Table S1. Serious Adverse Events

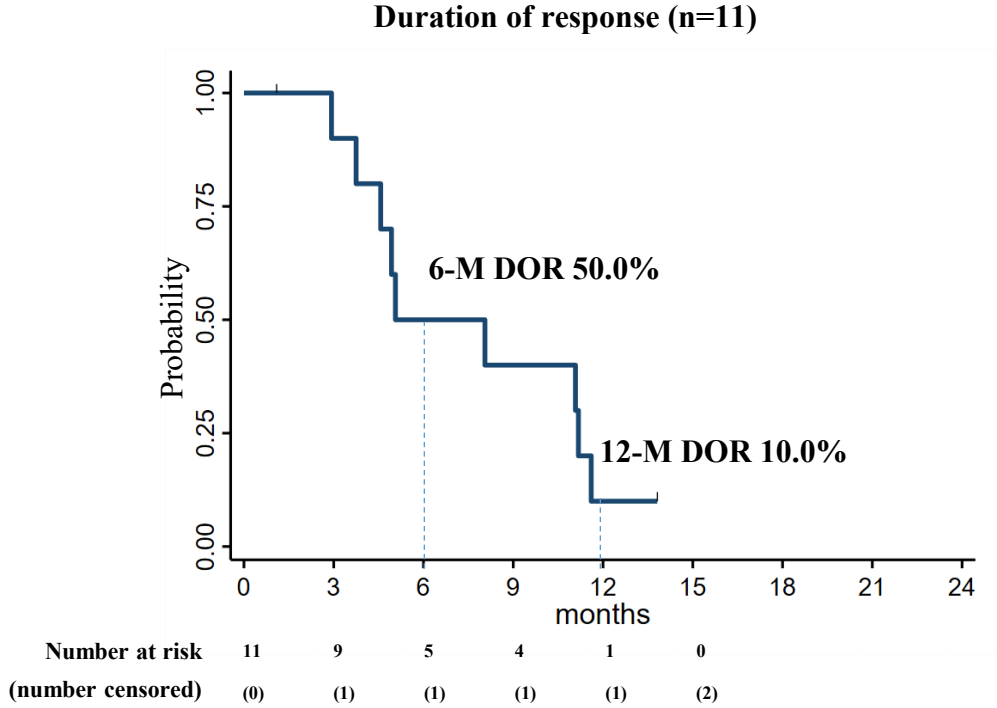
Patient No.	Event Name	Weeks from start of treatment to SAE onset	Grade	Relevance
1	Edema	2.7	G3	Related
2	Pulmonary infection	13.4	G3	Not Related
3	Colitis	13.9	G2	Related
4	Edema	45.0	G2	Related
5	Pneumonitis	8.1	G3	Related
6	Pneumonitis	7.3	G3	Related
7	Peripheral sensory neuropathy	24.7	G2	Related
7	Pleural effusion	24.7	G2	Related
8	Urticaria	12.3	G3	Not Related
9	Febrile neutropenia	4.1	G3	Related
9	Pneumonitis	5.0	G3	Related
10	Lower gastrointestinal bleeding	9.0	G3	Related
11	Dehydration	15.3	G3	Related
11	Hypoxia	27.1	G2	Related
11	Dyspnea	27.1	G3	Related
11	Edema	27.1	G3	Related
12	Gingival infection	2.6	G3	Related
13	Pulmonary infection	12.1	G3	Related
13	Bronchopulmonary hemorrhage	24.0	G3	Related

Table S2. Clinical background of the patients with grade 3 pneumonitis

Age	Sex	Smoking status	Brinkman Index*	Histology	Previous chemotherapy	Period from the previous therapy (days)
64	Male	Former or current	860	Adenocarcinoma	Carboplatin, Pemetrexed, Pembrolizumab	19
78	Male	Former or current	2080	Adenocarcinoma	Carboplatin, Pemetrexed, Pembrolizumab	424
63	Male	Former or current	450	Adenocarcinoma	Carboplatin, Pemetrexed, Pembrolizumab	33

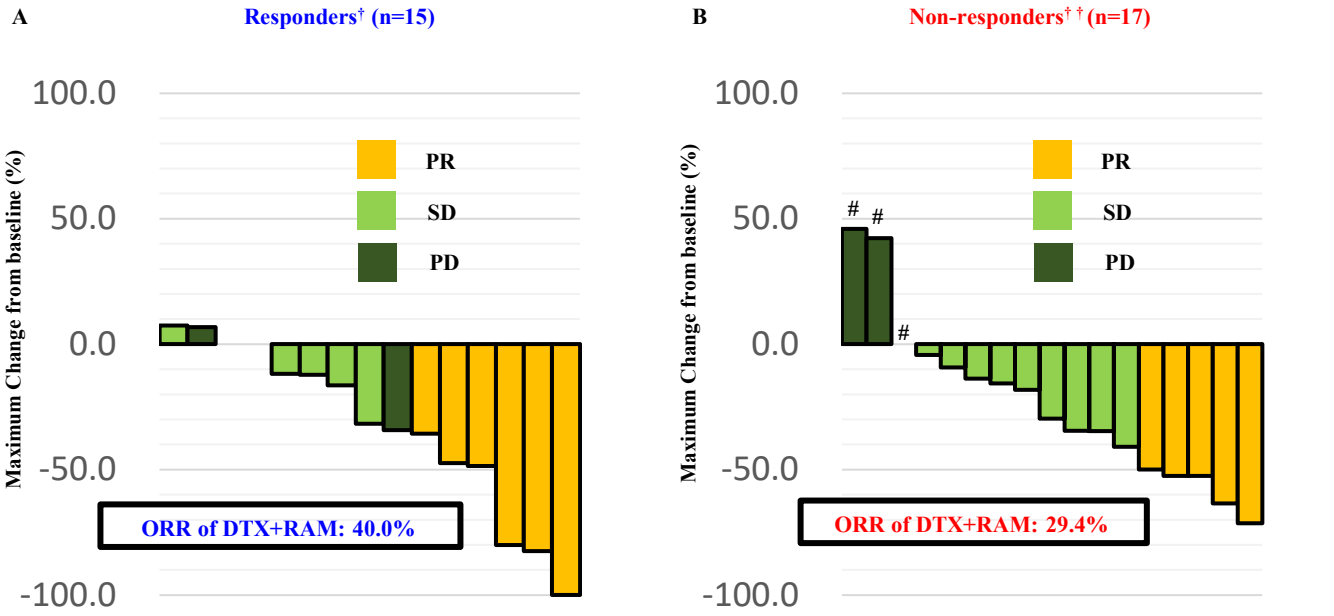
*Brinkman Index was defined as the number of cigarettes smoked per day multiplied by the number of years of smoking

Figure S1. Kaplan-Meier analysis of duration of response



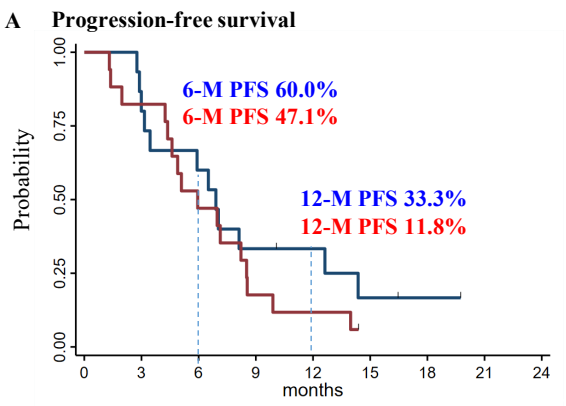
Median DOR: 5.1 months (95%CI: 2.9-11.2)

Figure S2. Maximum size change in the target lesion from baseline by comparing responders with non-responders of prior ICI plus platinum-based chemotherapy

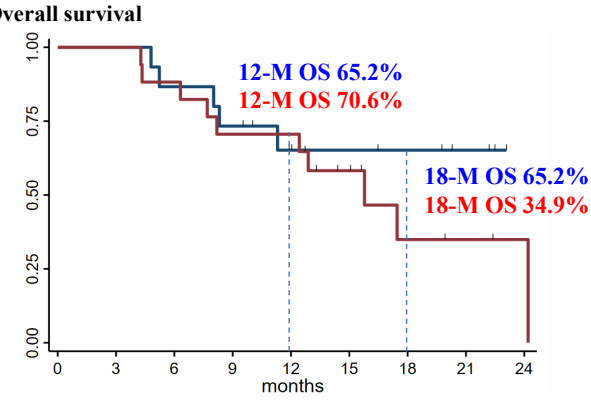


†Patients with CR/PR by ICIs plus platinum-based chemotherapy, ††Patients with SD/PD by ICIs plus platinum-based chemotherapy,
#Patients with PD by ICIs plus platinum-based chemotherapy

Figure S3. Kaplan-Meier analysis of PFS (A) and OS (B) according to Responders vs. Non-responders of Prior ICIs plus platinum-based chemotherapy



Number at risk	15	12	9	5	4	2	1	0
(number censored)	(0)	(0)	(0)	(0)	(1)	(1)	(2)	(3)
Number at risk	17	14	8	3	2	0	0	0
(number censored)	(0)	(0)	(0)	(0)	(0)	(1)	(1)	(1)



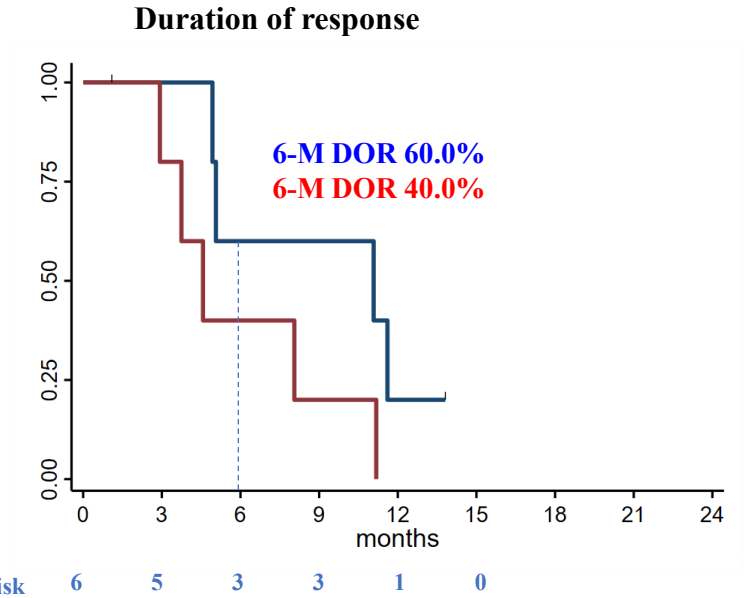
Number at risk	15	15	13	11	6	6	5	3	0
(number censored)	(0)	(0)	(0)	(0)	(4)	(4)	(5)	(7)	(10)
Number at risk	17	17	15	12	12	6	3	2	1
(number censored)	(0)	(0)	(0)	(0)	(0)	(4)	(5)	(6)	(7)

Previous chemo-ICI therapy	Median PFS
Responders† (n=15)	6.9 months (95%CI: 3.0-12.6)
Non-responders†† (n=17)	6.0 months (95%CI: 4.2-8.5)

Previous chemo-ICI therapy	Median OS
Responders† (n=15)	NR (95%CI: 8.0-NR)
Non-responders†† (n=17)	15.8 months (95%CI: 7.7-NR)

†Patients with CR/PR by prior ICIs plus platinum-based chemotherapy, ††Patients with SD/PD by prior ICIs plus platinum-based chemotherapy

Figure S4 Kaplan-Meier analysis of DOR according to Responders vs. Non-responders of Prior Chemo-ICI therapy



Number at risk	6	5	3	3	1	0
(number censored)	(0)	(1)	(1)	(1)	(1)	(2)
Number at risk	5	4	2	1	0	0
(number censored)	(0)	(0)	(0)	(0)	(0)	(0)

Previous chemo-ICI therapy	Median DOR
Responders† (n=6)	11.1 months (95%CI: 4.9-NR)
Non-responders†† (n=5)	4.6 months (95%CI: 2.9-NR)

†Patients with CR/PR by prior chemo-ICI therapy, † † Patients with SD/PD by prior chemo-ICI therapy

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Phase II study of docetaxel plus ramucirumab after treatment of platinum based chemotherapy combined with immune check point inhibitors in patients with non-small cell lung cancer (SCORPION Study)

Study Protocol

Principal investigator:
Department of Respiratory Medicine, Nagoya University Hospital
Hospital Assistant Professor Masahiro Morise
Address: 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550
Direct phone number 052-744-2167
FAX number 052-744-2176
e-mail: morisem@med.nagoya-u.ac.jp

Co-investigator(Clinical Study Office):
Department of Respiratory Medicine, Nagoya University Hospital
Reiko Matsuzawa
Address: 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550
Direct phone number 052-744-2167
FAX number 052-744-2176
e-mail: rmatuza@med.nagoya-u.ac.jp

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I. The Aim of the Study

This study aimed to evaluate the efficacy and safety of docetaxel (DTX) + ramucirumab (RAM) as second-line treatment in patients with non-small-cell lung cancer (NSCLC) previously treated with platinum-based chemotherapy combined with immune checkpoint inhibitors (ICIs).

Primary endpoint: Objective response rate

Secondary endpoint: Safety, progression-free survival (PFS), overall survival (OS)

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II. Study Rationale

II-1 Background of the Etiology of Lung Cancer

The disease rate and mortality rate of primary lung cancer has increased in the last two decades. In Japan, approximately 113,000 developed primary lung cancer in 2014, and the annual number of deaths caused by primary lung cancer was 73,800 [1].

NSCLC accounts for approximately 85% of all types of lung cancer in patients requiring clinical assessment and treatment, with a survival period (median) of 4–5 months among treatment-na ï ve patients with metastatic NSCLC and a one-year survival rate of 10% without therapeutic intervention [2]. Two thirds of patients are diagnosed with advanced NSCLC with metastasis or without indication for radical thoracic irradiation. These patients present with advanced inoperable disease for which treatment remains obscure. Treatment is provided to improve symptoms, optimize quality of life, and prolong survival.

II-2 Current Evidences of Second-Line Treatment for Advanced NSCLC

Platinum-based chemotherapy had been established as the standard first-line treatment for patients with advanced NSCLC in the 1990s. Osimertinib, alectinib, and crizotinib were the standard first-line treatment in patients with driver oncogene abnormality, such as EGFR, ALK, and ROS1. In these patients, platinum-based chemotherapy was administered after driver gene-targeted therapy was unsuccessful. However, almost all patients showed resistance to platinum-based chemotherapy; therefore, second-line or third-line treatments were recommended. At present, DTX, pemetrexed, erlotinib, and ICIs are approved for patients who exhibited disease progression following one prior regimen for advanced NSCLC [3, 4].

The approval of DTX was based on data from two phase III trials: TAX 317 [5] and TAX 320 [6]. In TAX 317, patients with advanced NSCLC who had disease progression on or after at least one prior platinum-containing chemotherapy were randomized to receive either DTX every 3 weeks or best supportive care (BSC). In the initial trial design, 100 mg/m2 DTX was used as a 1-h intravenous (IV) infusion every 3 weeks but was subsequently modified to 75 mg/m2 DTX every 3 weeks due to an unexpectedly high occurrence of adverse events (AEs). A total of 204 patients were enrolled in this trial. Compared with BSC, there was a significantly prolonged median survival and a higher 1-year survival rate for patients treated with 75 mg/m2 DTX (median survival 7.5 months vs. 4.6 months; p = .010; 1-year

survival rate, 37% vs. 12%), although the response rate was low (5.5%). DTX-treated patients at both dose levels demonstrated a significantly longer time to progression. No other significant differences were observed in the hematologic side effects between 75 mg/m2 DTX arm and BSC, except for Grade 3/4 neutropenia in 67% of patients. Grade 3/4 nonhematologic toxicity, except for diarrhea, occurred at a similar rate in both the DTX and BSC groups.

In TAX 320, patients with advanced NSCLC who exhibited disease progression on or after at least one prior platinum-containing chemotherapy were randomized to receive 100 mg/m2 DTX every 3 weeks, 75 mg/m2 DTX every 3 weeks, or a comparator regimen of either 30 mg/m2 vinorelbine per week or 2 mg/m2 x 3 days ifosfamide every 3 weeks. There was no restriction on prior regimens, and patients with prior paclitaxel exposure were eligible as well (30-40%). A total of 373 patients were enrolled in this trial, of which 125 received 75 mg/m2 DTX. The OS (intention-to-treat group) was higher in patients treated with DTX. Also, there was a significantly greater 1-year survival rate with 75 mg/m2 DTX than with vinorelbine or ifosfamide (32% vs. 19%; p = .025). The response rate observed in the 75 mg/m2 DTX arm was 6.7%, which was significantly greater than in the control arm. Prior exposure to paclitaxel did not decrease the likelihood of response, nor did it affect survival. Grade 4 neutropenia occurred in 54% of patients in the 75 mg/m2 DTX group, which was significantly greater than in the control group(31%). Grade 4 febrile neutropenia with significantly greater frequency were also observed in the 75 mg/m2 DTX group compared to the control group (8% vs. 1%). Grade 3/4 nonhematologic side effects were not more common among patients treated with DTX than among controls.

Based on these results, since the 2000s, DTX has been regarded as the standard treatment for patients who exhibited disease progression following one prior regimen for advanced NSCLC. However, programmed cell death protein-1 (PD-1) inhibitor, nivolumab, showed greater survival benefit compared to DTX in both squamous NSCLC and nonsquamous NSCLC in 2015. Subsequent to nivolumab, pembrolizumab for patients with NSCLC with tumor PDL expression > 1% and atezolizumab for all patients with NSCLC were approved as second-line treatment based on the phase III trial results.

