) from the date when CR or PR of best overall response is first recorded.

## 12. Statistical matters

The outline of statistical analysis is shown below. More detailed analysis method should be provided in a separately specified statistical analysis plan.

## 12.1. Analysis population

The definitions of the analysis population in this study are as follows. Handling of each case is decided by the coordinating investigator and the statistical analysis supervisor through discussion prior to the data lock.

1) All subjects registered

   All subjects registered in this study.

2) Full analysis set (FAS)

   Consist of all subjects registered who received at least one dose of the study drug and were evaluated for efficacy at least once.

3) Analysis population of measurable tumor response

   Consist of all subjects registered who received at least one dose of the study drug and were found to have measurable lesions in the imaging at baseline. The major analysis will be performed for ORR specified in RECIST guideline v1.1 and other RECIST-based endpoints in the analysis population of measurable tumor response.

4) Safety analysis set

   Consists of subjects registered who received at least one dose of the study drug.

## 12.2. Data handling

### 12.2.1. Handling of protocol deviation data

The coordinating investigator decides on how to handle the deviations that require consultation.

### 12.2.2. Handling of missing, rejected and abnormal data

The test/observation items that were not tested or observed at all should be treated as missing data. The data will not be complemented for the missing data with an estimated or calculated value.

## 12.3. Statistical analysis method

The efficacy endpoints are analyzed in FAS and the analysis population of measurable tumor response, and analyzed mainly in FAS.

The safety endpoints are analyzed in the safety analysis set.

### 12.3.1. Demographic and other baseline characteristics

Summary statistics should be calculated for demographic and other baseline characteristics. For categorical data, frequencies and percentages should be presented. For continuous data, mean value, standard deviation, median, minimum, and maximum values should be presented.

12.3.2. Analysis of the primary endpoint

For the primary analysis of this study, if the lower limit of the confidence interval for the 12-month proportion progression-free (by the Diagnostic Radiology Central Review Committee) obtained in this study in the FAS is greater than the threshold of 28%, then the combination therapy in this study is considered a promising therapy. The 12-month proportion progression-free should be estimated using the Kaplan-Meier method, and Greenwood's formula should be used to calculate the 90% confidence interval.

12.3.3. Analysis of the secondary endpoints

**Progression-free survival (assessed by the attending physician)**

Progression-free survival should be estimated using the Kaplan-Meier method, and the median value and its 95% confidence interval should be calculated. Confidence interval for the median value should be calculated using the method of Brookmeyer and Crowley.

In addition, proportion progression-free at 6, 18, and 24 months should be estimated.

**Overall survival**

Overall survival should be estimated using the Kaplan-Meier method, and the median value and its 95% confidence interval should be calculated. Confidence interval for the median value should be calculated using the method of Brookmeyer and Crowley. In addition, the overall survival rate at 24 months (2 years) should be estimated.

**Response rate**

The proportion of the best overall response of CR and PR in the analysis population of measurable tumor response and its 95% confidence interval (Exact method) should be calculated.

**Disease control rate**

The proportion of the best overall response of SD or better in the analysis population of measurable tumor response and its 95% confidence interval (Exact method) should be calculated.

**Duration of response**

Duration of response should be estimated using the Kaplan-Meier method, and the median value and its 95% confidence interval should be calculated. Confidence interval for the median value should be calculated using the method of Brookmeyer and Crowley.

**Time to death or distant metastasis**

Time to death or distant metastasis should be estimated using the Kaplan-Meier method, and

the median value and its 95% confidence interval should be calculated. Confidence interval for the median value should be calculated using the method of Brookmeyer and Crowley.

**Safety**

For all adverse events, the CTCAE v5.0 -JCOG is used to determine the frequency and the percentage of events by grade, grade 3 events, and grade 4 events. In addition, the frequency and the percentage are calculated by preferred term (PT) and by System Organ Class (SOC) of MedDRA/J.

