Randomized phase II study of **C**arboplatin + pac**L**itaxel + b**E**vacizumab or cispl**A**tin + pemet**R**exed + bevacizumab in patients with previously untreated locally advanced or metastatic non-squamous non-small cell lung cancer

CLEAR study

Protocol

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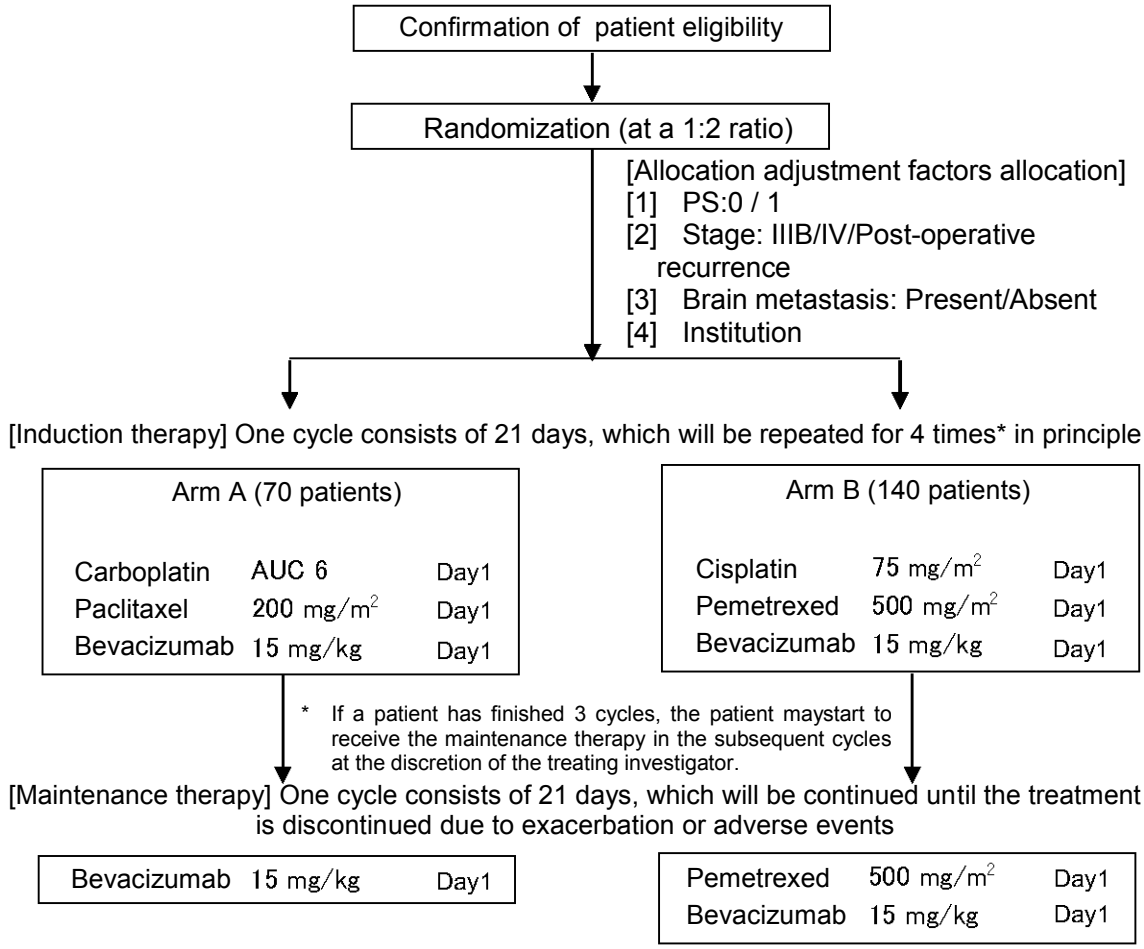
0. Synopsis

Protocol title:
A randomized phase II study of carboplatin+paclitaxel+bevacizumab combination therapy and cisplatin+pemetrexed+bevacizumab combination therapy in patients with untreated advanced/recurrent non-squamous non-small cell lung cancer

Study method: Open-label, randomized, comparative phase II study with central registration



[Figure 1] Study design

Objective:

Combination therapy with carboplatin+paclitaxel+bevacizumab and combination therapy with cisplatin+pemetrexed+bevacizumab will be compared for efficacy and safety in patients with untreated advanced/recurrent non-squamous non-small cell lung cancer.

Primary endpoint: Progression free survival (PFS) by central radiographic assessment

Secondary endpoints: Overall survival (OS), tumor response (response rate, disease control rate, duration of response, time to treatment failure), safety profile

Study population:
[Inclusion criteria]
Patients who fulfill all of the following are eligible to enter the study. Both sexes will be included in the study.