On the other hand, ramucirumab (RAM) is a recombinant human immunoglobulin G, subclass 1 mAb targeting human VEGFR-2 (also known as human kinase insert domain-containing receptor, or KDR). In terms of standard second-line treatment, DTX + RAM showed greater survival benefit compared to DTX monotherapy. The

major clinical trial results of DTX + RAM in patients with NSCLC were as follows:

REVEL Study (Global Phase III Study) [7]

In 2014, the phase III study results showed comparison of the OS of DTX + RAM versus DTX in patients with stage IV NSCLC who have had disease progression during or after one prior first-line platinum-based chemotherapy with or without maintenance therapy. A total of 1253 patients were randomized 1:1. The median OS (primary endpoint) of DTX + RAM and DTX were 10.5 months [95% confidence interval (CI), 9.5–11.2] and 9.1 months (95% CI, 8.4–10.0), respectively, and the hazard ratio (HR) was 0.857 (95% CI, 0.751–0.979, p = .024).

JVCG Study (Japanese Randomized Phase II Trial) [8]

In 2016, the randomized phase II study results showed comparison of the PFS of DTX + RAM versus DTX in patients with stage IV/recurrent NSCLC who have had disease progression during or after one prior first-line platinum-based chemotherapy with or without maintenance therapy. The median PFS (primary endpoint) of DTX + RAM and DTX were 5.22 months (95% CI, 3.52–6.97) and 4.21 months (95% CI, 2.83–5.62), respectively, and the HR was 0.857 (95% CI, 0.59–1.16).

In the phase II study, the major AEs induced by DTX + RAM (n = 96) were neutropenia (95.7%), stomatitis (54.3%), nasal hemorrhage (47.9%), peripheral edema (36.2%), and febrile neutropenia (36.2%), which confirmed DTX + RAM tolerability.

II-3 Rationale of this Phase II Study

Several phase III studies, including KEYNOTE-189, showed the survival superiority of platinum-based chemotherapy combined with ICIs compared with platinum-based chemotherapy alone [9, 10]. Based on these data, platinum-based chemotherapy combined with ICI became the fist-line standard treatment instead of platinum-based chemotherapy alone, and based on the results of the REVEL study, DTX + RAM became the most promising second-line treatment. Previous reports showed that the efficacy of cytotoxic chemotherapy was possibly improved with the pretreatment of ICI, while AEs were also increased. Notably, RAM was reported to harbor immune modulation effects due to VEGF pathway inhibition; thus, DTX + RAM is considered as a promising strategy after the administration of platinum-based chemotherapy combined with ICI. Because the half - life period of ICI was reported to be approximately 6 months, it is important that the efficacy and safety of DTX + RAM is evaluated in patients previously treated with first-line platinum-based chemotherapy combined with ICI.

Therefore, the phase II study of DTX + RAM was conducted to evaluate the efficacy and safety of DTX + RAM following the administration of platinum-based chemotherapy combined with ICI.

II-4 Drug Information

i. The Name of the Drug

Docetaxel

Ramucirumab

ii. Route of Administration, Usage, and Dose

DTX : 60 mg/m2, IV, approximately 60-min infusion (up to 90 min), day 1 of each cycle, every 3 weeks

Patients should be premedicated with corticosteroids, such as 16 mg dexamethasone, 1 day prior to the start of DTX administration in order to reduce the incidence and severity of fluid retention, as well as the severity of hypersensitivity.

RAM : 10 mg/kg, IV, approximately 60-min infusion (up to 25 mg/min), day 1 of each cycle, every 3weeks

iii. Patients

Patients with advanced/recurrent NSCLC who have had disease progression during or after first-line platinum-based chemotherapy combined with ICI

iv. Risks and Benefits of DTX + RAM

DTX + RAM is approved for pretreated patients with NSCLC in Japan. The Japanese Lung Cancer Guideline Committee recommends DTX + RAM as a second-line or later treatment for patients with NSCLC with ECOG performance status (PS) of 0-2 [11]. It is considered as a first-line treatment for patients who have had disease progression during or after one prior first-line ICI combined with platinum-based therapy. DTX + RAM treatment is reinversed in Japan; thus, no particular benefits and risks were identified by participating in this study.

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Ⅲ. Inclusion and Exclusion Criteria and Discontinuing Criteria of Protocol Treatment

Ⅲ-1 Criteria for Patient Enrollment

Ⅲ-1-1 Inclusion Criteria

Patients were eligible for this study only if all of the following criteria were met. Refer to the Japan Clinical Oncology Group (JCOG) shared reference interval list for the reference interval of laboratory test items.

1. The patients had histologically or cytologically confirmed NSCLC.
2. The patient had Stage Ⅲ without indication for definitive radiation therapy, Stage Ⅳ, or postoperative recurrent NSCLC.
3. The patients who had disease progression during or after first line platinum-based chemotherapy combined with immune checkpoint inhibitors with or without maintenance therapy for advanced or metastatic NSCLC.

   • Maintenance therapy was defined as therapy given within 42 days after the last dose of platinum-based chemotherapy in patients with ongoing clinical benefit (complete response [CR], partial response [PR], or stable disease [SD]) after platinum-based first line chemotherapy.

   • Prior bevacizumab as first line and/or maintenance therapy was allowed.

   • The patients with a targetable driver oncogene alteration had to experienced disease progression during or after platinum-based chemotherapy combined with immune checkpoint inhibitors with or without maintenance therapy after first line therapy with appropriate molecular targeted therapy.
4. At least 20 years of age on the day of signing informed consent.
5. The patients had an ECOG PS of 0 or 1.
6. The patients had measurable disease at the time of enrollment documented by CT scan or MRI as defined by RECIST version 1.1.
7. The patients had resolution to Grade ≤ 1, by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Japanese translation version by JCOG), of all toxicity due to prior chemotherapy, locoregional therapy, surgery, or other anticancer therapy.
8. The patients without symptomatic brain metastases, meningeal carcinomatosis, or spinal metastases requiring radiotherapy or surgery.

The patients with treated brain metastases were eligible, if their neurological

function is clinically stable at least 14 days had elapsed from completing steroid treatment after cranial irradiation (whole brain, focal, and stereotactic radiotherapy) or at least 28 days after surgical resection. In addition, the patients must have had no evidence of Grade ≥ 1 central nerve system (CNS) hemorrhage based on MRI or contrast enhanced CT scan performed within 21 days before enrollment.

9. The patients without Grade ≥ 3 superior vena cava syndrome, pericardial effusion, pleural effusion, or ascites. Grade ≤ 2 pleural effusion at least 14 days after drainage was allowed.

10. The patients had adequate organ function, defined as:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x ULN. 5.0 x ULN or less if the transferase elevation was due to liver metastases.
- The patients did not have:
  - Cirrhosis at a level of Child-Pugh B or worse.
  - Cirrhosis (regardless of degree) and previous history of hepatic encephalopathy or clinically meaningful ascites. Clinically meaningful ascites was defined as requiring ongoing treatment with diuretics and/or paracentesis.
- Serum creatinine (Cr) ≤ 1.5 x ULN or calculated creatinine clearance ≥ 40 mL/min (per Cockcroft-Gault formula or equivalent and/or 24-hour urine collection).

  Cockcroft-Gault glomerular filtration rate = (140 - age) x (weight in kg) x (0.85 if female) / (72 x Cr).
- Absolute neutrophil count (ANC) ≥ 1.5 x 10^3 /μL.
- Hemoglobin (Hb) ≥ 10.0 g/dL.
- Platelets (PLT) ≥ 100 x 10^3 /μL.

The patients had adequate coagulation function, defined as: international normal ratio (INR) ≤ 1.5, prothrombin time (PT) and partial thromboplastin time (PTT or APTT) ≤ ULN + 5 seconds (when not receiving anticoagulation therapy). Active bleeding (bleeding within 14 days before the initial dose of study treatment) and pathological conditions with a high risk of bleeding (e.g., tumor invasion into major vessels) were not allowed.

11. No evidence of interstitial pneumonia or pulmonary fibrosis on chest CT scan.

12. The Patient's urinary protein ≤ 1+. When urinary protein ≥ 2, a 24-hour urine should be collected. If the protein in the 24-hour urine storage is less

than 1,000 mg, the patient is eligible.

13. Eligible patients of reproductive potential (both sexes) agreed to use medically approved methods of birth control during the study period and at least 4 months after last dose of study treatment, or until the investigator allowed to become pregnant. Acceptable contraceptive methods include vasectomy, tubal ligation, contraceptive methods using spermicidal agents (e.g., condoms, pessaries), intrauterine devices (IUDs) inserted more than 3 months before the initial dose of study treatment, and oral contraceptives taken more than 3 months before the initial dose of study treatment.

14. Female patients of childbearing potential had a negative serum or urine pregnancy test within 7 days prior to enrollment .

15. The patients had a life expectancy of ≥ 3 months.

16. Prior radiation therapy was allowed if:

- In the case of chest radiation therapy, at least 90 days had elapsed from the completion of radiation therapy prior to registration.
- In the case of focal or palliative radiation therapy for bone metastases, at least 14 days had elapsed from last radiation therapy prior to registration (and provided that 25% or less of the total bone marrow had been irradiated).
- In the case of CNS radiation therapy, at least 14 days had elapsed from completion of radiation therapy prior to registration.

17. The patients had provided signed informed consent to participate in the study.

III-1-2 Exclusion Criteria

Patients were excluded from the study if they met any of the following criteria:

1. The patient’ s tumor wholly or partially contained small cell lung cancer.
2. The patients had undergone major surgery within 28 days prior to enrollment or subcutaneous venous access device placement within 7 days prior to enrollment. The patients with postoperative bleeding or wound complications from a surgical procedure performed in the last 2 months.
3. The patients had a planned major surgery during the study period.
4. The patients were receiving concurrent treatment with other anticancer therapy, including other chemotherapy, immunotherapy, hormonal therapy, chemoembolization or targeted therapy. If prior anticancer therapy was administered, the last dose must have been at least 28 days from the time of

enrollment. If prior anticancer therapy included bevacizumab, the last dose of bevacizumab must have been at least 28 days from the time of enrollment.

5. The patients had radiologically documented evidence of major blood vessel invasion or narrowing by cancer.

6. The patients had radiologically evidence of intratumoral cavitation, regardless of histology.

7. The patients with a history of deep vein thrombosis (DVT), pulmonary embolism (PE), or other significant thromboembolism within 3 months prior to enrollment. Venous port or catheter thrombosis and superficial vein thrombosis were not considered ″significant″.

8. The patients with a history of hemoptysis within 2 months prior to enrollment.

9. The patients received antiplatelet agent (for example, aspirin ≥ 325 mg/day, clopidogrel, ticlopidine, and dipyridamole), vitamin K antagonists at therapeutic doses, or similar therapeutic anticoagulation at effective doses within 14 days prior to enrollment.

10. The patients had clinically relevant congestive heart failure (NYHA II-IV) or arrhythmias not controlled by drugs.

11. The patients had experienced any arterial thrombosis, including myocardial infarction, unstable angina, cerebrovascular attack or transient ischemic attack within 6 months prior to enrollment.

12. The patients had uncontrolled hypertension, defined as ≥ 150 / ≥ 90 mmHg, despite standard medical management.

13. The patients had a serious or non-healing wound, ulcer or bone fracture within 28 days prior to enrollment.

14. The patients had significant bleeding disorder, vasculitis, or Grade ≥ 3 gastrointestinal bleeding within 3 months prior to enrollment.

15. The patients had gastrointestinal perforation and/or fistula within 6 months prior to enrollment.

16. The patients had a bowel obstruction, history or presense of inflammatory bowel disease, extensive bowel resection (hemicolonectomy or extensive small intestine resection due to chronic diarrhea), Crohn's disease, ulcerative colitis, or chronic diarrhea.

17. The patients had Grade ≥ 2 peripheral neuropathy.

18. The patients had a serious disease or medical condition including:

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- Known positive test for human immunodeficiency virus (HIV), active hepatitis B*, or hepatitis C virus antibody (HCVAb).

*Active hepatitis B were defined as:

-Positive for hepatitis B surface antigen (HBsAg+).

-Positive for anti-hepatitis B core antibody (HBcAb+) and hepatitis B virus DNA (HBV DNA).

-Positive for anti-hepatitis B surface antibody (HBsAb+) and HBV DNA.

- Known acquired immunodeficiency syndrome (AIDS)-related illness.
- Active or uncontrolled clinically serious infection.
- Previous or concurrent malignancy (excluding NSCLC) except for basal or squamous cell skin cancer, in situ carcinoma of the cervix, or other solid tumors treated curatively and without recurrence for at least 3 years prior to enrollment.
- Radiologically evidence of interstitial lung disease on chest CT scan or X-ray.
- Serious medical conditions or serious systemic co-morbidities (for example, unstable angina, poorly controlled diabetes mellitus) that might have increased the risk associated with study participation.
- Clinically significant fluid retention (for example, ascites or pleural effusion) that was not be controlled by repeated drainage.
- Known allergy or hypersensitivity reactions to any of the treatment components.
- Known history of drug abuse.

19. The patients were pregnant or breastfeeding.

20. Prior therapy with ramucirumab or docetaxel.

III-2 Discontinuation criteria of protocol treatment

The criteria for subject enrollment must be observed. If a subject is enrolled who is in violation of the enrollment criteria, the study treatment for the subject shall, in principle, be terminated and the Secretariat shall be notified.

<u>The investigator or research associate will discontinue administration of ramucirumab in the following cases</u>

- When the principal investigator or subinvestigator determines that discontinuation of study treatment is appropriate from the standpoint of subject protection

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- Unacceptable adverse events or toxicities (e.g., moderate toxicity of intolerable persistence) judged by the investigator or principal investigator to be caused by ramucirumab
- Development of a Grade 3 or 4 infusion-related reaction that the investigator or subinvestigator determines to be due to ramucirumab
- If grade 3 or 4 arterial thromboembolism develops
- Worsening of pulmonary embolism/deep vein thrombosis during anticoagulation therapy
- Grade 3 or 4 venous thrombosis judged to be life-threatening by the principal investigator or subinvestigator, or the development of grade 3 or 4 venous thrombosis that is symptomatic and cannot be adequately treated with anticoagulation therapy
- Grade 3 or 4 bleeding or hemorrhagic event
- Grade 4 hypertension or uncontrolled hypertension develops
- Persistent or recurrent proteinuria with a 24-hour protein level greater than 3 g, three episodes of proteinuria with a 24-hour protein level of 2 g or greater, or failure to recover to a 24-hour protein level of less than 2 g within 3 weeks of dose postponement
- If gastrointestinal perforation develops
- When the diagnosis of reversible posterior leukoencephalopathy syndrome is confirmed
- Grade 4 non-hematologic toxicity (excluding fever or abnormal laboratory values) judged by the investigator or subinvestigator to be causally related to ramucirumab
- If more than 3 dose reductions of ramucirumab are required or if a dose deferral (>21 days from the start of the next cycle) is required beyond 6 weeks after the last dose of study drug (ramucirumab or docetaxel) (deferral due to the onset of proteinuria is listed separately)
- If hemoptysis develops
- Grade 3 or 4 congestive heart failure
- New onset of hepatic encephalopathy or hepatorenal syndrome due to cirrhosis

Subjects who discontinue ramucirumab may continue study treatment and continue receiving docetaxel.

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Discontinuation of docetaxel in the event of an adverse event is detailed in section VI-3-4. Docetaxel should be discontinued in the following cases

- If more than two dose reductions of docetaxel are required or if a dose delay (more than 21 days beyond the scheduled start of the next cycle) is needed beyond 6 weeks after the last dose of study drug (ramucirumab or docetaxel)
- Unacceptable adverse events or toxicities (e.g., moderate toxicity of intolerable persistence) clearly attributable to docetaxel in the judgment of the investigator or principal investigator
- Common Terminology Criteria for Adverse Events v4.0 Japanese translation JCOG version Any occurrence of a potentially life-threatening event causally related to docetaxel, regardless of grade

Subjects who discontinue docetaxel may continue the study and continue receiving ramucirumab.

The investigator or principal investigator will discontinue all medications (ramucirumab and docetaxel) for subjects on ongoing study treatment if

- PD based on imaging evaluation or PD based on worsening disease
- If the subject does not comply with the study protocol (if the subject does not come to the hospital on the scheduled visit date, the reason and the next scheduled visit date should be confirmed by the staff of the site, and the date, content, and means of communication should be recorded in the original documents).
- When the principal investigator or subinvestigator determines that further administration is inappropriate due to concomitant disease or changes in the subject's condition
- If the subject withdraws consent (even if the subject withdraws consent for continued administration, long-term follow-up can still be conducted if the subject has not withdrawn consent for follow-up). Confirm with the subject whether it is possible to collect follow-up information on anticancer treatment and survival status, and if so, to what extent, and document this in the medical record. (Surveys scheduled for the follow-up period after discontinuation will be conducted whenever possible.)
- Unacceptable adverse events or toxicities (e.g., moderate toxicity of intolerable persistence) that the principal investigator or a subinvestigator determines cannot be attributed to any of the drugs

• Any occurrence of an event, regardless of the Common Terminology Criteria for Adverse Events v4.0 Japanese Translation JCOG Grade, that is considered life-threatening and is causally related to the study treatment, as determined by the principal investigator or study investigator who cannot identify which drug is responsible for the event.