**Subgroup analyses**

Subgroup analyses should be performed for the following stratification factors: Progression-free survival and overall survival should be estimated using the Kaplan-Meier method, and the median value and its 95% confidence interval should be calculated for each subgroup. For reference, the hazard ratio for the treatment effect and its 95% confidence interval should be calculated, using the Cox proportional hazard model.

Sex, age (< 65 and ≥ 65 years, < 75 and ≥ 75 years), tissue (squamous cell carcinoma/non-squamous cell carcinoma), smoking history (current, former/ non-smoker), disease stage (IIIA, IIIB/IIIc), maximum response (CR + PR/SD), PD-L1 expression (≥ 25%/1% to 24%), driver gene mutation (EGFR/ALK/ROS1 gene mutation, etc.) (negative/positive)

# 13. Ethical matters

All researchers related to this clinical study will conduct the study in accordance with the Declaration of Helsinki (amended in Fortaleza in October 2013), the standards specified in Article 14, Paragraph 3 and Article 80-2 of the Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act, and the "Ministerial Ordinance on Good Clinical Practice (GCP)" (Ordinance No. 9 of the Ministry of Health, Labour and Welfare dated January 22, 2016).

Also, all the said researchers shall comply with the study protocol unless interfering with the safety or human rights of the subjects.

## 13.1. Protection of patient's privacy

Information, which may identify the subjects such as the name of a subject, should not be notified from the study site to the coordinating investigator and other relevant persons.

The subjects should be identified or checked using enrollment numbers to be issued at the time of enrollment, subject ID codes*, gender and/or date of birth so that any third party can identify the subjects such as their names.

In addition, prepared CRFs and other relevant documents shall be used only for the purpose of this study.

* Subject ID code: A subject ID code refers to a number (code) used when the study site provides a subject's information to the external party.

## 13.2. Acquisition of informed consent

The investigator/subinvestigator should adequately explain the items listed below to the subjects using written information for subjects, which has been determined by the head of the study site based on the approval of the institutional review board (IRB), prior to their enrollment. Also, the investigator/subinvestigator should give the subjects an opportunity to ask questions and an ample of time to decide whether or not to participate in the study.

After confirming that the subjects have fully understood the contents of the study, written voluntary consent for participation in the study should be received personally from the subjects.

The investigator/subinvestigator should affix his/her seal or signature to an informed consent form and promptly hand a copy of the dated informed consent form to the subject. The original of the informed consent form should be kept in his/her medical chart.

## 13.3. Items to be explained to patients with explanatory documents

(1) That the study involves research.
(2) The purpose of the study.
(3) The name, title and contact address of the investigator or subinvestigator
(4) The method of the study (including those aspects of the study that are experimental, inclusion/exclusion criteria for subjects, and the probability for random assignment to each treatment if randomization is performed).
(5) The expected clinical benefits and risks or inconveniences to the subject (When there is no intended benefit to the subject, the subject should be made aware of this.). The subject shall be notified all the latest information related to foreseeable risks based on the clinical study.
(6) If the subjects are patients, the alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
(7) The expected duration of the subject's participation in the study.
(8) That the subject's participation in the study is voluntary and that the subject or his/her representative may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
(9) That the monitor(s), the auditor(s), the IRB, and the regulatory authority(ies) will be granted direct access to the subject's original medical charts without violating the confidentiality of the subject, and that, by signing the informed consent form, the subject or his/her representative is authorizing such access.