(1) Patients who have been histologically and cytologically diagnosed with non-squamous non-small cell lung cancer (patient with mixed histology will be categorized into the predominant histological type. However, those that include small cell cancer must not be registered)
(2) Patients with Stage IIIB/IV or post-operative recurrent cancer who have not been treated with chemotherapy and are not indicated for radical radiotherapy (patients who have undergone adjuvant chemotherapy and experienced relapse in ≥48 weeks after the last dose, and have not undergone the 1st line therapy after the relapse may be registered. Adjuvant chemotherapy with uracil/tegafur (UFT) will be excepted from the restriction on the time to recurrence.)
(3) Patients who are negative for epidermal growth factor receptor (EGFR) mutation (Exon 19 deletion or Exon 21 L858R) and negative or unknown for anaplastic lymphoma kinase (ALK) fusion gene
(4) Patients with ECOG Performance Status (PS) 0-1
(5) Patients with measurable lesions per Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1
(6) Patients aged between 20 and 74 years at the time of informed consent
(7) Patients with functional bone marrow, liver, and kidney as indicated by the following indices of organ functions:

1)	Neutrophil count	≥1,500 /mm^3
2)	Platelet count	≥100,000 /mm^3
3)	Hemoglobin	≥9.0 g/dL
4)	AST/ALT	≤2.5-fold the upper limit of normal
5)	Total bilirubin	≤1.5 mg/dL
6)	Serum creatinine or estimated CCr	≤1.5 mg/dL or ≥50 ml/min
7)	Urinary protein	≤1+ or <1.0g/24 hours
8)	PT-INR	≤1.5 (except patients on prophylactic anticoagulation therapy)
9)	SpO_2	≥90%

(8) Patients for whom the following periods of time has elapsed after the last therapy as of the scheduled date to start the study treatment
    1) Radiotherapy
        • ≥2 weeks after the last radiation to parts other than the chest
    2) Surgery/Procedure (including pleurodesis, thoracic drainage)
        • ≥4 weeks after the day of surgery
        • ≥2 weeks after the day of procedure (the day of pleurodesis, removal of thoracic drainage)
        • ≥4 weeks after the day of surgical procedure for brain metastasis
(9) Patients whose life expectancy is ≥90 days after the day of registration
(10) Patients who have been fully informed of the details of the study before registration and then provided written informed consent in person

[Exclusion criteria]
Patients who meet any of the following criteria will be excluded from the study.

(1) Patients who have been treated with pemetrexed, paclitaxel, or bevacizumab
(2) Patients who have experienced hemoptysis of ≥2.5 mL within 3 months or with such

complication
(3) Patients who have previously received radical or palliative radiation therapy to the chest
(4) Patients whose radiographic examinations indicate apparent tumor infiltration to the pulmonary hilar vessels, heart and great vessels
(5) Patients with exposed tumor in the central airway up to the segmental bronchi (patients with suspected exposed tumor must undergo brochoscopy)
(6) Patients whose radiographic examinations indicate apparent cavity in the lung lesions
(7) Patients with clinically significant infections
(8) Patients with fever (≥38°C)
(9) Patients with serious complication (cardiovascular disease, interstitial pneumonia, poorly-controlled diabetes etc.)
(10) Uncontrolled ascites, pleural effusion, pericardial fluid
(11) Patients with active multiple primary cancer
* Except carcinoma in situ considered to have been cured by local treatment or diseases equivalent to intramucosal carcinoma
(12) Patients with history of multiple primary cancer within 5 years
* Except non-melanoma skin cancer or cervical cancer, thyroid gland cancer, early-stage gastric cancer, and early-stage colon cancer
(13) Patients with serious allergy to drugs
(14) Patients with active peptic ulcer
(15) Patients complicated with gastrointestinal perforation or such history within 1 year prior to the registration
(16) Patients with complication or history of intestinal diverticulitis, inflammatory intestinal disease (ulcerative colitis, Crohn's disease etc.)
(17) Patients with active hepatic disease (viral hepatitis, alcoholic hepatitis, autoimmune hepatitis, hepatic cirrhosis)
(18) Patients complicated with arterial/venous thromboembolism, or with a history of arterial thrombosis or serious venous thrombosis within 1 year
(19) Patients with poorly-controlled hypertension (roughly defined by systolic pressure of ≥150 mmHg or diastolic pressure of ≥100 mmHg despite treatment with oral antihypertensives)
(20) Patients who currently use or have recently (within 10 days prior to the start of bevacizumab) used aspirin (>325 mg/day) or clopidogrel (>75 mg/day). Patients who currently use or have recently (within 10 days prior to the start of bevacizumab) used oral or non-oral anticoagulants or thrombolytic agents. Prophylactic use of anticoagulants is allowed.
(21) Patients with symptomatic brain metastasis or who needs anti-edematous agents such as steroids to control the symptoms of brain metastasis
(22) Pregnant women, breast-feeding women or patients who are not willing to use contraception
(23) Patients who have been considered ineligible for any other reason by the treating investigator for the safe conduct of the study