• If pregnancy during the period of treatment becomes apparent

In addition, if all treatment is discontinued

• Record the reason for discontinuation in the subject's medical record and case report form (eCRF).

• Perform the discontinuation-of-treatment examinations listed in the study schedule. If treatment is discontinued because of PD based on imaging evaluation, imaging studies during the study treatment period may be considered as the discontinuation study.

• If the drug is discontinued for reasons other than PD based on imaging evaluation (e.g., determination of PD due to worsening disease or toxicity), imaging studies should be continued according to the evaluation schedule [every 6 weeks (±7 days) after initial study drug administration] until PD is objectively demonstrated on imaging.

IV. Case Registration Methods

IV-1. Registration Procedure

1) The principal investigator and subinvestigators (hereafter referred to as ″investigators, etc.″) will explain the study to the candidate patients and obtain their written consent. 2) Confirm that all eligibility criteria are met and none of the exclusion criteria apply.

2) The principal investigator enters the necessary information in the EDC and registers the cases.

3) If there are no eligibility issues, a case number will be issued, and the case will be registered. When registering a case, the registration number and patient identification code should be assigned to each registered case and the case should be anonymized.

4) The registration number and patient identification code issued should be appropriately stored and managed at the site.

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IV-2 Precautions

1) Enrollment after the start of protocol treatment is not permitted without exception.
2) Once a patient is registered, the registration will not be cancelled (deleted from the database). In the case of duplicate registration, the first registration number shall be used in principle.
3) When mis-registration or duplicate registration is found, promptly notify the CRO that manages the data.

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V. Study design

V-1 Primary and secondary endpoints

The endpoints of this study were as follows:

Primary endpoint: objective response rate (ORR)

Secondary endpoints: safety, progression-free survival (PFS), and overall survival (OS)

V-2 Type and method of the study

This is an open-label, single-arm, multicenter Phase II study.

V-3 Dosage and administration of study treatment

The dosage and administration of study treatment is intravenous docetaxel 60 mg/m^2 plus intravenous ramucirumab 10mg/kg on day 1 of a 21-day cycle.

V-4 Study periods

Registration period: 1 year and 10 months

Follow-up period: 9 months from the time of last patient enrollment.

V-5 Discontinuation criteria of partial or entire study

V-5-1 Discontinuation of the study by the medical institution

If it is deemed necessary by the principal and/or sub investigator for medical, safety, regulatory, ethical, or other reasons that fall under applicable laws and regulations or criteria for conducting clinical trials of pharmaceutical products, the participation of the relevant medical institution in this study may be terminated.

V-5-2 Discontinuation of the entire study

If it is deemed necessary by the principal investigator for medical, safety, regulatory, ethical, or other reasons that fall under applicable laws or regulations or criteria for conducting clinical trials of pharmaceutical products, the entire study may be terminated.

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V-6 Original source documents that are directly described in the case report form

The original source documents for this study are defined as follows:

Medical records

Documents of informed consent

Laboratory data

cycle	Before Enrollment		1			2			3			4			5			6			7			8			Continue until disease progression or untolerable toxicity
week	within 28 days	within 14 days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
ramucirumab (once in 3weeks)			■			■			■			■			■			■			■			■			
docetaxel (once in 3weeks)			■			■			■			■			■			■			■			■			

week	within 28 days	within 14 days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	Discontinuation
Blood examination		○	○	○	○	○			○			○			○			○			○			○			Continue until disease progression or untolerable toxicity					○
Urinanalysis		○	○	○	○	○			○			○			○			○			○			○								○
SpO2		○	○	○	○	○			○			○			○			○			○			○								○
PS, Hight, Weight		○	○			○			○			○			○			○			○			○								○
Chest X-ray		○	○			○			○			○			○			○			○			○								○
Infection (HBV, HCV, HIV)	※1○																															
Electrocardiogram	○																															
contrast MRI/CT of the brain	○																															
contrast CT of the chest and abdomen	○								○						○						○											○
Bone Scan/PET	○																															
Concomitant drug		○				←																				→						
Adverse Event			○	○	○	←																				→						

※1 allowed if done before registration

※2 Height measurements to be performed at baseline only.

Supplement of examination items

*During the treatment period after cycle 2, the evaluation date is defined as the date of ramucirumab + docetaxel administration (-3 days allowed).

*Pre-registration Assessments:

Age, sex, ECOG PS, smoking history, histology, driver oncogene alteration status, previous treatment regimen (with/without taxane, with/without bevacizumab, and type of immune checkpoint inhibitor), efficacy and duration of previous treatment, date of last administration of immune checkpoint inhibitor

*Pre-registration examinations:

Urinalysis; qualitative test for urine protein

Peripheral blood count and biochemistry; white blood cell count (WBC), absolute neutrophil count (ANC), hemoglobin (Hb), platelet count (PLT), alanine aminotransferase (AST), aspartate aminotransferase (ALT), total bilirubin,

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creatinine (Cr)

Body weight, ECOG-PS, blood pressure

*Chest and abdominal CT imaging will be performed every 6 weeks (±7 days) starting from ramucirumab + docetaxel cycle 1 day 1. Head MRI/CT should be performed every 6 weeks (±7 days) if brain metastases are present at baseline, otherwise as needed.

Pre-enrollment screening tests performed in routine clinical practice prior to obtaining informed consent are allowed. The discontinuation examination should be performed within 28 days of the decision to discontinue study treatment. If study treatment is discontinued due to PD based on imaging evaluation, the imaging may be considered as the discontinuation examination.

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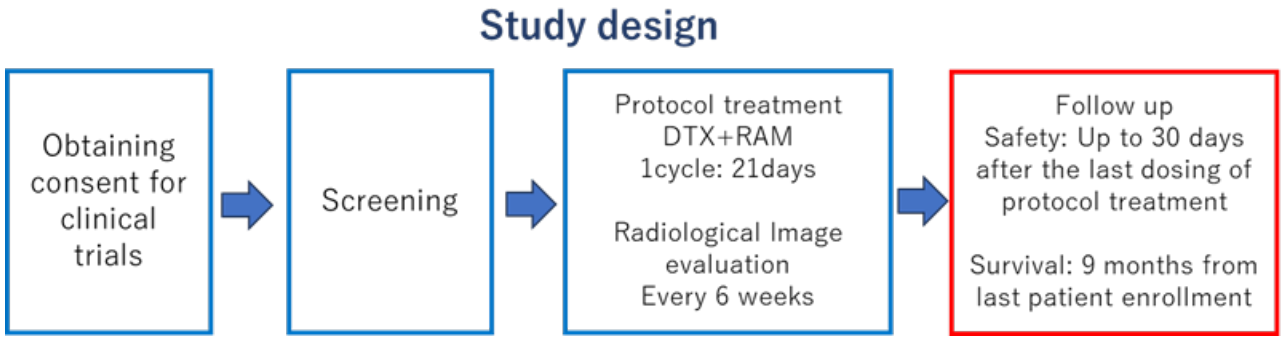
VI. Study Treatment

VI-1 Names, dosage, route of administration, and details of schedule for hospitalization and hospital visits.



VI-1-1 Outline of study design

This is a single-arm, multicenter, Phase II study of previously treated advanced or metastatic NSCLC patients with disease progression during or after primary chemotherapy (with or without maintenance therapy) including platinum-based chemotherapy and immune checkpoint inhibitors.

The terminology used to describe the study period is defined below.

- **Enrollment period:** From enrollment to the initial administration of study treatment.
- **Treatment period:** From the initial administration of study treatment to within 30 days of the last dose of study treatment (the last dose day is defined as day 0) or to the day before the start of post-treatment, whichever is earlier.
- **Follow-up period:** 31 days after the last dose of study treatment, or if post-treatment was started earlier, from the day before the initial administration of post-treatment to the end of the follow-up period of this study.

Imaging examinations and tumor assessments will be scheduled every 6 weeks (±7 days) after the initial dose of study treatment until PD is seen on imaging. Once imaging-based PD is observed, follow-up information on subsequent anti-tumor therapy and survival status will be collected approximately every 3 months.

VI-1-1. Enrollment and Treatment period

The initial dose of study treatment should be administered within 14 days of enrollment. If necessary, premedication will be given prior to administration of study treatment for each cycle.

VI-2 Administration of study treatment

For one cycle of 3 weeks (21 days), ramucirumab and docetaxel will be administered on day 1.

Dosage and administration are shown below.

- Ramucirumab is administered intravenously at a dose of 10 mg/kg in approximately 1 hour on day 1 of each cycle.
- Docetaxel is administered intravenously at 60 mg/m^2 in approximately 1 hour after ramucirumab on day 1 of each cycle.

Treatment initiation criteria for each cycle are defined in VI-3-1. If an adverse event occurs that is related to the study treatment, the dose of the study drug should be reduced.

TABLE. Treatment Regimens

study drug	dose	route	time
ramucirumab	10 mg/kg	IV	Intravenous administration in approximately 60 minutes on Day 1 of each cycle
docetaxel	60 mg/m^2	IV	Intravenous administration in approximately 60 minutes (maximum 90 minutes) on Day 1 of each cycle

Abbreviation: IV = Intravenous

Ramucirumab and docetaxel are administered every 3 weeks until PD, unacceptable toxicity, noncompliance with the study protocol by the subject, withdrawal of consent, or discontinuation of study treatment by the principal and/or sub investigator. It is anticipated that holidays, difficulty of hospital visits, or other circumstances may make it impossible to administer the next dose exactly 3 weeks after the previous dose. In that case, a postponement of up to 7 days after the planned start of the next cycle is allowed. Further postponement of the schedule should be avoided as much as possible.

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VI-2-1 Premedication

VI-2-1-1 Premedication for ramucirumab

All patients should be premedicated prior to ramucirumab administration. Recommended premedications include histamine H1 antagonists such as diphenhydramine hydrochloride (or equivalent). Additional premedication is allowed at the discretion of the principal and/or sub investigator.

VI-2-1-2 Premedication for docetaxel

The principal and/or sub investigator should thoroughly read the attached document (including warnings, precautions, contraindications, and adverse reactions) and administer docetaxel according to the institution's procedures. To reduce the incidence and severity of fluid retention and the severity of hypersensitivity, premedication with a corticosteroid such as dexamethasone 16 mg/day is allowed prior to docetaxel administration. Antiemetic premedication is also allowed at the discretion of the principal and/or sub investigator.

VI-2-2 Ramucirumab

The principal and/or sub investigator refer to the attached document (including warnings, precautions, contraindications and adverse events) and administer ramucirumab according to institution' s procedures.

If the discontinuation criteria are not met, ramucirumab is administered intravenously at 10 mg/kg in approximately 1 hour every 21 days. The initial dose of ramucirumab will be determined by the subject's baseline body weight (kg). If the body weight used to calculate the previous dose changes (increases or decreases) by more than 10%, the dose must be recalculated. For subjects undergoing repeat drainage procedures to remove pleural effusion or ascites, the dry weight is defined as the weight measured after drainage and before fluid retention. If dry weight can be measured within 30 days prior to study treatment administration, dry weight should be used for dose calculation. If dry weight is not measured, actual body weight may be used.

VI-2-3 Docetaxel

The principal and/or sub investigator refer to the attached document and

administer docetaxel according to the institution's procedures. Docetaxel is administered intravenously at 60 mg/m^2 in approximately 1 hour.

Docetaxel should be administered according to standard methods (for example, the attached document or the procedure manual at the institution).

VI-3 Treatment modification criteria

VI-3-1 Cycle initiation criteria

All of the following criteria must be met to start the next cycle:

- Total bilirubin ≤ 1.5 mg/dL
- AST and ALT ≤ 2.5 x ULN
- ANC ≥ 1.5×10^3 /μL, PLT ≥ 100×10^3 /μL
- Adverse events related with ramucirumab or docetaxel have recovered to grade ≤ 2 (Common Terminology Criteria for Adverse Events v4.0, Japanese translation JCOG version) or severity at baseline

If either criterion is not met, the initiation of the next cycle is postponed for up to 3 weeks until toxicity recovers. If toxicity has not recovered and the next cycle cannot be initiated within 3 weeks, one or both drugs will be discontinued based on causal relationship. If clinically warranted, continuation of either drug is allowed if the postponement does not exceed 6 weeks after the last dose.

If the initiation of the next cycle is postponed due to toxicity of either ramucirumab or docetaxel, the other drug administration should be postponed in order to maintain the schedule of administering both drugs simultaneously. When either ramucirumab or docetaxel is discontinued, the continuation of the other agent according to the schedule is allowed if clinically necessary. When docetaxel is discontinued and ramucirumab is continued, pegfilgrastim, recommended as supportive care, is not required. When ramucirumab is discontinued and docetaxel is continued, pegfilgastim is recommended in principle, but may be discontinuation of pegfilgrastim is allowed at the discretion of the investigator.

The body surface area and the dose must be recalculated prior to the initiation of each cycle if the weight has changed (increased or decreased) by more than 10% compared with the last dose. The error in the actual dose should be within ±10% of the calculated dose. The dose of ramucirumab will be determined by the subject's body weight (kg) at baseline. A delay of up to 7 days from the

scheduled initiation of the next cycle due to holidays, difficulty hospital visits, or other circumstances is allowed at the discretion of the principal and/or sub investigator.

VI-3-2 Dose Modification: ramucirumab

If a non-fatal reversible Grade 3 adverse event (for example, fatigue, anorexia, fever) develops and recovers to Grade ≤ 1 at the initiation of the next cycle, ramucirumab can be continued with dose reduction. In this case, ramucirumab can be continued same dose, but if a similar adverse event occurs again, the dose of ramucirumab must be reduced to 8 mg/kg. Furthermore, if a similar event occurs again after the dose reduction to 8 mg/kg, ramucirumab can be reduced 6 mg/kg. If ramucirumab dose is reduced due to an adverse event for which a causal relationship cannot be ruled out, subsequent dose increase is not allowed.

When any Grade 4 adverse event develops, other than fever or laboratory abnormalities, for which a causal relationship to ramucirumab cannot be ruled out, ramucirumab must be discontinued.

If Grade 4 fever or laboratory abnormalities have recovered to Grade ≤ 1 or to baseline severity by the initiation of the next cycle, ramucirumab can be continued at the discretion of principal and/or sub investigator. In this case, ramucirumab can be continued same dose, but if a similar adverse event occurs again, the dose of ramucirumab must be reduced to 8 mg/kg. Furthermore, if a similar event occurs again after the dose reduction to 8 mg/kg, ramucirumab can be reduced to 6 mg/kg. If ramucirumab dose is reduced due to an adverse event for which a causal relationship cannot be ruled out, subsequent dose increase is not allowed.

Administration criteria of ramucirumab in cases of injection-related reactions, thrombosis, hypertension and proteinuria are shown in VI-3-3-1, VI-3-3-5.

The dose reduction of ramucirumab is allowed if the principal and/or sub investigator determines that the worsening of symptoms or laboratory values is clinically significant.

VI-3-3 Treatment Criteria for Each Adverse Event due tp Ramucirumab

Adverse events requiring caution, whether or not causally related to ramucirumab, are infusion related reaction, hypertension, arterial and venous thromboembolic event, hemorrhage (bleeding adverse events), proteinuria, gastrointestinal perforation and reversible posterior leukoencephalopathy

syndrome (RPLS), congestive heart failure, surgical wound healing disorders.

VI-3-3-1 Infusion related reaction

The definition of infusion related reaction due to ramucirumab refers to ″General disorders and administration site conditions″ in the CTCAEv4.0 Japanese translation JCOG version which is based on CTCAE v4.03/MedDRA v12.0. The definition of symptoms occurring during or after ramucirumab administration also follows the adverse event categories such as allergic reaction, anaphylaxis, or cytokine release syndrome which are listed to ″immune system disorders″ in the JCOG version of the CTCAE v4.0. If the symptoms develop during or after administration of ramucirumab, it is recommended that the principal and/or sub investigator use the adverse event term that appropriately describe the event (including terms not listed in this section). The grade of the adverse event described above shall be determined according to the following table.

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Table JCOG v 4.0 infusion-related reactions

adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Reaction to injection	Mild, transient reaction; does not require interruption of infusion; does not require treatment	Requires interruption of therapy or infusion, but responds rapidly to treatment for symptoms (e.g., antihistamines, NSAIDs, narcotic agents, IV fluids); requires prophylactic medication for ≤24 hours	Prolonged (e.g., failure to respond promptly to treatment of symptoms or brief infusion cessation); recurrence after improvement; sequelae requiring hospitalization	Life-threatening; requires emergency treatment	death
Definition: adverse reaction to the infusion of a drug or biological agent					
allergic reaction	Transient flushing or skin rash; <38° C (100.4° F) drug fever; does not require treatment	Requires interruption of therapy or infusion, but responds rapidly to treatment for symptoms (e.g., antihistamines, NSAIDs, narcotic agents); requires prophylactic medication for ≤24 hours	Prolonged (e.g., failure to respond promptly to treatment of symptoms or brief infusion cessation); recurrence after improvement; secondary onset (e.g., renal failure, pulmonary	Life-threatening; requires emergency treatment	death

			infiltration) requiring hospitalizatio n		

Definition: local or systemic adverse reaction resulting from exposure to an antigenic substance

Anaphylaxie	-	-	Symptomatic bronchospasm with or without urticaria; requiring parenteral therapy; allergic edema/angioedema; hypotension	Life-threatening; requires emergency treatment	death

Definition: an excessive immune response characterized by an acute inflammatory reaction caused by the release of histamine or histamine-derived substances from mast cells. Clinically, the patient presents with dyspnea, dizziness, hypotension, cyanosis, loss of consciousness, and may even die

cytokine release syndrome	Mild reaction; does not require interruption of infusion; does not require treatment	Requires interruption of therapy or infusion, but responds rapidly to symptomatic treatment (e.g., antihistamine	Prolonged (e.g., not responding promptly to treatment of symptoms or brief infusion cessation); relapse after improvement	Life-threatening; requires positive pressure respiration or artificial respiration	death

	s, NSAIDs, narcotics, IV fluids); requires prophylactic dosing for ≤ 24 hours	Yes; secondary (e.g., renal failure, pulmonary infiltration) requiring hospitalization
Definition: nausea, headache, tachycardia, hypotension, skin rash, respiratory urgency. Caused by release of cytokines from cells.		