(10) If the results of the study are published, the subject's identity will remain confidential.
(11) The person(s) at the study site to contact for further information regarding the study and the rights of subjects, and whom to make inquiries or contact in the event of study-related injury.
(12) The compensation and/or treatment available to the subject in the event of study-related injury.
(13) Type of the IRB investigating and reviewing the appropriateness of the study, matters to be reviewed by each IRB, and other study-related matters concerning the IRB.
(14) That the subject may check written procedures and other relevant documents of the IRB and should make a request if he/she wishes to do so. If the written procedures, etc. of the IRB are disclosed on a website, its address, and if they are not disclosed, the written procedures, etc. are accessible to the public.
(15) The approximate number of subjects involved in the study.
(16) That the subject or his/her representative will be informed immediately if information becomes available that may be relevant to the subject's or his/her representative's willingness to continue participation in the study.
(17) The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.
(18) The anticipated expenses, if any, to the subject for participating in the study.
(19) The anticipated payment (e.g., agreement on calculating the amount of payment), if any, to the subject for participating in the study.
(20) The subject's responsibilities
(21) Matters concerning intellectual property rights
(22) Matters concerning the conflict of interest (COI)
(23) Other necessary matters

### 13.4. Preparation and revision of the explanatory documents and informed consent forms/provision of information for subjects

1) The investigator at each study site should prepare the site version of written information for subjects and an informed consent form using the samples of the written information for subjects and an informed consent form created by the coordinating investigator.
2) If information, which may affect the subjects' willingness to continue taking part in the study, is obtained, the investigator or subinvestigator should promptly notify the information to the subjects and confirm their willingness to continue participating in the study. Also, the investigator or subinvestigator should record the date of providing the information to the subject, the details of the notified information and the confirmation result in the original

medical records such as a medical chart.

3) When it is found to be necessary to amend the informed consent form and written information for subjects (if new important information, which may be relevant to the subjects' consent, is obtained), the investigator should promptly amend the informed consent form and written information for subjects based on the concerned information and receive the approval of the IRB beforehand. In addition, the investigator and subinvestigator should give an explanation again to all subjects participating in the study using the revised written information for subjects and receive written voluntary informed consent for continue taking part in the study from the subjects.

## 13.5. Approval of the institutional certification body

13.5.1. Approval of the IRB

When participating in the clinical study, a decision of the head of the study site based on the approval of the IRB at each study site for the appropriateness of conducting the study shall be obtained.

When approval is obtained, the original of an approval certificate should be properly retained at the study site, its copy should be sent to the coordinating investigator, and the coordinating investigator should properly keep the copy

13.5.2. Review on Continuation by the IRB

1) The investigator should submit a written summary of the current status of the clinical study once a year or more frequently upon request of the IRB to the head of the study site to undergo a review on continuation by the IRB.
2) The head of the study site should seek opinion on the continuation of the clinical study from the IRB in the following cases where: A report on the current status of the study or reports on adverse drug reactions (ADRs) during the study are received; deaths, which may be attributable to ADRs associated with the investigational drug, or other SAEs occurred and reported by the investigator; information, which may affect the subjects' willingness as to whether or not to remain participating in the study, is obtained; and such is found to be necessary for other reasons.
3) When a monitoring or audit report for the study is received, the head of the study site should seek the opinion from the IRB on the appropriateness of conducting the study at the concerned study site

## 13.6. Responsibility and compensation for patient's health hazard

In the case where any injury attributable to the conduct of the study occurred in the subjects, the

investigator/sponsor-investigator should give the best treatment to the subjects. When it is determined to be an unknown SAE attributable to the study, it should be handled in accordance with a separately specified summary of the compensation system. Furthermore, the subjects' health insurance will apply to other necessary measures for injuries.

# 14. Monitoring and audit

## 14.1. Monitoring

The sponsor-investigator should prepare written monitoring procedures and have monitors perform monitoring in accordance with the written procedures while taking account of the opinions of the IRB at the study site to verify that the protection of human rights, the maintenance of safety, and the improvement of welfare for the subjects are implemented, that the study has been conducted in compliance with the latest protocol and GCP Ordinance, and that it can be validated that clinical study data and other relevant items reported by the investigator or subinvestigator are accurate and complete as compared with study-related records such as source documents.