Abbreviations: CTCAE v 4.0 = Common Terminology Criteria for Adverse Events v 4.0; NSAIDs = non-steroidal anti-inflammatory drugs

For Grade 2 allergic/infusion related reactions, detailed below, will be managed as in routine practice. If there is any uncertainty about the grade of the adverse event, contact the study office.

Guidelines for infusion related reactions are as follows:

Grade 1

- Set the infusion speed to 50%.
- Observe for any deterioration of the condition.
- Premedication with intravenous diphenhydramine hydrochloride 50 mg (or equivalent) should be administered at the subsequent dose. Additional premedication is allowed at the discretion of the principal and/or sub investigator.

Grade 2

- Discontinue administration.
- Intravenous diphenhydramine hydrochloride 50 mg (or equivalent), oral acetaminophen 650 mg, and oxygen inhalation.
- When the infusion related reaction disappears or is recovered to Grade 1, resume study treatment at 50% infusion rate. Duration of administration should not exceed 2 hours.
- Observe for any deterioration of the condition.
- Premedication with intravenous diphenhydramine hydrochloride 50 mg (or equivalent) should be administered at the subsequent dose. Additional premedication is allowed at the discretion of the principal and/or sub investigator.

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When a second infusion related reaction (grade 1 or 2) develops, intravenous dexamethasone 8-10 mg (or equivalent) should be administered. Premedication with intravenous diphenhydramine hydrochloride 50 mg (or equivalent), oral acetaminophen 650 mg, and intravenous dexamethasone 8-10 mg (or equivalent) should be administered at the subsequent dose.

Grade 3

- Discontinue administration and remove the dosing tube.
- Intravenous diphenhydramine hydrochloride 50 mg (or equivalent), intravenous dexamethasone 8-10 mg (or equivalent), and bronchodilators should be administered as needed. Other medications or procedures should also be considered.
- When a Grade 3 infusion related reaction develops, ramucirumab will not be administered and the patient will be observed post-administration according to the study protocol.

Grade 4

- Discontinue administration and remove the dosing tube.
- Intravenous diphenhydramine hydrochloride 50 mg (or equivalent) and intravenous dexamethasone 8-10 mg (or equivalent) should be administered as needed. Other medications or procedures should be considered.
- Administer epinephrine or bronchodilators as needed.
- Hospitalization for observation as needed.
- When a Grade 4 infusion related reaction develops, ramucirumab will not be administered and the patient will be observed post-administration according to the study protocol.

VI-3-3-2 Hypertension

Guidelines for hypertension (adverse events expected to occur with ramucirumab) that occurred during the study period are as follows:

Grade <3

- Without symptoms, continue ramucirumab and initiate antihypertensive therapy.
- If symptomatic, interrupt ramucirumab and initiate antihypertensive therapy until symptoms resolve.
- When ramucirumab is interrupted more than once because of hypertension (symptomatic hypertension, marked elevation of blood pressure not controlled by antihypertensive agents), the dose of ramucirumab must be reduced to 8

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mg/kg. When further interruption of ramucirumab occurs, the dose should be reduced to 6 mg/kg.

Grade 3 (≥160 / ≥ 100 mmHg; requires medical therapy; requires 2 or more medications or stronger therapy than before)

- Without symptoms, antihypertensive treatment must be intensified and ramucirumab is continued. If blood pressure is ≥ 160 / ≥ 100 mmHg 3 weeks after the addition of antihypertensive treatment, ramucirumab should be discontinued while antihypertensive treatment is continued.
- If symptomatic, interrupt ramucirumab and continue antihypertensive therapy until hypertensive symptoms resolve.
- When ramucirumab is interrupted more than once because of hypertension (symptomatic hypertension, marked elevation of blood pressure not controlled by antihypertensive agents), the dose of ramucirumab should be reduced to 8 mg/kg. When further interruption of ramucirumab occurs, the dose should be reduced to 6 mg/kg.

Grade 4 or treatment-resistant

Discontinue ramucirumab if Grade 4 hypertension [life-threatening (for example, malignant hypertension, transient or permanent neurologic impairment, hypertensive crisis; requires emergency treatment)] develops. Administration of ramucirumab should also be discontinued in cases of poor control (> 160 / > 100 mmHg for more than 4 weeks) despite administration of antihypertensive agents (treatment with at least 3 drugs and at the highest dose of each drug). Docetaxel can be continued at the discretion of the principal or sub investigator.

VI-3-3-3 Thrombosis

When grade ≤ 3 venous thrombosis (DVT and/or PE) develops, ramucirumab can be continued if the principal and/or sub investigator determines that the event is not fatal. When DVT and/or PE develops or worsens during anticoagulation therapy, ramucirumab should be discontinued.

Grade 3 and 4 arterial thromboembolic events should result in discontinuation of ramucirumab.

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VI-3-3-4 Hemorrhage (bleeding event)

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Serious bleeding adverse events have been reported in clinical trials of ramucirumab. Some malignancies have been associated with hemorrhagic complications, although the incidence varies (variceal bleeding due to portal hypertension in hepatocellular carcinoma, lower gastrointestinal bleeding due to intestinal metastases in ovarian cancer). Discontinue ramucirumab when grade 3 or 4 hemorrhage (bleeding events) develops.

VI-3-3-5 Proteinuria

When proteinuria 2+ or greater occurs during ramucirumab treatment, continue ramucirumab and perform a 24-hour urine collection before the next cycle; if the 24-hour protein level is less than 2 g, do not change the ramucirumab dose and continue treatment. If the 24-hour protein level is higher than 2 g and less than 3 g, suspend the next cycle of ramucirumab for 3 weeks and perform another 24-hour urine collection to confirm the protein level (docetaxel can be administered during the ramucirumab deferral period if it is determined that proteinuria is not causally related to docetaxel). Once the 24-hour protein level has recovered to less than 2 g, the dose of ramucirumab can be reduced to 8 mg/kg (once every 3 weeks) and ramucirumab can be resumed. If proteinuria of higher than 2 g in 24 hours is observed again, ramucirumab can be reduced again to 6 mg/kg (once every 3 weeks). Discontinue ramucirumab if the 24-hour proteinuria exceeds 3 g, if the 24-hour proteinuria exceeds 2 g on three times, or if the 24-hour proteinuria does not recover to less than 2 g within three weeks.

VI-3-3-6 Gastrointestinal tract perforation

Some angiogenesis inhibitors have been associated with a low frequency of gastrointestinal perforation, particularly in colorectal cancer (in combination with anti-VEGF antibodies and cytotoxic chemotherapy) and advanced ovarian cancer. Some of these events have been associated with extensive abdominal/peritoneal disease. Gastrointestinal perforation has also been reported in clinical trials of ramucirumab. Due to the low incidence of events observed to date or the presence of significant complications or risk factors, it is difficult to define a relationship between gastrointestinal perforation and ramucirumab. Therefore, ongoing investigations are very important. If gastrointestinal perforation is observed, ramucirumab should be discontinued.

VI-3-3-7 Congestive heart failure in patients receiving ramucirumab in combination with mitoxantrone or after prior anthracycline administration

An increased risk of congestive heart failure (CHF) has been associated with

several angiogenesis inhibitors, particularly in patients with metastatic breast cancer who have received prior anthracyclines or have other risk factors for CHF, including prior radiation therapy to the left side chest wall. Findings ranged from asymptomatic decreased left ventricular (LV) ejection fraction to symptomatic CHF requiring treatment or hospitalization. Use caution when administering ramucirumab to patients with pre-existing clinically significant cardiac disease such as coronary artery disease or CHF. Patients with symptomatic CHF, unstable angina, or symptomatic or poorly controlled cardiac arrhythmias should be excluded from clinical trials of ramucirumab. Discontinue ramucirumab if grade 3 or 4 CHF develops.

VI-3-3-8 Surgery and wound healing disorders

Impaired surgery and wound healing have been seen with some angiogenesis inhibitors. Ramucirumab should not be administered to patients who have undergone major surgery within 28 days prior to enrollment or central venous access device placement within 7 days prior to enrollment. Patients with postoperative and other unrecovered wound complications are excluded as patients scheduled for major surgery.

VI-3-3-9 Reversible posterior leukoencephalopathy syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS) is a clinical and radiological syndrome that often consists of brain imaging findings showing reversible neurological dysfunction of the cerebral cortex and subcortical edema involving the posterior circulation, especially the occipital lobes (Hinchey et al. 1996). The most commonly observed symptoms of RPLS are generalized seizures, headache, delirium, and cortical blindness, but the presentation is diverse and sometimes associated with focal neurological deficits (Garg 2001; Hinchey et al. 1996; Lee et al. 2008). MRI is the most reliable diagnostic modality (Lee et al. 2008). Clinical symptoms and MRI abnormalities usually resolve within days to weeks if properly managed, although permanent neurological dysfunction has also been reported (Garg 2001; Hinchey et al. 1996; Lee et al. 2008; Tajima et al. 1999).

RPLS has been associated with multiple clinical conditions, including hypertensive encephalopathy, eclampsia, and renal failure with hypertension, as well as with the use of immunosuppressive and cytotoxic agents (Garg 2001; Marinella and Markert 2009). Recent findings suggest that RPLS is associated with the use of the anti-VEGF drug bevacizumab, which is listed in the drug's prescribing information (Avastin 2011; Marinella and Markert 2009).

Although the detailed pathogenesis of RPLS is unknown, pathophysiology

suggests that abnormal cerebrovascular autoregulation may cause blood-brain barrier disruption and angiogenic edema (Schwartz 1996). Although the pathogenesis of RPLS is considered multifactorial, drug-induced endothelial damage and acute hypertension are is often attributed to cerebrovascular dysfunction in RPLS (Marinella and Markert 2009). RPLS should be identified and treated promptly to minimize the possibility of permanent neurological damage. Treatment includes careful blood pressure control, discontinuation of the study drug, and administration of anticonvulsants to subjects who develop seizures (Stott et al. 2005).

In CP12-0920 (I4T-MC-JVBB), a phase III, placebo-controlled, double-blind, randomized trial in metastatic colorectal cancer, one serious adverse event of RPLS was reported. This event was judged to be related to the administration of all study drugs, which included the blinded study drugs. Because hypertension has been identified as a risk for ramucirumab, the principal and/or sub investigator should manage blood pressure according to guidelines. In addition, in the presence of seizures, headache, nausea, delirium, visual changes, and other unexplained neurologic symptoms, especially if accompanied by hypertension and hyperintense MRI findings on T2-weighted and inversion recovery imaging (flare imaging), the principal and/or sub investigator should consider the diagnosis of RPLS. If the diagnosis of RPLS is confirmed, ramucirumab should be discontinued.

VI-3-4 Treatment criteria for each adverse event due to docetaxel

The principal and/or sub investigator should thoroughly refer to the docetaxel attached document for warnings, precautions, contraindications, and adverse events, and follow the procedures of the institution. Dose changes once implemented should be continued. Treatment dose should be modified based on the most severe hematologic or non-hematologic toxicities that occurred in the previous cycle. If several different toxicities occur and the recommended doses for each toxicity are inconsistent, the dose reduction required for the most severe toxicity should be implemented.

Subjects who initiate docetaxel dosage at 60 mg/m^2 and develop febrile neutropenia (ANC < 1.0 x 10^3 /L and body temperature ≥ 38.3° C at any time or body temperature 38℃ sustained for ≥ 1hour), neutropenia (ANC < 500/mm^3) sustained for > 1 week, severe or repeated skin reactions, or other Grade 3 or 4 nonhematologic toxicities, docetaxel should be interrupted until these toxicities will be resolve and resumed at 50 mg/m^2. When any of the above toxicities occur again, docetaxel should be discontinued. When Grade ≥ 3 peripheral neuropathy develops, docetaxel should be discontinued. If a delay over 6 weeks from the last

dose of docetaxel, that is over 21 days from the scheduled start of the next cycle, is occurred, docetaxel should be discontinued. Ramucirumab can be continued even if docetaxel is discontinued.

When Grade 3 or 4 nausea or vomiting develops, antiemetic therapy should be added and docetaxel should be continued without dose modification. If nausea and vomiting do not improve with antiemetic therapy, the dose of docetaxel should be reduced.

VI-3-4-1 Hypersensitivity reactions

Hypersensitivity reactions should be carefully monitored (especially during the initial and second doses). Severe hypersensitivity reactions characterized by generalized skin rash/erythema, hypotension, bronchospasm, or fatal anaphylaxis have been reported even after 3 days of corticosteroid premedication. When a severe hypersensitivity reaction develops, docetaxel should be discontinued immediately and appropriate treatment for hypersensitivity should be instituted, and docetaxel should not be administered again.

Hypersensitivity reactions may occur within several minutes of initial administration of docetaxel. The interruption due to mild reactions such as flushing or localized skin reactions is not required.

Mild cases: continue docetaxel administration and follow-up. No treatment for hypersensitivity is necessary.

Moderate cases: Interrupt docetaxel. And administer diphenhydramine 25-50 mg and dexamethasone 10 mg intravenously. If the symptoms will be resolved, docetaxel can be restarted. If the symptoms develop again, docetaxel should be discontinued.

Severe and life-threatening cases: discontinue docetaxel. As in moderate cases, administer diphenhydramine and dexamethasone intravenously. Add epinephrine or bronchodilators as needed. Do not restart docetaxel.

How to administer in the next cycle after the onset of hypersensitivity: If docetaxel is administered the subsequent cycle, premedication with intravenous diphenhydramine 50 mg and dexamethasone 10 mg 30 minutes before the docetaxel administration is recommended in addition to oral dexamethasone.

Hypersensitivity reaction recures frequently. If a moderate symptom develops, docetaxel should be administered over 2 hours with the premedication described above for the subsequent cycles. At this time, the subject should be explained the

possibility of recurrence of allergic reactions and the subject should be carefully monitored.

When delayed hypersensitivity reactions such as localized or generalized pruritus develop 1 week after docetaxel administration, symptomatic treatment (for example, oral antihistamines) should be administered. Depending on the severity, premedication with an antihistamine (oral or intravenous) should be added in the next cycle. Docetaxel dose should not be reduced.

VI-3-4-2 Hematological toxicity

Neutropenia (ANC < 2000/mm^3) occurs in almost all subjects receiving docetaxel 60-100 mg/m^2. Grade 4 neutropenia (< 500/mm^3) in 85% and 75% of subjects receiving at dose of 100 mg/m^2 and 60 mg/m^2, respectively. Therefore, blood cell counts should be monitored frequently so that docetaxel dose can be modified promptly. Docetaxel should not be administered if neutrophil counts are less than 1500/mm^3.

VI-3-4-3 Fluid retention

Severe fluid retention, which occurred after administration of docetaxel, has been reported. It is characterized by unacceptable peripheral or generalized edema, pleural effusions requiring urgent drainage, dyspnea at rest, cardiac tamponade, and marked abdominal distention due to ascites. To reduce the incidence and severity of fluid retention, premedication with corticosteroids should be administered prior to docetaxel. When fluid retention occurs, peripheral edema develops in the lower extremities and then fluid retention spreads throughout the body, resulting in weight gain (median: +2 kg). If a pleural effusion is present, the patient should be monitored closely for worsening of the effusion after the first dose of docetaxel.

VI-3-4-4 Skin

Localized erythema with edema of the extremities followed by desquamation has been observed. Dose modification is recommended if severe skin toxicity develops.

VI-4 Recommended supportive care, acceptable treatments, and prohibited treatments before and during the clinical trial

Participant in this study may receive palliative supportive care for symptoms and toxicities associated with administration of the drug due to other diseases.

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Supportive cares include prophylactic G-CSF administration for febrile neutropenia, antidiarrheals, antiemetic agents, narcotic and non-narcotic analgesics, appetite stimulants, granulocyte growth factors, and erythropoiesis factors. Supportive care provisions are listed below.

Pegfilgrastim

The JVCG study showed that docetaxel + ramucirumab combination therapy had a high incidence of febrile neutropenia (34.0%). According to the Guidelines for the Appropriate Use of G-CSF Ver. 5 (Japanese Society of Clinical Oncology), primary prophylactic administration of G-CSF is recommended in using the treatment regimen that causes febrile neutropenia in 20% or higher. For this reason, prophylactic pegfilgrastim is used in this study.

Recommended Schedule

Pegfilgrastim 3.6mg subcutaneously should be administered between Day 2 and 4 of each cycle (preferably between 24 and 72 hours after ramucirumab + docetaxel).

Refer to the Pegfilgrastim package insert (warnings, directions for use, contraindications and side effects, etc.) carefully and administer by the procedures of the institution.

Combination use of bone modified agent is allowed. No other chemotherapy, radiation therapy, biologics, or other study drugs can be administered to participant in this study.

When the palliative surgery or surgery deemed unavoidable by primary and/or sub investigator will be done in study treatment period, imaging evaluation will be performed prior to surgery to document the tumor disease status. During the study treatment period, non-urgent, standby surgeries should be avoided as much as possible. Ramucirumab should be interrupted for at least 28 days prior to surgery. Ramucirumab can be resumed at least 28 days after surgery, if the principal and/or sub investigator determines that the participant has recovered sufficiently after surgery. Imaging evaluation for tumor disease is required prior to resuming ramucirumab.

If the patient underwent surgery prior to determination of PD, imaging studies should be performed every 6 weeks until PD is confirmed.

Concomitant medications with caution

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When the following drugs are used concomitantly, they should be administered with caution according to the following:

- Patients receiving anticoagulants should be carefully evaluated whether the study treatment can be administered because of developing bleeding event.

Prohibited concomitant medications

No concurrent chemotherapy, hormone therapy, immunotherapy, radiation therapy, or surgery for cancer other than ramucirumab or docetaxel are allowed from enrollment to the end of study treatment.

VI-5 Procedures for verifying compliance with other arrangements, such as the administration of drugs to participants

Study treatment will be administered at the institution under the supervision of the principal and/or sub investigator. The compliance with treatment will be verified. Data on the administration of ramucirumab and docetaxel will be recorded in the medical record and eCRF.

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Ⅶ. Evaluating of Efficacy

Ⅶ-1 Efficacy Measures

Subjects with measurable disease will be enrolled according to RECIST v 1.1. Disease assessments will be performed at baseline (within 28 days prior to enrollment) and every 6 weeks (±7 days) calculated from the date of first dose, and efficacy will be evaluated according to RECIST v 1.1.

Ⅶ-2 Methods of evaluation, recording, and analysis of effectiveness evaluation indicators and the timing of their implementation

Refer to the schedule for timing of imaging inspections. Measurements will be taken and recorded in metric system.

Ⅶ-2-1 Baseline Assessment

In accordance with ″Ⅸ-1 Pre-registration Assessment Items,″ contrast CT of the chest (slice thickness 5 mm or less), contrast CT of the upper abdomen to pelvis (slice thickness 5 mm or less), and contrast MRI or contrast CT of the head (slice thickness 5 mm or less) are used to identify neoplastic lesions before registration and classify each lesion into ″measurable lesions″ and ″unmeasurable lesions The lesions are classified into ″measurable lesions″ and ″non-measurable lesions″. If contrast studies are deemed inappropriate, such as a history of allergy to contrast media, CT and MRI studies with simple imaging are acceptable.

Tumor diameter is measured on CT cross-sectional images, not on 3D reconstructed images in sagittal or coronal sections. Baseline evaluation will be performed using the most recent imaging studies within 28 days prior to enrollment. If imaging studies are repeated after enrollment and before the start of treatment, the most recent imaging studies should be used.

Ⅶ-2-2 Definition of measurable lesions

A measurable lesion is a lesion that meets one of the following criteria

1) Lesions other than lymph node lesions (non-lymph node lesions) that meet one of the following criteria

① Max. diameter 10 mm or more at CT with a slice thickness of 5 mm or less

② Osteolytic bone metastatic lesion with soft tissue component that meets ①

③ Cystic metastatic lesions that satisfy ① in the absence of other measurable noncystic lesions

2) Lymph node lesions with a short diameter of 15 mm or more on CT with a slice thickness of 5 mm or less

(Lymph node lesions with a short diameter between 10 mm and 15 mm are considered non-target lesions; lymph nodes with a short diameter less than 10 mm are not considered lesions.)

All lesions other than those listed above are considered non-measurable lesions.

Note that the following lesions are considered unmeasurable lesions regardless of the test method or size of the lesion.

- Bone lesions (excluding osteolytic lesions with measurable soft tissue component)
- Cystic lesions (excluding 1)-3) above)
- Lesions with a history of local treatment such as radiotherapy
- chondromalacial meningeal lesion
- Ascites, pleural effusion, pericardial effusion
- Lymphangiopathy of the skin and lungs
- Abdominal masses or enlargement of abdominal organs that are palpable but not measurable by imaging techniques
- Superficial skin lesions

VII-2-3 Target lesion selection and baseline recording

Among the measurable lesions identified at the time of registration, up to five lesions in order of increasing diameter (long diameter for non-lymph node lesions and short diameter for lymph node lesions) and up to two lesions per organ※ will be selected as target lesions. The selection of target lesions is based on the consideration that the organs with measurable lesions should be included as evenly as possible and that the lesions should be reproducible for repeated measurement (avoid lesions that are difficult to measure even if they have large diameters).

For each selected target lesion, record the site (code), method of examination, date of examination, long diameter of non-lymph node target lesions, short diameter of lymph node target lesions, and sum of diameters of all target lesions (″diameter sum″) in order from head to tail in the ″Pretreatment Record - Tumor Evaluation.

*How to count organs

(1) Organs with left and right sides (lungs, kidneys, etc.) are combined into one organ.

(2) All lymph nodes, regardless of site, are considered one organ.

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Ⅶ-2-4 Baseline recording of non-target lesions

All lesions not selected as target lesions, whether measurable or not, should be recorded as non-target lesions with the lesion site (code), test method, and test date in the ″Pretreatment Report - Tumor Evaluation. Multiple non-target lesions in the same organ may be recorded as one lesion (e.g., multiple enlarged pelvic lymph nodes, multiple liver metastases).

Ⅶ-2-5 Determination of tumor shrinkage effect

Starting on the date of the first docetaxel + ramucirumab dose, target lesions and non-target lesions will be assessed every 6 weeks (±7 days) according to ″Ⅷ-2 Examination and Evaluation During Treatment″ using the same examination methods as at enrollment, and the diameter of target lesions and disappearance or progression of non-target lesions will be recorded in ″Treatment Course Record - Tumor Evaluation″. Tumor Evaluation″.

Ⅶ-2-6 Criteria for determining efficacy of targeted lesions

CR (Complete Response): Complete response

When all non-lymph node target lesions have disappeared and the short diameter of all lymph node target lesions is less than 10 mm. If lymph node target lesions are selected at baseline, the target lesion effect may be CR even if the diameter sum is not 0 mm.

Partial Response (PR)

Target lesion diameter summation reduced by at least 30% relative to baseline diameter summation

PD (Progressive Disease): Progressive

20% or greater increase in the diameter sum of the target lesion relative to the smallest diameter sum over time (if baseline is the smallest over time, this is the smallest diameter sum), and an absolute increase in diameter sum of at least 5 mm

SD (Stable Disease): Stable

No contraction corresponding to PR and no increase corresponding to PD

NE (Not all Evaluated): with evaluation deficiencies

When testing cannot be performed for any reason, or when CR, PR, PD, or SD cannot be determined

Percentage reduction in diameter sum =
(Diameter sum before treatment - Diameter sum at evaluation) / Diameter sum before treatment x 100%

Percentage increase in diameter sum =

(Diameter sum at time of evaluation - Minimum diameter sum)/Minimum diameter sum

× 100%

※ The diameter of the target lesion should be measured as much as possible (e.g., even if it is less than 5 mm), but if the diameter of the target lesion is determined to be ″too small to measure,″ the diameter should be set to 0 mm when it is determined that no tumor lesion remains, regardless of the CT slice thickness, If the tumor lesion is judged to be ″too small to measure,″ the diameter is set to 0 mm if there is no residual tumor lesion, and 5 mm if there is residual tumor lesion.

※ PD if the reduction ratio satisfies the condition of PR and at the same time the increase ratio satisfies the condition of PD.

※ If one lesion is isolated during treatment, add each diameter to the diameter sum.

※ If multiple lesions fuse during treatment and the boundaries of the lesions become indistinguishable, the diameters of the fused lesions are added to the diameter sum. If the lesions are in contact with each other but the boundaries of the lesions are identifiable, the diameter of each lesion is added to the diameter sum.

Ⅶ-2-7 Efficacy Criteria for Non-Target Lesions

CR (Complete Response): Complete response

All non-lymph node non-target lesions have resolved and the short diameter of all non-lymph node non-target lesions is less than 10 mm.

Non-CR/non-PD: Non-CR/non-PD

One or more residual non-target lesions (including residual lymph node non-target lesions with a short diameter of 10 mm or more)

PD (Progressive Disease): Progressive

An ″apparent exacerbation″ of a preexisting non-target lesion (including recurrence).

With measurable lesions: for a target lesion effect of SD or PR to be judged ″clearly worsening″ based on changes in non-target lesions, a significant worsening of non-target lesions must be observed that is sufficient to warrant discontinuation of therapy as an increase in overall tumor volume. In the case of SD or PR, ″apparent progression″ is defined as an increase in tumor volume

of the non-target lesion that far exceeds the decrease in tumor volume when the target lesion is effective, otherwise it is Non-CR/non-PD.

With only unmeasurable lesions: as a rule of thumb, an increase in non-target lesions that would clearly exceed a tumor volume equivalent to a 20% increase in diameter and a 73% increase in tumor volume is considered an ″apparent progression″.

NE (Not all Evaluated): with evaluation deficiencies

When the test cannot be performed for some reason, or when neither CR, Non-CR/non-PD, nor PD can be determined.

VII-2-8 Appearance of new lesions

If a lesion that was not present at baseline is found after the start of treatment, it is assumed that a ″new lesion″ has appeared.

However, to be considered a ″new lesion,″ the lesion must not be a change on the image due to a difference in imaging method or a change in imaging modality from the examination at baseline evaluation, or a change on the image due to a pathology other than tumor. For example, a cystic lesion arising within a lesion due to necrosis of a liver metastatic lesion is not considered a new lesion. A new lesion is considered a new lesion if it is newly detected by examination of a site that was not required at baseline (pre-enrollment evaluation).

If one lesion disappears and later reappears, the measurement is continued. However, the effect at the time the lesion reappears depends on the status of the other lesions. If the lesion reappears after the overall effect is CR, it is determined to be PD at the time of reappearance. On the other hand, if the overall effect is PR or SD, once a lesion reappears after it has disappeared, the diameter of that lesion is added to the diameter sum of the remaining lesions to calculate the effect. In other words, with many lesions remaining, even if one lesion reappears after apparently ″disappearing,″ it is not judged to be PD on its own, but only when the sum of diameters of all lesions meets the criteria for PD. This is because it is recognized that most lesions do not truly ″disappear″ but simply do not show up due to the resolution limitations of the imaging modality used.

If there is a possibility that the lesion is a new lesion but it cannot be confirmed, it is not considered a new lesion, and imaging studies should be repeated at a clinically appropriate time. If the new lesion is confirmed on repeat imaging studies, the appearance of the new lesion is defined as the date of the imaging study when the lesion is confirmed as a new lesion.

The appearance of an FDG-PET-positive lesion (FDG uptake greater than twice that of the surrounding tissue on attenuation-corrected images) in an

area that was negative on baseline FDG-PET is considered the appearance of a new lesion.

If FDG-PET was not performed at baseline and FDG-PET performed after the start of treatment results in the appearance of an FDG-PET-positive lesion, new lesions are considered to have appeared if CT or MRI confirms a lesion in the FDG-PET-positive area that was not present at baseline.

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Ⅶ-2-9 Overall Response

The overall response (Overall response) will be determined from the combination of the effect of target lesions, the effect of non-target lesions, and the presence or absence of new lesions, every 6 weeks (±7 days) starting on the date of the first dose of docetaxel + ramucirumab, according to Table Ⅶ-2-9 a below. In the absence of non-target lesions at baseline, the overall effect will be determined by the effect of target lesions and the presence or absence of new lesion appearance.

Table Ⅶ-2-9 aTotal effect at each time point: with target lesions (with or without non-target lesions)

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Ⅶ-2-10 Best Overall Response

CR > PR > SD > PD > NE is defined as ″good″ in that order, and the best overall effect is defined as the best overall effect throughout the entire course.

However, for the best overall effect to be SD, the overall effect must be SD or better until the judgment at 6 weeks after the start of treatment. If the patient is SD at the 4-week judgment (first judgment) and PD at the 6-week judgment from the start of treatment, the best overall effect is PD. If the patient is SD at the first determination and then lost to follow-up, the best overall effect is NE.

If imaging is not available due to apparent worsening of disease or death before the first efficacy evaluation, the patient is classified as PD. If the imaging results are not available due to discontinuation of toxicity or patient refusal prior to the first efficacy evaluation, the patient will be considered NE.

Ⅶ-3 Definition of Analysis Population

The analysis population used in the central monitoring, main analysis, and final analysis is defined as follows.

Ⅶ-3-1 All registered cases

The population of enrolled patients, excluding duplicate enrollments and mis-enrollments, is defined as ″all enrolled cases″.

Ⅶ-3-2 All Eligible Cases

From the total enrollment cases, the ″all eligible cases″ will be the population excluding ″ineligible cases (posterior ineligible, ineligible at enrollment, and violating enrollment)″ as determined by review at the study office and the CRO that manages the data. Ineligible cases″ determined solely by the site principal investigator, research associate investigator, and site coordinator will be included in the ″All Eligible Cases.

Ⅶ-3-3 All treated cases

Of all enrolled patients, all patients who received some or all of the study treatment are considered ″all-treated″.

The CRO who manages the data may decide, with the consent of the Clinical Study Office, whether to determine ″No treatment cases″ for which no study treatment was administered at all and whether to exclude them from the safety analysis. In addition, whether to include ineligible cases in the analysis will be decided by the Clinical Study Office in consultation with the CRO who manages the data for this study, after reviewing the details of ineligibility.

Ⅶ-4 Endpoint Definition

Ⅶ-4-1 Response rate

Of the enrolled patients with measurable disease, the response rate is defined as the percentage of patients for whom the ″Ⅶ-2-10 Best Overall Response″ is either CR or PR.

Ⅶ-4-2 Overall survivalOverall survival

The period beginning on the date of registration and ending on the date of death from any cause.

- Survival cases are terminated as of the date of the last confirmation of survival (telephone confirmation of survival is acceptable, but should be documented in the medical record). (Survival confirmation by phone call is acceptable, but the fact that the patient survived must be documented in the

patient's medical record.)

- Untraceable cases are terminated at the last date of confirmed survival prior to the loss of follow-up.

VII-4-3 Progression-free survival (PFS: Progression-free survival)

The period beginning on the date of registration and ending on the earlier of the date the exacerbation is determined to have occurred or the date of death from any cause.

- Progression" includes both PD (progression) based on diagnostic imaging in "VII-2-9 Overall Effects" and progression of the underlying disease that cannot be confirmed by diagnostic imaging tests (clinical progression). In the case of progression based on imaging diagnosis, the date of progression is defined as the date of examination when the imaging examination is performed, and in the case of clinical progression, the date of clinical judgment is defined as the date of progression. Even in cases such as when the tumor diameter becomes extremely small, which would be PD according to the efficacy criteria but is clinically judged to be "clearly not progression," PD according to the efficacy criteria is given priority as progression (in such cases, the clinical judgment on whether or not the study treatment should be continued is given priority). In addition, even if the disease is not PD according to the efficacy criteria, if the disease is judged to be clearly exacerbated clinically, the clinical judgment shall be given priority as exacerbation.

- In the case of a patient who survives without progression, the case is terminated on the last day when it is clinically confirmed that there is no progression (the last day of confirmation of progression-free survival) (Confirmation of progression-free status by imaging or laboratory tests is not required; clinical confirmation of progression-free status during outpatient consultations, etc. is acceptable. Only telephone contact is not acceptable. If information on progression or no progression is obtained from a hospital transfer or a medical institution to which the patient was referred, the patient should receive and keep a medical information form that describes the basis for the diagnosis. (In this case, telephone contact alone is also not acceptable.)

- In cases where chemotherapy is discontinued due to toxicity or patient refusal, and another treatment is added as posttreatment, the event and discontinuation are treated in the same manner. In other words, the discontinuation is not considered at the time of treatment discontinuation or at the date of post-treatment initiation.

- If the diagnosis of exacerbation is based on diagnostic imaging, the event is defined as the "date of examination" of the imaging test that is later confirmed, not the date of examination of the "imaging suspicion. When an exacerbation is clinically determined to be exacerbation without imaging diagnosis, the event shall be defined as the date when the exacerbation is determined to be exacerbation.

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- If the definitive diagnosis of recurrence or new lesion is made by biopsy pathology, the event is defined as the date of clinical diagnosis if the clinical diagnosis of recurrence or new lesion can be made, or the date of biopsy if the clinical diagnosis of recurrence cannot be made and the diagnosis of recurrence is made by biopsy pathology.
- The occurrence of a second cancer (iatrogenic overlapping cancer) is neither an event nor a censored event, but rather a progression-free survival period until another event is observed.

Ⅶ-4-4 Disease Control Rate

Percentage of subjects achieving PR, CR, or SD among those treated. A minimum of 6 weeks of disease control is required from the date of initiation of treatment.

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Ⅷ.Safety Assessment

Ⅷ-1 Identification of Safety Assessment Indicators

An adverse event is any unwanted or unintended sign, symptom, or illness that occurs in a subject under study treatment, whether or not causally related to the study drug.

If an adverse event of Grade 1 or greater is observed before the start of treatment (at baseline evaluation), it is treated as an adverse event only if the grade of the adverse event is worse than the value before the start of treatment.

Event names and grades of adverse events are based on the Common Terminology Criteria for Adverse Events v4.0 Japanese translation JCOG version (CTCAE v4.03/MedDRA v12.0 compliant).

As for anticipated adverse drug reactions in the study treatment, refer to the package insert and interview form for the respective drug.