## 14.2. Report on monitoring

1) 1) When it is identified that the study at the study site is not carried out in accordance with the GCP Ordinance or protocol as a result of monitoring, a monitor should immediately notify such a fact to the investigator at the study site.
2) 2) When on-site monitoring was performed, monitors should submit a monitoring report presenting matters listed below at each time to the sponsor-investigator, the head of the study site pertaining to the monitoring, and the coordinating investigator:
   (1) Date and time when the monitoring was implemented;
   (2) Names of monitors;
   (3) Name of the investigator/subinvestigator to whom an explanation was asked at the time of monitoring;
   (4) Summary of monitoring results;
   (5) Matters informed to the investigator pursuant to the provisions of the preceding paragraph; and
   (6) Measures to be taken for the matters set forth in the preceding item and monitoring findings on the said measures

The status of the progress of the study, enrollment eligibility, safety and other relevant matters should be reported to the sponsor-investigator and the head of the study site pertaining to monitoring.

### 14.3. Audit

The sponsor-investigator should prepare a written plan and operating procedures for audits to ensure the quality of the study and evaluate whether or not the study being conducted in compliance with the GCP Ordinance, protocol and procedures independently and separately from usual monitoring and quality control activities for the clinical study, and have auditors perform audits in accordance with the plan and procedures while taking account of the opinions of the IRB at the study site.

### 14.4. Report on audit

When an audit was carried out, auditors prepare an audit report recording matters verified at the audit and audit certificate demonstrating that the audit has been conducted, and submit them to the sponsor-investigator, the head of the study site, and the coordinating investigator.

## 15. Study quality control and quality assurance

### 15.1. Data quality control

The sponsor-investigator should implement the quality control of this study, and keep and retain control records to ensure the implementation and safety of the study, and the accuracy and reliability of data.

### 15.2. Data quality assurance

The quality assurance of the study should be ensured by auditors in accordance with the Sections "14.3. Audits" and "14.4. Report on audit."

### 15.3. Record access

The head of the study site shall collaborate in monitoring and audits implemented by the sponsor-investigator and inspections by the IRB and other relevant parties. When monitoring, audits or inspections are to be carried out, the head of the study site should grant access to all study-related records such as source documents upon request of the monitors, auditors, IRB and other relevant parties.

### 15.4. Data handling and record retention

15.4.1. Handling of the CRF and data

The study site should pay careful attention to the protection of personal information with regard to the handling of CRFs or test reports and their copies to prevent the leakage, loss, transcription and

unauthorized copying of the information.

15.4.2. Retention of records

CRFs or test reports and their copies should be archived until the days stipulated below.

1) Study site

Essential documents, which should be retained by the head of the study site or the IRB, should be properly kept by a record archiving manager designated by the head of the study. The duration of archiving shall be the day specified in the following Item (1) or (2) whichever is later. When the sponsor-investigator needs to retain these documents at the study site for a period longer than this, the actions for the archiving period and method should be discussed with the sponsor-investigator.

(1) Date of marketing approval for the investigational drug (when development discontinuation or the fact of not attaching the results of the clinical study to an approval application is notified, the day 3 years from the day of receiving such a notification)

(2) Day 3 years after the discontinuation or completion of the study

2) Sponsor-investigator

The sponsor-investigator should properly retain study-related records for a period until the day set forth in the following Item (1) or (2) whichever is later in accordance with separately stipulated “Procedures for record archiving.” The sponsor-investigator may request the head of the study site, with which he/she affiliates, to carry out activities for retaining the records. When the sponsor-investigator is disengaged from his/her affiliated study site, the head of his/her affiliated study site may take charge of the record archiving activities.

When it is no longer necessary to archive the records, the sponsor-investigator shall notify such a fact to the head of the study site or the IRB organizer via the head of the study site.

(1) The day when the investigational drug supplier receives drug marketing approval for the investigational drug (when development discontinuation or the fact of not attaching the results of the clinical study to an approval application is notified, the day 3 years from the day of receiving such a notification)

(2) Day 3 years after the discontinuation or completion of the study

In the case where drug approval is granted for the investigational drug, the sponsor-investigator should take necessary measures for the handling of the said records such as concluding a contract with the investigational drug supplier because an approval holder is required to archive the said records for a given period pursuant to the provisions of Article 101 of the Enforcement Regulations of the Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act.