Ⅷ-2 Methods of evaluation, recording, and analysis of safety evaluation indicators and the timing of their implementation

In this study, adverse events will be evaluated from the start of study treatment until 30 days after the last dose of study treatment (the last dose of study treatment will be counted as day 0), or until the start of post-treatment if post-treatment is started before that date, whichever comes first. If post-treatment is initiated before that date, then the period will be the earlier of the following: (1) within 30 days from the start of study treatment to the date of the last dose of study treatment (starting on day 0 as the last day of study treatment) or before the start of post-treatment if post-treatment is initiated earlier.

The last dose of study treatment is the last dose of ramucirumab or docetaxel, whichever is administered later.

Collect adverse events after 30 days of the last dose of study treatment, if post-treatment has not been started and the event is judged to be causally related to the study treatment.

Adverse events due to new onset of primary disease progression (PD) after the progression of the primary disease (PD) has been confirmed will not be included in the collection. For safety analysis, the percentage of adverse events occurring from the start of study treatment to within 30 days of the last dose of study treatment or before the start of post-treatment if post-treatment was started before that time, whichever is earlier, will be summarized by worst grade (Common Terminology Criteria for Adverse Events v4.0 JCOG version in Japanese translation).

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VIII-3 Procedures for collecting, recording and reporting information on diseases, etc.

In accordance with the provisions of this chapter based on the ″Clinical Research Act″ (Act No. 16 of 2009), the ″Enforcement Regulations of the Clinical Research Act″ (Ordinance of the Ministry of Health, Labour and Welfare No. 17 of 2018) and related notifications, ″In the event of a serious adverse event (″illness etc.″ under the Clinical Research Act), the Principal Investigator shall report to the Research Office/Research Director (principal investigator) The investigator shall report to the Research Office/Principal Investigator (Principal Investigator). If signs (including abnormal laboratory values) or symptoms are included in the diagnosis, efforts will be made to name the diagnosis based on the Common Terminology Criteria for Adverse Events v4.0 Japanese translation JCOG version, rather than individual signs and symptoms, whenever possible. The principal investigator will make the final decision as to whether or not a disease or condition is attributable to the conduct of this study.

VIII-3-1 Definition of Serious Adverse Events

Serious adverse events are defined as any of the following. These are classified as ″diseases, etc.″ under the Clinical Research Act.

(1) Death or threatened death*1

(2) Infectious diseases that may lead to death or fatalities (e.g., fulminant hepatitis, HIV infection, etc.)

(3) Diseases requiring hospitalization or extended hospitalization for treatment*2

(4) Obstacles*3

(5) Diseases, etc. that may lead to disability

(6) Diseases, etc. that are serious according to 1) through 5) *4

(7) Congenital diseases or anomalies in later generations

However, the following are excluded

- Hospitalization or death due to progression of primary disease (PD)

- Hospitalization or prolongation of hospital stay for the purpose of reducing the burden on subjects who are seen remotely

- Pre-planned hospitalization or extended hospital stay

- Hospitalization or prolonged hospital stay not related to adverse events

- Hospitalization for less than 24 hours or prolongation of hospital stay for the sole purpose of observation

- Hospitalization for follow-up of adverse event that has resolved or mildly resolved/extended hospital stay

- Other hospitalization/extended hospital stay not medically necessary

*1: When the subject is at risk of death when the adverse event occurs. For example, life-threatening cases due to serious liver disease (fulminant hepatitis, liver failure symptoms, etc.), renal disease (acute renal failure, etc.), cardiac disease (acute heart failure), digestive symptoms with bleeding, shock, anaphylaxis-like symptoms, accidents, etc.

*2: Among hospitalizations, hospitalizations due to recurrence (including laboratory admissions) are not subject to emergency reporting.

*3: When the adverse event has been treated but recovery is not expected or significant impairment has occurred.

*4: When urgent intensive care is required for a short period of time

1) Death

(i) All deaths during study treatment or within 30 days of the last treatment date, or before the start of post-treatment if post-treatment was started before that date, whichever is earlier (regardless of whether the death is causally related to the study treatment or not)

(ii) Death after 31 days from the last treatment date for which a causal relationship to the study treatment cannot be ruled out (definite, probable, or possible).

(2) Diseases, etc. that may lead to death

(i) Grade 4 adverse events occurring during study treatment or within 30 days of the last treatment date or before the start of post-treatment if post-treatment was initiated before that date, whichever occurs first (excluding events in Table VII-3)

(ii) Grade 4 adverse events (excluding events in Table VII-3) occurring after 31 days from the date of last treatment, for which a causal relationship to the study treatment cannot be ruled out (definite, probable, or possible)

(3) Illnesses that require hospitalization or extended hospitalization for treatment

(i) Grade 3/2/1 adverse events that occurred during study treatment or within 30 days of the last treatment date or before the start of post-treatment if post-

treatment was initiated before that date, whichever occurs first, and that require hospitalization for more than 24 hours or an extended hospital stay* to treat the adverse event (Table VII-) (excluding events in Table VII-3)

(ii) Grade 3/2/1 adverse events occurring on or after 31 days from the date of last treatment and requiring hospitalization for more than 24 hours or prolonged hospitalization* for treatment of the adverse event, for which a causal relationship to study treatment cannot be denied (definite, probable, or possible) (Table VII-3) (excluding events in Table VII-3)

For ″hospitalization or prolonged hospitalization,″ the term ″hospitalization or prolonged hospitalization″ refers to a hospitalization/ prolonged hospitalization that is medically necessary for more than 24 hours to treat an adverse event.

4) Disability, 5) Diseases that may lead to disability, etc.

Permanent or marked disability or dysfunction (excluding myelodysplastic syndrome (MDS), secondary cancers, etc.), or those that are at risk of becoming so.

(6) Diseases, etc. that are serious according to 1) through 5)

(7) Congenital diseases or anomalies in later generations

Table VIII-3 Adverse events excluded from reporting

However, both 1) through 4) are exempted from emergency reporting if any of the following a) through c) apply.

a) Adverse events (including death) occurring after 31 days from the date of the last study treatment, for which a causal relationship to the treatment can be ruled out (either unlikely or not related). In addition, if post-treatment is started after discontinuation of study treatment, adverse events occurring after the start of post-treatment are not reportable.

(b) Myelodysplastic syndrome (MDS: Myelodysplastic syndrome), secondary cancer development

c) Adverse events not subject to urgent reporting as defined below

In this study, events that are considered unlikely to be life-threatening due to the nature of the disease or treatment for which the method of treatment has already been established are exempt from emergency reporting. Specifically, the following adverse events that do not result in death will be excluded from

emergency reporting, and these adverse events will be evaluated in the central monitoring report.

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SOC※ (CTCAE ver 4.0)	AE term
Blood and lymphatic system disorders	Anemia, myelocytopenia
gastrointestinal disorder	constipation
General and systemic disorders and conditions at the site of administration	generation of heat
clinical examination	Increased alkaline phosphatase, decreased CD4 lymphocytes, elevated cholesterol, increased CPK, increased GGT, increased lipase, decreased lymphocyte count, decreased neutrophil count, decreased platelet count, increased serum amylase, decreased leukocytes
Metabolic and nutritional disorders	Obesity, anorexia, hyperuricemia, hypoalbuminemia, hypertriglyceridemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia
Renal and urinary tract disorders	chronic kidney disease
Respiratory, thoracic and mediastinal disorders	sleep apnea
Skin and subcutaneous tissue disorders	oligohidrosis

SOC: System Organ Class

VIII-3-2 Reporting of Serious Adverse Events

Procedures for reporting serious adverse events to the administrator of the implementing medical institution and the principal investigator by the principal investigator or subinvestigator at the medical institution where the event occurred.

(1) Initial Report

In the event of a serious adverse event (see ″VIII-3-1 Definition of Serious Adverse Events″), the principal investigator or a subinvestigator will immediately take appropriate measures. The research assistant physician will immediately report the event to the principal investigator.

The investigator shall report the serious adverse event in writing (Drug Disease Report Form (Uniform Form 8)) or ″Medical Device Disease or Failure Report Form (Uniform Form 9)″ (E-mail) or by fax to the administrator of the implementing medical institution and the contract research organization within 24 hours after learning of the occurrence of the event. The reporter's judgment on the causal relationship should be stated in the ″Comments (Opinion of the reporter)″ column of the Uniform Form 8 or 9. The contract research organization shall promptly report to the principal investigator and the secretariat.

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Trustee Agency Contact
EPS Corporation
Acropolis Tokyo, 6-29 Shin Ogawa-cho, Shinjuku-ku, Tokyo 162-0814, Japan
E-mail: prj-dtxram@eps.co.jp
fax: 03-5946-8287
TEL: 03-6759-9904

(2) Additional Report

The principal investigator of the medical institution where the serious adverse event occurred shall follow up on the serious adverse event (if necessary, promptly enter additional information in a document (Drug Disease Report (Uniform Form 8) or Medical Device Disease or Failure Report (Uniform Form 9)) and send it to the administrator of the medical institution where the event occurred and the principal investigator. The report shall be sent to the administrator of the medical institution conducting the study and the principal investigator.

Reporting Obligations and Reporting Procedures of Principal Investigators/Research Office to the Authorized Clinical Research Review Committee and to the Principal Investigators and the Minister of Health, Labour and Welfare at each Medical Institution.

The principal investigator shall report serious adverse events reported in the initial report and additional reports to the Authorized Clinical Research Review Committee and each principal investigator (based on ″Article 13 of the Clinical Research Act″ and ″Articles 54 and 55 of the Enforcement Regulations of the Clinical Research Act″) as necessary, after determining the seriousness, causal relationship, and predictability of the serious adverse events reported in the initial and additional reports (2) The investigator shall report the results of the clinical research to the Authorized Clinical Research Review Committee and each principal investigator (based on ″Article 13 of the Clinical Research Act″ and ″Articles 54 and 55 of the Enforcement Regulations of the Clinical Research Act″), and provide information to the manufacturer or distributor of the study drug or device. The principal investigators who receive reports from the principal investigators will also report to the administrators of the respective medical institutions.

1) Reporting to the Accredited Clinical Research Review Committee, etc.

Serious adverse events requiring reporting and reporting period

(a) VIII-3-1-1) (excluding those caused by infectious diseases) where a causal relationship cannot be denied. 15 days

(a) Unforeseeable* VIII-3-1 2) to 7) (excluding infectious diseases), for which a

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causal relationship cannot be ruled out. 15 days

c. Infectious diseases** for which a causal relationship cannot be ruled out and which cannot be predicted 15 days

d) 2) to 7) (excluding c) of VIII-3-1 due to an infectious disease** for which a causal relationship cannot be ruled out. 15 days

(e) VIII-3-1 2) to 7) (excluding those listed in (a)) where a causal relationship cannot be denied. 30 days

*: Includes items that can be predicted from the precautions for use of the drug concerned, etc., and for which the trend of occurrence cannot be predicted, or for which a change in the trend of occurrence indicates the occurrence or threat of the occurrence of a health hazard or its spread.

**: In the case of a biologically-derived product, when there is a suspicion of contamination of said drug product, etc., with pathogens from biologically-derived raw materials or materials, etc.

If the Principal Investigator determines that the event is a serious adverse event requiring reporting to an accredited clinical research review committee, the following procedure will be used to report the event.

The Principal Investigator shall report to the Administrator of the Operating Medical Institution to which the Principal Investigator belongs using the ″Report on Drug Disease, etc. (Uniform Form 8)″ or ″Report on Medical Device Disease, etc. or Failure (Uniform Form 9)″ within the designated reporting period.

The Principal Investigator shall report to the Authorized Clinical Research Committee using the ″Report of Drug Disease, etc. (Uniform Form 8)″ or ″Report of Medical Device Disease or Failure (Uniform Form 9)″ within the designated reporting period.

The principal investigator shall promptly report to the principal investigator of each medical institution other than the medical institution where the serious adverse event occurred using the ″Report of Drug Disease (Uniform Form 8)″ or ″Report of Medical Device Disease or Failure (Uniform Form 9)″. Each principal investigator shall promptly report to the administrator of the medical institution where the study was conducted.

The Principal Investigator shall promptly report to the manufacturer or distributor of the pharmaceutical product using the ″Report of Disease, etc. of Pharmaceutical Product (Uniform Form 8)″ or ″Report of Disease, etc. or Failure of Medical Device (Uniform Form 9)″.

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Ⅷ-4 Principal Investigator/Research Office Responsibilities

Ⅷ-4-1 Determining whether there is a need to suspend registration and emergency notification to the facility

The Principal Investigator/Research Office will determine the urgency, importance, and degree of impact of the contents of the report, and take measures such as suspending enrollment as necessary. In contacting the principal investigators at each site, telephone contact may be made depending on the degree of urgency, but written (e-mail) contact will also be made promptly afterwards.

Ⅷ-4-2 Adverse Events in Central Monitoring

During central monitoring, the principal investigator/study office carefully reviews the adverse event reports in the central monitoring report generated by the CRO that manages the data and confirms that there are no omissions from the sites. Conversely, they also ensure that all reported adverse events are listed in the central monitoring report. If necessary, the safety of the product will be reviewed (reported to the Efficacy and Safety Evaluation Committee).

Ⅷ-5 Observation period for clinical research subjects after disease outbreak

The study has a follow-up period of 9 months from the last patient enrolled in the study, and the end of the follow-up period will be the observation period for any continuing disease for which a causal relationship between the study treatment and the patient cannot be ruled out.

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IX Assessment Items, Laboratory Tests, and Evaluation Schedule

IX-1 Pre-registration assessment items

IX-1-1. inspections to be performed prior to registration (any time prior to registration)

PT, APTT

HBs antigen, HBs antibody, HBc antibody, HCV antibody

If at least one of the HBs or HBc antibodies is positive, HBV-DNA should also be measured before starting treatment.

IX-1-2. inspection to be performed within 28 days prior to registration

Examination for staging

1) Cerebral contrast-enhanced MRI or cerebral contrast-enhanced CT (slice thickness of 5 mm or less): simple MRI or simple CT is acceptable when contrast media cannot be used due to contrast media allergy or renal impairment.

2) Contrast CT of the thorax, upper abdomen to pelvic region (slice thickness of 5 mm or less): simple CT is acceptable when contrast media cannot be used due to allergy to contrast media or renal impairment.

3) Bone scintigraphy/PET-CT

Other

Resting 12-lead ECG

IX-1-3. inspection to be performed within 14 days prior to registration

1) General condition: PS (ECOG), weight, height

2) Peripheral blood counts: white blood cell count, neutrophil count (ANC: rod-shaped nucleated cell + segmental nucleated cell), hemoglobin, platelet count

3) Blood Biochemistry: total protein, albumin, total bilirubin, AST (GOT), ALT (GPT), creatinine, LDH, calcium, sodium, potassium, CRP, FT3, FT4, TSH

* If the serum albumin level is less than 4.0 g/dL, a corrected calcium value should be calculated.

Corrected calcium level (mg/dL) = serum calcium level (mg/dL) + [4-albumin level (g/dL)] × 0.8

4) Urinalysis: urinary sugar, urinary protein

5) Self-assessment findings (described in CTCAE v4.0-JCOG)

Blood and lymphatic disorders: febrile neutropenia

General and systemic disorders and conditions at the site of administration: fever, fatigue, edema of extremities

Skin and subcutaneous tissue disorders: alopecia, other (skin rash), purpura
Gastrointestinal disorders: diarrhea, nausea, vomiting, oral mucositis
Metabolic and nutritional disorders: anorexia
Nervous system disorders: peripheral sensory neuropathy, peripheral motor neuropathy
Respiratory, thoracic and mediastinal disorders: pneumonia
Infectious and parasitic diseases: bronchial, pulmonary, upper respiratory, bladder, mediastinal, pleural, wound, and urinary tract infections
6) Chest X-ray (frontal view)
7) Transcutaneous oxygen saturation: SpO2

IX-2 Examination and evaluation during treatment

The frequency of the safety endpoints listed below is a minimum. It is not prohibited to perform the tests more closely than this at the discretion of the physician in charge.
However, for efficacy endpoints, the evaluation should be performed at the specified frequency, except in cases of suspected exacerbations, because a dense frequency is likely to cause bias in the evaluation of efficacy.