3) Investigator

The investigator should retain study-related documents as instructed by the head of the study site.

# 16. Change, discontinuation and termination regarding study implementation

## 16.1. Protocol revision

1) When it is found to be necessary to amend the protocol other than administrative matters (e.g., modifications in texts such as a change of a telephone number) of the study, the sponsor-investigator should make amendments after discussing the appropriateness of the changes and their effects on study evaluation with the other sponsor-investigators and coordinating investigator, and, as necessary, efficacy and safety evaluation committee and other relevant parties.
2) The sponsor-investigator should promptly notify the details of protocol amendments to all the heads of the study sites and the coordinating investigator, and take procedures specified at each study site.

## 16.2. Deviations, etc. from the protocol

1) The investigator or subinvestigator at each study site shall not make any protocol deviation or change before the investigator obtains written the approval of the IRB based on its prior review. However, this is not applicable to the case where it is necessary to make a deviation or change due to inevitable medical reasons such as avoiding immediate hazard to the subjects.
2) The investigator or subinvestigator should record all deviations from the protocol regardless of their reasons.
3) The investigator or subinvestigator may implement a protocol deviation or change when such is necessary for inevitable medical reasons such as avoiding immediate hazard to the subjects. In such a case, the investigator should immediately submit a document presenting such a fact and the reason to the head of the study site to promptly report such a fact and the reason to the IRB and other relevant parties via the head of the study site.

## 16.3. Discontinuation and interruption of study implementation

When the clinical study itself is discontinued or suspended, the sponsor-investigator should make a decision after consultation with the coordinating investigator, and promptly report the

decision and the reason to the head of the site and the regulatory authority in writing.

Discontinuation refers to premature discontinuation of the study for any of the following reasons:

- It is judged that there is a problem in the safety of this study
- The significance of this study is denied
- Completion of the study is considered difficult due to delay in patient enrollment, etc.

The follow-up period in the case of discontinuation will follow the description in this protocol starting from the last registration date. Even if the study is discontinued, the sponsor-investigator should discuss with the study drug provider so that the study drug can be continuously administered if the subject wishes to do so, unless there is any therapeutic problem.

### 16.4. Discontinuation and interruption at medical institutions

If the sponsor-investigator finds that the site has interfered with the proper conduct of the study by violating the GCP Ministerial Ordinance and the protocol (except for medically unavoidable reasons such as avoidance of urgent risks to subjects), the sponsor-investigator should discontinue the study at the site after notifying the coordinating investigator in advance. When the clinical study is suspended or discontinued, the sponsor-investigator should promptly report this fact and the reason to the head of the site and the coordinating investigator in writing. The coordinating investigator should promptly notify the sponsor-investigators of other sites of this fact and the reason. If the study is discontinued due to non-compliance, the sponsor-investigator should promptly report it to the regulatory authority.

If the head of the site is reported the suspension or discontinuation of the study from the sponsor-investigator, the head of the site will promptly notify the institutional review board in writing and provide detailed explanation.

### 16.5. Efficacy/Safety Assessment Committee

The Efficacy/Safety Assessment Committee should be established to objectively evaluate the efficacy and safety of this study from ethical and scientific viewpoints and to propose continuation, change, or discontinuation of the study to the sponsor-investigator. The Efficacy/Safety Assessment Committee should be operated in accordance with the separately specified “Procedures Related to the Efficacy/Safety Assessment Committee”.

## 17. Study termination and its reporting

After the termination of the study, the investigator should notify the head of the site of the termination of the study in writing and report the summary of the study results in writing. When informed by the investigator that the study will be terminated, the head of the site will notify the

institutional review board of the termination and a summary of the results in writing.