IX-2-1 Safety endpoints to be evaluated in the first cycle

IX-2-1 -1. Safety endpoints to be evaluated on day1 (described in CTCAE v4.0-JCOG)

(Omitted if inspections to be performed within 14 days prior to registration for (1) through (7) below are performed within 3 days of day 1 of the first cycle)

1) PS (ECOG), body weight
2) Peripheral blood counts: white blood cell count, neutrophil count (ANC: rod-shaped nucleated cell + segmental nucleated cell), hemoglobin, platelet count
3) Blood Biochemistry: total protein, albumin, total bilirubin, AST (GOT), ALT (GPT), creatinine, LDH, calcium*, sodium, potassium, CRP, CPK, blood sugar (fasting or at any time)
* If the serum albumin level is less than 4.0 g/dL, a corrected calcium value should be calculated.
Corrected calcium level (mg/dL) = serum calcium level (mg/dL) + [4-albumin level (g/dL)] × 0.8
4) Urine qualitative test: urinary sugar, urinary protein
5) Self-assessment findings (described in CTCAE v4.0-JCOG)
Blood and lymphatic disorders: febrile neutropenia
General and systemic disorders and conditions at the site of administration: fever, fatigue, malaise, edema of extremities, injection reaction
Skin and subcutaneous tissue disorders: alopecia, other (skin rash), purpura
Gastrointestinal disorders: constipation, diarrhea, nausea, vomiting, oral

mucositis
Metabolic and nutritional disorders: anorexia
Nervous system disorders: peripheral sensory neuropathy, peripheral motor neuropathy
Respiratory, thoracic and mediastinal disorders: pneumonia
Infectious and parasitic diseases: bronchial, pulmonary, upper respiratory, bladder, mediastinal, pleural, wound, and urinary tract infections
6) Chest X-ray (frontal view)
7) Transcutaneous oxygen saturation: SpO2

IX-2-1-2. safety endpoints to be evaluated on day8 (described in CTCAE v4.0-JCOG)

1) PS (ECOG)
2) Peripheral blood counts: white blood cell count, neutrophil count (ANC: rod-shaped nucleated cell + segmental nucleated cell), hemoglobin, platelet count
3) Blood Biochemistry: total protein, albumin, total bilirubin, AST (GOT), ALT (GPT), creatinine, LDH, calcium*, sodium, potassium, CRP, CPK, blood sugar (fasting or at any time)
* If the serum albumin level is less than 4.0 g/dL, a corrected calcium value should be calculated.
Corrected calcium level (mg/dL) = serum calcium level (mg/dL) + [4-albumin level (g/dL)] × 0.8
4) Urine qualitative test: urinary sugar, urinary protein
5) Self-assessment findings (described in CTCAE v4.0-JCOG)
Blood and lymphatic disorders: febrile neutropenia
General and systemic disorders and conditions at the site of administration: fever, fatigue, malaise, edema of extremities, injection reaction
Skin and subcutaneous tissue disorders: alopecia, other (skin rash), purpura
Gastrointestinal disorders: constipation, diarrhea, nausea, vomiting, oral mucositis
Metabolic and nutritional disorders: anorexia
Nervous system disorders: peripheral sensory neuropathy, peripheral motor neuropathy
Respiratory, thoracic and mediastinal disorders: pneumonia
Infectious and parasitic diseases: bronchial, pulmonary, upper respiratory, bladder, mediastinal, pleural, wound, and urinary tract infections

6) Transcutaneous oxygen saturation: SpO2

IX-2-2. safety endpoints to be evaluated at least once every 3 weeks after the

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second cycle

1) PS (ECOG), body weight
2) Peripheral blood count: white blood cell count, neutrophil count (ANC: rod-shaped nucleated cell + segmental nucleated cell), hemoglobin, platelet count
3) Blood Biochemistry: total protein, albumin, total bilirubin, AST (GOT), ALT (GPT), creatinine, LDH, calcium*, sodium, potassium, CRP, CPK, blood sugar (fasting or at any time)

* If the serum albumin level is less than 4.0 g/dL, a corrected calcium value should be calculated.

Corrected calcium level (mg/dL) = serum calcium level (mg/dL) + [4-albumin level (g/dL)] × 0.8

4) Urine qualitative test (urinary sugar, urinary protein)
5) Chest X-ray (frontal view)
6) Self-assessment findings (described in CTCAE v4.0-JCOG)

Blood and lymphatic disorders: febrile neutropenia
General and systemic disorders and conditions at the site of administration: fever, fatigue, malaise, edema of extremities, injection reaction
Skin and subcutaneous tissue disorders: alopecia, other (skin rash), purpura
Gastrointestinal disorders: constipation, diarrhea, nausea, vomiting, oral mucositis
Metabolic and nutritional disorders: anorexia
Nervous system disorders: peripheral sensory neuropathy, peripheral motor neuropathy
Respiratory, thoracic and mediastinal disorders: pneumonia
Infectious and parasitic diseases: bronchial, pulmonary, upper respiratory, bladder, mediastinal, pleural, wound, and urinary tract infections

7) Transcutaneous oxygen saturation: SpO2

IX-2-3 Safety endpoints to be evaluated at least once every two cycles after the second cycle

Blood biochemistry: FT3, FT4, TSH

IX-2-4. safety assessment items to be performed as needed

1) If dyspnea is observed
Arterial blood gas: PaO2
Chest X-P (frontal view)
2) If arrhythmia is observed
Resting 12-lead ECG
3) When endocrine abnormalities are suspected
ACTH, cortisol

IX-2-5 Efficacy endpoints

Imaging studies to determine the effect of tumor shrinkage should be performed every 6 weeks (±7 days) starting from the date of administration, using thoracoabdominal CT and imaging studies of sites where target lesions (see ″VII-2-3 Selection of target lesions and baseline record″) are present to evaluate tumor shrinkage according to ″VII-2-5 Determination of tumor shrinkage effect″. VII-2-5 Determination of tumor shrinkage effect″. The same examination methods as those used for the baseline evaluation should be used to evaluate the effect of tumor shrinkage.
For non-target lesions such as bone and brain that are not included in the imaging range of thoracoabdominal CT, head CT, MRI, bone scintigraphy, and PET should be performed as needed when symptoms appear or new lesions are suspected. However, head CT or MRI should be performed every 6 weeks for patients with brain metastases at baseline.

IX-3 Examination and endpoints at discontinuation of study treatment

Report the date of discontinuation of treatment and the reason for discontinuation of treatment in the eCRF.
PS (ECOG), peripheral blood count, blood biochemistry, urinalysis, autosomnogram, body weight, SpO2, and thoracoabdominal CT will be evaluated within 28 days after discontinuation of study treatment. However, if the study is discontinued due to worsening of disease, the CT scan of the chest and abdomen can be substituted for the CT scan that was used as the basis for determining the worsening of disease.

IX-4 Examinations and endpoints after discontinuation of study treatment

For all patients after discontinuation of study treatment, the nature of post-treatment, date of death or last confirmed date of survival, and in cases of death, the cause of death will be investigated.
Patients who discontinued study treatment for reasons other than exacerbation of the primary disease shall be evaluated for exacerbation (date and site of exacerbation) thereafter until exacerbation, according to the schedule in ″VII-2 **Methods of evaluation, recording and analysis of efficacy measures and the timing of their implementation.** However, if post-treatment is started before the exacerbation, it shall be up to the date of the start of post-treatment.
If the ″overall response″ is SD at the time of discontinuation of study treatment, the evaluation of tumor shrinkage effect for the calculation of ″response rate″ shall continue until the ″overall response″ becomes CR/PR/PD or until the start of post-treatment. If the ″overall response″ is CR, PR, or PD at the time of discontinuation of study treatment, no further evaluation of tumor shrinkage effect is required, but the presence or absence of progression should be reported in the eCRF.

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X. data collection

X-1 Case Report

X-1-1. use of EDC system

The EDC system will be used in this study to collect and record data and to prepare case report forms.

The original case report form shall be an electronic file generated by the EDC system.

X-1-2 Preparation, submission and storage of case report forms

The site principal investigator shall verify that the eCRF to be submitted is accurate and complete, and shall electronically sign it. The site principal investigator shall receive and store the electromagnetic media on which a copy of the case report form from the site is electronically filed from the CRO that manages the data.

The Principal Investigator shall receive and retain an electromagnetic medium containing all original case report forms as electronic files from the CRO that manages the data once all case report forms for the study have been generated and electronically signed by the Institutional Principal Investigator.

In addition, data in the eCRF that are based on source documents must be consistent with the source documents. If there is any discrepancy with the source documents, the Institutional Principal Investigator or the physician in charge, etc. shall prepare a record explaining the reason for the discrepancy and submit it to the CRO that manages the data and retain a copy of it.

X-1-3 Inquiries about case report forms and EDC system

Contact]

CRO for data management

Data center (in EPS Co., Ltd.)

TEL： 052-581-5554 FAX： 052-533-1296

E-mail: prj-dtxram-dc@eps.co.jp

XI. Access to original documents, etc.

In conducting this study, all clinical research-related records, including original documents, will be made available for direct inspection by the principal

investigator and the implementing medical institution during monitoring, audits, and investigations by the accredited clinical research review committee and regulatory authorities related to the clinical research. In addition, observational studies involving patients participating in this study will be permitted to be conducted concurrently with this study.

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XII. Sample Size and Statistical Methods

XII-1 Number of cases and rationale for setting the number of cases, including planned enrollment and considerations for the power of the clinical study and clinical reasons

Target number of cases: 32

<Statistical Rationale for Setting>

The number of patients required is calculated based on the following assumptions: the threshold response rate is set to 10%, the expected response rate is set to 30%, α (one sided) = 0.1 and β = 0.1, the number of patients required by the accurate method based on the binomial distribution is 29 cases, but inappropriate cases are anticipated, and the target number of cases is set to 32 cases.

In a phase III trial comparing pemetrexed and DTX, the response rate for DTX alone was 8.8%, and in the global phase III REVEL trial comparing the RAM+DTX combination to DTX alone, the response rate for DTX alone as second-line therapy was 13.6%. In the Phase III trial comparing gefitinib with DTX, the response rate for DTX monotherapy was 12.8%. Based on these results, a threshold response rate of 10% was set for this trial.

In the REVEL study, the response rate for the RAM+DTX combination was 13.6%, and in a phase II study comparing RAM+DTX combination therapy and DTX alone as second-line therapy in Japan, the response rate for RAM+DTX combination therapy was 28.9%. Based on these results, the expected response rate in this study was set at 30%.

No interim analysis is planned for this study, and no early termination of the study will be planned if the number of patients does not reach the planned number. In principle, missing value completion and analysis corresponding to outliers will not be performed.

XII-2 Analysis and Criteria for Primary Endpoints

We check whether the lower limit of the 80% confidence interval of the response rate based on the best overall efficacy determination exceeds the threshold of 10%. If the lower limit of the 80% confidence interval for the response rate is above the threshold, we conclude that the protocol treatment is effective.

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XII-3 Analysis of secondary endpoints

The safety evaluation is performed based on the total number of occurrences in all treated cases, 95% confidence intervals are calculated using the Clopper-Pearson method.

The population of all treated patients other than patients judged as ineligible for efficacy analysis will be included in the OS analysis, evaluable cases based on the definition of endpoints will be included in the analysis of PFS. OS and PFS were calculated by the Kaplan-Meier method, and Greenwood's formula was used for interval estimation.

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XIII. Informed Consent to the Subjects of Clinical Research

XIII-1 Procedures for obtaining informed consent, etc.

Prior to patient enrollment, the principal investigator and the subinvestigator will provide the patient with an explanatory document approved by an accredited clinical research review committee and fully explain the following information.

Items to be included in the written explanation and consent document].

(1) Clinical trials

(1) Purpose and significance of the research

(2) Voluntary nature of consent to participate in research and the freedom to withdraw consent after the declaration of consent

(2) Explanation of research plan

(1) Criteria for requesting participation in research

(2) Research Methods

(3) Responses to research subjects after the completion of the research

(4) When you want to know more about the implementation plan, etc.

(3) Anticipated benefits and disadvantages of conducting the research

(4) What to do if you do not participate in the study

(5) Protection of personal information

(6) Disclosure of research information

(7) Methods of disclosure of research information and publication of research results

(8) Intellectual property rights arising from research

(9) Storage and disposal methods for samples and information used in research

(10) Examination and treatment costs

(11) Response to adverse events and health hazards, etc.

(12) Monitoring and auditing

(13) Research Funding and Conflicts of Interest

(14) Research that cannot be identified at the time consent is obtained

(15) Possibility of providing research results to other institutions

(16) Others

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(17) Approved Clinical Research Review Committee

(18) Contact for inquiries and complaints

XIII-2 Procedures for obtaining informed consent

After explaining the study, giving the patient sufficient time to think about it, and ensuring that he or she fully understands the study, ask the patient to participate in the study. If the patient agrees to participate in the study, a designated consent form is used and signed by the patient. The physician in charge will make sure that the consent form includes the name of the physician who provided the explanation and the date of the explanation, the name of the patient who received the explanation and consented, and the date of consent.

One copy of the consent document should be handed to the patient personally and one copy should be kept at each institution under the control of the principal investigator at each institution. The original should be kept in the patient's medical record or in a storage area designated by the medical institution.

XIV. Certified Review Board (CRB) approval and notification to the Minister of Health, Labour and Welfare

XIV-1. Response to CRB Comments

When the principal investigator receives an opinion from the CRB, the principal investigator shall promptly report the content of the opinion to the administrator of the site and provide the information to the other principal investigators. Other principal investigators who receive information from the CRB will promptly report the content of the information to the site administrator. If the CRB provides an opinion, the principal investigator will respect that opinion and take the necessary measures.

The principal investigator shall retain the original CRB approval document after CRB approval.

XIV-2 Clinical research and approval of the administrator of the implementing medical institution at the starting of the clinical trial

The Principal Investigator must submit to the CRB and obtain its approval for the implementation of this research a research plan (Form 1), a research protocol (including an explanatory consent document), a document describing the outline of the drug, etc., a procedure manual in case of illness, etc., a monitoring procedure manual, an audit procedure manual, a conflict of interest management standard and conflict of interest management plan, a document describing the

names of the principal investigator and subinvestigators, and other documents requested by the CRB.

After hearing the CRB's opinion, the Principal Investigator and the Responsible Investigator shall submit the implementation plan, research protocol (including the explanation and consent document), documents describing the outline of drugs, etc., procedures in case of illness, etc., monitoring procedures, audit procedures, conflict of interest management standards and conflict of interest management plan, and documents describing the Principal Investigator and the Responsible Investigator. The Principal Investigator and Responsible Investigator shall, after hearing the opinions of the CRB, submit the implementation plan, research protocol (including the explanation and consent document), documents describing the outline of drugs, etc., procedure manual in case of occurrence of diseases, etc., monitoring procedure manual, audit procedure manual, conflict of interest management standards and conflict of interest management plan, documents describing the names of the Responsible Investigator and the Research Assigned Investigator, relevant statistical analysis plan (if prepared), documents requested by the CRB and any other documents requested by the manager of the implementing medical institution. The approval of the administrator of the medical institution concerned must be obtained as to whether or not this research can be conducted at the medical institution concerned by submitting the documents required by the administrator.

XIV-3. Submission of implementation plan to the Minister of Health, Labor and Welfare

The PI shall submit the implementation plan to the Minister of Health, Labour and Welfare by submitting the implementation plan (Form 1) to the Regional Health and Welfare Bureau that has jurisdiction over the location of the CRB that conducted the review. When the PI submits the implementation plan to the MHLW, the PI shall promptly notify the CRB to that effect. The PI shall also report to the administrator of the implementing medical institution and provide information to the other principal investigators to that effect.

Other principal investigators who receive information from the principal investigator shall promptly report the content of such information to the administrator of the implementing medical institution. When the CRB expresses its opinion to the principal investigator, the principal investigator must respect that opinion and take the necessary action.

XIV-4. Periodic reports to CRB

The Principal Investigator shall report the status of the implementation of the Specified Clinical Research ("Periodic Report") to the Administrator of the Operating Medical Institution and then to the CRB every year, starting from the date of submission of the implementation plan to the Minister of Health, Labour and Welfare, and within two months after the expiration of the said period. The Principal Investigator will also promptly provide information to other principal investigators to that effect. In this case, the other principal investigators shall promptly report the details of such information to the administrator of the implementing medical institution. (3) If the CRB receiving the report expresses an opinion to the principal investigator, the principal investigator must respect that opinion and take the necessary measures.

The contents of the periodic report shall be as follows

1. Number of subjects in the study (number of cases planned to be conducted, number of cases in which consent was obtained, number of cases conducted, number of cases completed, number of cases discontinued, and number of cases for which compensation was provided during the study period)
2. (Briefly summarize and describe the occurrence of illnesses, etc. in the clinical research as a whole, including those that have already been reported and reviewed).
3. Incidence of noncompliance with the Enforcement Regulations of the Clinical Research Act (Ordinance of the Ministry of Health, Labour and Welfare No. 17 of 2018) or the research protocol, and subsequent actions
4. Evaluation of the safety and scientific relevance of the study (This section describes the evaluation of the safety and scientific relevance of the study, based on the status of the clinical research, including the occurrence and progress of diseases, etc., the status of non-compliance cases and subsequent responses, and information on efficacy or ineffectiveness related to drugs used in the study in research reports published during the relevant period, etc.).
5. The Principal Investigator(s), the Research Assigning Physician(s) and the person(s) responsible for conducting the statistical analysis, and the person(s) listed in the research protocol who will clearly benefit from conducting this research, shall reconfirm the following items and submit the Conflict of Interest Management Standards and the Conflict of Interest Management Plan. If, as a result of the confirmation, there are no changes in the Conflict of Interest Management Criteria and Conflict of Interest Management Plan, the CRB shall be informed of

such changes.

- Provision of research funds, etc. or other involvement in clinical research by manufacturers and distributors of pharmaceuticals, etc. (including subsidiaries, etc.) (2) Provision of research funds, etc. or other involvement in clinical research by a pharmaceutical manufacturer, etc. (including subsidiaries, etc.)
- Contributions, remuneration for writing manuscripts, giving speeches and other services, and other involvement by manufacturers and sellers of pharmaceuticals, etc.

When making a periodic report, the principal investigator must attach the research protocol (including the explanation and consent document), documents describing the outline of the drug, etc., the procedure manual in case of occurrence of disease, etc., the monitoring procedure manual, the audit procedure manual, the conflict of interest management standards and conflict of interest management plan, documents describing the names of the principal investigator and sub-investigators, the statistical analysis plan (if prepared), and any other documents required by the CRB (limited to those that the CRB does not have up to date). (only if the CRB does not have the most recent version).

XIV-5. Periodic report to the Minister of Health, Labor and Welfare

The principal investigator shall report to the Minister of Health, Labour and Welfare on the status of the implementation of the clinical research by recording a periodic report (Appendix Form 3) in the jRCT within one month from the date of the CRB's opinion on the name of the CRB described in the implementation plan, the appropriateness of continuation of the research by the CRB, and the number of subjects who participated in this research. The CRB shall report to the Minister of Health, Labour and Welfare by recording the periodic report (Exhibit 3) in the jRCT within one month from the date of the CRB's opinion.