# 18. Study cost payment

## 18.1. Study operation cost

The cost for operation of this study will be supported by AstraZeneca K.K.

## 18.2. Costs required for protocol treatment

The study drug (Durvalumab) is provided by AstraZeneca K.K. To costs for tests and diagnostic imaging during the study period and concomitant medications to be used in the study, the patients' health insurance will be applied. To other necessary measures for health injuries, the patients' health insurance will be applied.

# 19. Matters concerning conflict of interest (COI)

This clinical study will be supported by AstraZeneca K.K. but conducted as an investigator-initiated clinical study. The WJOG will control the conflict of interest (COI) of researchers involved in the study and persons supporting the study as follows:

1. The COI of study-related persons should be followed as stipulated by the participating sites.
2. The ethics committee, WJOG will control the COI of persons playing central roles of the study such as the coordinating investigator, study secretary, committee chairperson and members, chief director and secretary-general.
3. The COI of individual WJOG secretariat staff involved in this study will be controlled in the same manner.

# 20. Disclosure of study results and attribution of the results

## 20.1. Disclosure of the results

After completion of the study, the results will be summarized, adjusted by the coordinating investigator and investigator, etc. who conducts the study, and published in appropriate academic societies and academic journals in Japan and overseas.

## 20.2. Clinical study report

After completion of the study, a clinical study report should be adjusted and prepared by the coordinating investigator and investigator, etc. who conducts the study pursuant to "Procedure on preparation of clinical study reports" separately specified.

### 20.3. Intellectual property right

The protocol, registration form and CRF design of this study as well as the database file prepared as a result of study implementation and its output forms shall belong to WJOG. The intellectual property rights related to the study drug invention* are attributed to AstraZeneca K.K.

The intellectual property that arises in the exploratory research belongs to the researcher.

When intellectual property rights including a patent right (except intellectual property rights relating to the study drug invention) arise in this study, the rights shall be divided according to the contribution level between the WJOG and the medical institution.

* "Study drug invention" refers to any invention regarding the study drug (including but not limited to new indications or dosage of the study drug) devised, made or conducted in other ways by the WJOG, the investigator or those who are related to a medical institution of the study alone or with others for this investigator-initiated clinical study. The study drug invention includes the ones related to (a) metabolic activity, pharmacological activity, adverse reactions, drug metabolism, mechanism of action, safety and drug interaction of the study drug, or (b) biomarkers, tests, diagnostic methods or diagnostic agents that are used in some way to anticipate the patient's reaction or tolerance to the study drug or to select the patients to be treated with the study drug. Provided, however, that the intellectual property obtained in an accompanying research belongs to the accompanying researcher.

### 20.4. Secondary use of data

If the coordinating investigator, investigator, etc. who conducts the study, and the WJOG (permanent) board decided that it is beneficial to make secondary use of the data obtained in this study for integrated analysis/meta-analysis etc., the secondary use of the data is permitted with personal information excluded.

### 20.5. Provision of data

After completion of the clinical study, this clinical study data and the relevant forms that have been anonymized may be provided for a fee or free of charge at the instruction/guidance of the regulatory authorities, or at the request of the related companies.

**2.** Preliminary registration of the study plan

Before this clinical study is started, WJOG will register the study in advance with the Japan Pharmaceutical Information Center Clinical Trials Information (Japic CTI).

## 21. Study implementation structure

See the separate volume "Clinical Study Implementation Structure.".

## 22. Others

1) Training for study staff

The sponsor-investigator/ investigator should provide study staff related to this clinical study at the site with training on the procedures for the study and systems to be used prior to enrollment of the first patient at the study site, and record its results.

2) Contracts between WJOG and sites

The WJOG should conclude a support agreement with each study site to support the conduct of the study, expenses, acquisition of the study drug, purchasing clinical study liability insurance, and other activities delegated to the coordinating investigator from the sponsor-investigator/investigator.

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## 24. Revision history

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