XIV-6. Changes in Implementation Plan, etc.

The Principal Investigator shall obtain the CRB's opinion and approval when making changes to the implementation plan, research protocol (including the explanatory consent document), Conflict of Interest Management Standards, or Conflict of Interest Management Plan.

In cases involving changes in the implementation plan, the revised implementation plan shall be submitted to the Minister of Health, Labour and Welfare (Form 2). If, during the continuation of a multicenter collaborative study, the study is no longer being conducted at one of the institutions, the principal investigator will submit a revised implementation plan after the observation period for the subjects at that institution has ended.

In the event of a ″change in progress″ as described in (a) through (e) below, the principal investigator shall make the change in the implementation plan and disclose the status by recording it in the database (jRCT) maintained by the MHLW.

(a) Pending: Not yet recruiting at any of the implementing medical institutions.

(b) Recruiting: Currently recruiting subjects for clinical research.

(c) Suspended: Recruitment is temporarily suspended.

(d) Not recruiting: The clinical research is ongoing but recruitment has ended.

(e) Completion of research

XIV-6-1 Procedures in the event of changes to the research plan after the study has begun

1） Procedures to be performed by the Principal Investigator

If any of the following changes (1), (2), or (3) occur in the implementation of this

study after the study has started, the principal investigator shall apply to the Accredited Clinical Research Review Committee for a change and obtain the opinion of the Committee. If there is no change in the implementation plan, notification to the Minister of Health, Labour and Welfare is not required. If there are any changes in the implementation plan, notification to the Minister of Health, Labour and Welfare is required.

（1）When changing the content of the protocol or the explanatory consent document (revision or amendment)

（2）No change to the protocol or consent document, but change to the implementation plan (jRCT registration details)

（3）Changes to the Conflict of Interest Management Standards or Conflict of Interest Management Plan

Since notification of changes in the implementation plan (jRCT registration details) to the Minister of Health, Labour and Welfare must be made prior to any changes, except for changes in the progress of the research, the principal investigator must inform the principal investigator and the administrative office/contracting organization of the changes in advance, including the replacement of principal investigators and subinvestigators at each participating medical institution If there are any changes that need to be notified to the PI, the PI shall notify the Administrative Office and the Contract Research Organization in advance. In addition, if there are any changes that need to be communicated, the information should be promptly provided to the other principal investigators.

When a principal investigator receives an opinion from an accredited clinical research review committee, the principal investigator shall promptly report the contents of the opinion to the administrator of the medical institution to which he/she belongs, and provide this information to the other principal investigators.

<Procedures in the case that changes need to be notified to the Accredited Clinical Research Review Committee and the Minister of Health, Labour and Welfare before the changes are made.

(1) Change of implementation plan

After obtaining the opinion of the accredited clinical research review committee on any of the above changes (1), (2), or (3), if any changes are made to the implementation plan (contents of jRCT registration), the changes should be entered in jRCT. In addition, the principal investigator shall submit the following notification to the Minister of Health, Labour and Welfare. After the effective date of the pre-determined changes, the relevant clinical research will be conducted in accordance with the changes.

- Notification of Changes to Implementation Plan Items (Ministerial Ordinance Form 2)
- Modified implementation plan (output of jRCT changes)
- Notification of Review Results from an Accredited Clinical Research Review Committee

<Procedures in the event that changes need to be notified to an accredited clinical research review committee or the Minister of Health, Labour and Welfare after the changes are made.

(2) Change in progress

(2) Among changes in the implementation plan (contents of jRCT registration), changes in ″Matters concerning confirmation of the implementation status of the specified clinical research and the progress of the specified clinical research″ should be made without delay after the change. jRCT's ″Research progress″ should be changed and input and registered. After that, the principal investigator shall promptly apply for the change to the approved clinical research review committee. After obtaining the approval of the Accredited Clinical Research Review Committee, the Principal Investigator submits the following notification to the Minister of Health, Labour and Welfare.

- Notification of Changes to Implementation Plan Items (Ministerial Ordinance Form 2)
- Modified implementation plan (output of jRCT changes)
- Notification of Review Results from an Accredited Clinical Research Review Committee

(3) Change of implementation plan after the first case registration

At the time of initial application, the ″Date of registration of the first case″ in the implementation plan is submitted with a blank space. After the first case registration, the implementation plan is changed without delay. In this case, the ″Date of registration of the first case″ of the jRCT is entered and registered. Thereafter, the principal investigator promptly applies for the change to the accredited clinical research review committee. After approval is obtained from the Accredited Clinical Research Review Committee, the following notification will be submitted to the Minister of Health, Labour and Welfare.

- Notification of Changes to Implementation Plan Items (Ministerial Ordinance Form 2)

- Modified implementation plan (output of jRCT changes)
- Notification of Review Results from an Accredited Clinical Research Review Committee

(4) Minor changes specified by Ordinance of the Ministry of Health, Labour and Welfare (application for change to the Certified Clinical Research Review Committee is not required)

When the Principal Investigator makes the following minor changes to the implementation plan and registration of a jRCT, he/she is not required to obtain the opinion of the Authorized Clinical Research Review Committee, and shall notify the Authorized Clinical Research Review Committee of the changes within 10 days of the date of such changes. In addition, a notification form (Ministerial Ordinance Form 3) shall be submitted to the Minister of Health, Labour and Welfare.

Article 42 of the Enforcement Regulations of the Clinical Research Act: Scope of Minor Changes to the Research Plan

- A change in the name of a person engaged in the specified clinical research that does not involve a change in the person engaged in the specified clinical research
- Change due to a change in the name of the area or a change in the lot number

2) Procedures to be followed by the principal investigator at each participating medical center

If any changes are to be made to the part of the implementation plan "Matters Concerning the Principal Investigator in Multicenter Research" that applies to the medical institution to which he or she belongs, the principal investigator and the administrative office must be informed of the planned changes before the changes are made. The principal investigator should confirm the institutional requirement confirmation form according to the details of the change, prepare documents to be submitted to the Accredited Clinical Research Review Committee, such as documents concerning conflicts of interest and a list of subcontractors, and notify the principal investigator and the Administrative Office of the change.

The latest implementation plan for your institution (the same as the jRCT registration details) should be checked on the jRCT website (https://jrct.niph.go.jp/).

XIV-6-2 Protocol Content Changes

(1) Classification of changes in protocol content

In this study, changes in protocol content after CRB approval are divided into two types: amendments and revisions. In addition, the addition of

supplementary explanations that do not fall under the category of changes in protocol content is distinguished as Memorandum. Definitions and handling are as follows.

① Protocol Amendments

For partial protocol changes that may increase the risk to patients participating in the study or substantially affect the primary endpoint of the study

i. Application for protocol modification shall be submitted to the CRB. Version control: The number of versions shall be raised to a whole number (Ver. 2.0, 3.0...). However, if the protocol is changed based on the CRB's opinion, the number of versions shall be raised to the second decimal place (Ver. 2.01, 3.01...).

ii. After approval of the protocol change by the CRB, the principal investigator submits a notification of the change in the implementation plan to the regional health bureau.

iii. The principal investigator will report to each principal investigator.

iv. Each principal investigator will report to the administrator of the implementing medical institution. Unless there is a specific reason, case registration will not be interrupted during this period.

*Follow the ″Regulations for Handling Specific Clinical Research Methods″ separately stipulated for procedures, etc. related to applications for changes.

② Revision of protocols (Revision)

For protocol changes that are not likely to increase the risk to patients participating in the study and do not substantially affect the primary endpoint of the study

i. If the need for protocol revision is recognized, the secretariat will prepare a revision proposal after reviewing the appropriateness of the change and its impact on the evaluation of the study. Management of the number of versions of the protocol and the explanatory consent document due to revision: The number of versions should be given to the first decimal place (Ver1.1, 1.2...). However, when the content of the protocol is changed based on the opinion of the CRB, the second decimal place should be raised (Ver. 1.11, Ver. 1.12, Ver. 1.13, Ver. 1.14). (Ver1.11, 1.12...).

ii. After approval of the protocol modification by the CRB, the principal investigator submits a notification of modification of the protocol to the

regional health bureau.

iii. The principal investigator will report to each principal investigator.

iv. Each principal investigator shall report to the administrator of the implementing medical institution.

*Follow the ″Regulations for Handling Specific Clinical Research Methods″ separately stipulated for procedures, etc. related to applications for changes.

③ Memorandum

Memorandums are prepared not to change the protocol contents, but to unify the interpretation of the contents and to alert the investigators. The Memorandum will be issued after confirmation by the Principal Investigator and the Research Office at the time of distribution to the parties concerned.

④ Patient explanation and re-consent at the time of protocol revision/revision

If there are any changes in the study, the investigators and subinvestigators will provide appropriate explanations to the enrolled patients. If a protocol amendments with requirement of the re-consent for the patient in writing was performed, the consent of the patient should be obtained again in writing.

(2) Deviation from protocol, etc.

The principal investigator at each site must not deviate from or alter the protocol without prior agreement by the principal investigator, prior approval from the CRB review, and permission from the administrator of the site. However, this shall not apply to cases where it is medically unavoidable, such as when it is necessary to avoid immediate danger to the patient.

- The principal investigator may deviate from or modify the protocol when such deviation or modification is medically unavoidable, such as to avoid immediate danger to the patient. In such cases, the principal investigator shall record all details and reasons for the deviation or change, and the principal investigator shall report the deviation or change to the principal investigator.
- If the Principal Investigator determines that protocol revision or amendment needs to be considered for deviations, he/she will discuss the matter with the respective investigator(s).
- If this results in a protocol revision or amendment, a notification of the change shall be submitted to the CRB as indicated in XIV-6-2 Protocol Content Change.
- If there are frequent deviations on the central monitoring report, the protocol shall be reviewed as necessary.

XV. Ethical Considerations

Even if patients do not participate in this study, the RAM+DTX combination is the recommended standard of care in the second-line treatment of non-small cell lung cancer, and the potential disadvantages of participating in this study would be the same as those of receiving the same treatment in a clinical practice setting.

XVI. Payment and Compensation Related to the Clinical Trial

XVI-1 Insurance coverage and description

Join

<If you are a member, what does it include?>

Indemnity insurance, compensation

XVI-2 Non-insurance coverage and its contents

None

XVII. Handling and storage of records (including data)

The Principal investigator (Head of the clinical trial)

After decommissioning the EDC system, the principal investigator will retain the information entered into the eCRF on a DVD-ROM or other electronic media for five years from the date of completion of the study. When the information is destroyed, the DVD-ROM should be shredded or otherwise destroyed so that the data cannot be read.

Principal investigators

The principal investigator or subinvestigator will prepare records (including entries in the medical record) regarding the following matters and keep them for at least five years from the date of completion of this study. (1) The investigator or subinvestigator shall make a record of the following matters (including entry

in the medical record) and retain it for at least five years from the date of completion of this research. When amending such records, the principal investigator shall record the name of the amender and the date of the amendment, and retain them together with the amended records. When destroying the information, the materials shall be shredded or otherwise destroyed so that the contents or data are unreadable.

- Date, time and place of use of pharmaceuticals, etc.
- Correspondence Table
- Matters related to medical treatment and examination of subjects of specific clinical research
- Matters Related to Participation in Specific Clinical Research

In addition, the principal investigator shall retain the following documents for at least five years from the date of completion of the study

(1) Research protocol, implementation plan, documents pertaining to the explanation to the subject of the specified clinical research and his/her consent, summary report, and other documents or their copies (including eCRF copies) prepared by the principal investigator in accordance with the enforcement regulations of the Clinical Research Act.

(2) Documents received from the approved clinical research review committee pertaining to the review opinion services.

(iii) Documents concerning monitoring and audits (limited to cases where audits are conducted) (iii) Documents related to monitoring and audits (only when audits are conducted)

(4) Source documents, etc.

(5) Contracts related to the implementation of clinical research (excluding those related to the provision of funds from drug manufacturers and distributors, etc.)

(6) Documents describing the outline of drugs, etc. to be used in this research and records of the management of drugs, etc.

(7) Documents necessary to conduct this research.

Even if the specified clinical research is no longer continued at one institution during the continuation of the multicenter collaborative research, the person who was the principal investigator at the institution shall retain the records for five years from the date the research was terminated (five years counting from the date the entire research was terminated).

If the Principal Investigator ceases to belong to the Performing Medical Institution before the end of 5 the specified clinical research, the Principal Investigator shall designate a person from among those who belong to the Performing Medical

Institution to preserve the records.

XVII-1 Whether or not samples and information are provided to other institutions

Yes

XVII-2 Methods of storage and disposal of samples and information

Retain until the later of five years after completion or discontinuation of the study or three years after the date on which the final publication of the study results is reported.

XVIII. Duration of Clinical Research

Enrollment period: 22 months (November 7, 2019 (date of enrollment in jRCT) to August 2021)

- However, protocol revision procedures are not required for registration extensions of 6 months or less.

Observation period: 9 months (August 2021 - May 2022) from the end of the last case enrollment.

Study duration: 41 months (November 2019 - March 2023)

(the date the summary report was published in jCRT))

XIX. Publication of Information on Clinical Research

XIX-1 Recording and publication in the database maintained by the Ministry of Health, Labour and Welfare ("jRCT" (Japan Registry of Clinical Trials))

Yes

URL: https://jrct.niph.go.jp/

XIX-2 Agreements with funded drug manufacturers and distributors regarding the content and timing of publication of clinical research results

None

XX. Quality Control and Quality Assurance

XX-1 Monitoring Methods

Monitoring includes central monitoring based on data entered into the EDC and monitoring conducted at facility visits.

Monitoring shall be conducted in accordance with the ″Procedures for Conducting Monitoring.

・ Central Monitoring

As a rule, central monitoring is conducted twice a year to ensure that the study is being conducted safely and in accordance with the protocol and that data are being collected accurately.

A central monitoring report prepared by the CRO that manages the data will be submitted to the principal investigator for review.

Monitoring Items

(1) Status of Achievement of Accumulation

(2) EDC input status

(3) Eligibility

(4) Pretreatment background factors

(5) Under study treatment/discontinuation, reason for discontinuation

(6) Protocol deviations

(7) Serious adverse events

(8) Adverse events

(9) Other issues related to study progress and safety

・ monitoring

In principle, monitoring will be conducted twice for each site for the purpose of confirming matters that may affect appropriate implementation. The person in charge of monitoring will submit a ″Report on Monitoring Results (Form 3)″ to the principal investigator. In addition, a copy of the report shall be submitted to the principal investigator.

Monitoring Items

① Obtaining written consent
② Serious Adverse Event Reporting Documents Retention Status

XX-2 Audit

In this study, an audit will be conducted. The audit will be conducted independently of normal monitoring and other quality control operations.

XXI. Matters necessary for the proper conduct of clinical research

XXI-1 Provision of Research Funds by Manufacturers and Distributors of Pharmaceuticals to This Trial

Yes

Research funding is provided by Eli Lilly Japan K.K. under a contract with Nagoya University.

XXII. Clinical Research Implementation Structure

(Listed in the Appendix of the Research Protocol)

XXIII. Release of Study Results

The main published paper will be submitted to an English journal after final analysis.
In principle, the first author of the main paper of the research content will be the clinical trial office investigator. and the corresponding author of that will be the Principal Investigator(Head of the clinical trial). Thereafter, the principal investigator of each participating institution or a person designated by the principal investigator of each participating institution will be selected as a co-author in the order of the number of enrollments in accordance with the principles of the submission rules for papers, and last author will be the secretariat and the department head of the principal investigator's institution, in that order. The first author and co-authors for publication will be determined by the principal investigator (Head of the clinical trial) with reference to the number of enrollments in the study.

Conference presentations will also be made on the content of this study. The principal investigator (Head of the clinical trial) will determine the presenter(s) with reference to the number of participants enrolled in the study.

XXIV References

1. *National Cancer Center, Cancer Information Service, Cancer Registry and Statistics.*
Rapp, E., et al., *Chemotherapy can prolong survival in patients with advanced non-small-cell lung cancer--report of a Canadian multicenter* J Clin Oncol, 1988. **6**(4): p. 633-41.
3. Hanna, N., et al., *Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with* J Clin Oncol, 2004. **22**(9): p. 1589-97.
4. Shepherd, F.A., et al., *Erlotinib in previously treated non-small-cell lung cancer.* N Engl J Med, 2005. **353**(2): p. 123-32.
5. Shepherd, F.A., et al., *Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer* J Clin Oncol, 2000. **18**(10): p. 2095-103.
Fossella, F.V., et al., *Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung The TAX 320 Non-Small Cell Lung Cancer Study Group*. 18(12): p. 2354-62.
7. Garon, E.B., et al., *Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial.* The Lancet, 2014. **384**(9944): p. 665- 673.
8. Yoh, K., et al., *A randomized, double-blind, phase II study of ramucirumab plus docetaxel vs placebo plus docetaxel in Japanese patients with stage IV non-small cell lung cancer after disease progression on platinum-based therapy.* Lung Cancer, 2016. **99**: p. 186-93.
9. Gandhi, L., et al. *Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer.* n Engl J Med, 2018. **378**(22): p. 2078-2092.
10. Socinski, M.A., et al. *Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC.* New England Journal of Medicine, 2018. **378**(24): p. 2288-2301.
11. *Lung Cancer Practice Guidelines.* 2018.