Planned sample size: 2 arms: 210 patients (Arm A, 70 patients; Arm B, 140 patients)
Planned study period: May 2014 to April 2018 (48 months)
(Only survival outcome will be investigated after the end of follow-up period)
After the end of follow-up period, none of the observations/tests and reports (including reports of adverse events) will be necessary. In April 2018, the final survival outcome will be investigated by the method instructed by the Study Secretariat.
Planned registration period: May 2014 to April 2016 (24 months)
Planned follow-up period: 22 months after the registration of last patient
Planned time to investigate the final survival outcome April 2018

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1. Objective

Combination therapy with carboplatin+paclitaxel+bevacizumab and combination therapy with cisplatin+pemetrexed+bevacizumab will be compared for efficacy and safety in patients with untreated advanced/recurrent non-squamous non-small cell lung cancer.

Primary endpoint: Progression free survival (PFS) by central radiographic assessment

Secondary endpoints: Overall survival (OS), tumor response (response rate, disease control rate, duration of response, time to treatment failure), safety profile

2. Background and Rationale of Study Plan

2.1 Target disease

In Japan, more than 50,000 people annually die from lung cancer, which is the No.1 cause of death by cancer. The number of death is ever increasing. Lung cancer is categorized into two types: non-small cell lung cancer and small-cell lung cancer. The former comprises ≥80% of lung cancer. It is further categorized histologically into squamous cancer, adenocarcinoma, and large cell carcinoma. The half of non-small cell lung cancer is advanced at Stage IIIB/IV at the time of diagnosis[1]. It is mainly treated by drug therapy. Therefore, improving the efficacy of drug therapy for non-small cell lung cancer is essential to improve the overall treatment outcome of lung cancer.

2.2 Rationale for study population

In a phase II study (AVF2107 g study)[2] of bevacizumab (BEV), an angiogenesis inhibitor targeting human vascular endothelial growth factor (VEGF), in combination with the standard platinum-based combination therapy in patients with unresectable advanced/recurrent non-small cell lung cancer, hemoptysis, a life-threatening adverse event, occurred in 9.1% of the patients. Examination of the risk of hemoptysis revealed that squamous cancer is an independent risk factor of hemoptysis. Therefore, in subsequent studies that involve the use of BEV, patients to receive the drug are limited to those with non-small cell lung cancer except squamous cancer (ie, non-squamous non-small cell lung cancer). Meanwhile, pemetrexed (PEM) was found to be effective to non-squamous non-small cell cancer in studies as a first line therapy, maintenance therapy, and second line therapy (JMDB study[3], JMEN study[4], and JMEI study[5], respectively). The Japanese Guideline for Diagnosis and Treatment of the Lung Cancer (2013 Revision)[6] recommends PEM for the treatment of non-squamous non-small cell lung cancer. Since both BEV and PEM will be used in this study, the target patients will be limited to patients with non-squamous non-small cell lung cancer for the above reason.

Mutation (exon 19 deletion or exon 21 point mutation) of epidermal growth factor receptor (EGFR) gene is observed in 30-40% of Asian patients including Japanese[7] with adenocarcinoma, which comprises approximately 90% of non-squamous non-small cell lung cancer. Several studies including WJTOG0403 study[8] conducted by West Japan Thoracic Oncology Group (now West Japan Oncology Group) showed that EGFR tyrosine kinase inhibitor (EGFR-TKI) monotherapy had a response rate of over 70% in patients positive for EGFR gene mutation. Studies after studies have since compared EGFR-TKI with the standard platinum-based combination therapy in EGFR gene mutation-positive patients. In OPTIMAL study[9], the median PFS was 4.6 months for combination therapy with carboplatin (CBDCA) and gemcitabine (GEM) and 13.7 months for EGFR-TKI erlotinib (ERL) (HR=0.164 [0.105-

0.256]), indicating a significant prolongation of PFS in the ERL arm. Thus, the efficacy of EGFR-TKI may be superior to that of platinum-based combination therapy in EGFR gene mutation-positive patients. On the other hand, EGFR-TKI has never been shown to be superior to platinum combination therapy in EGFR gene mutation-negative patients. Hence, platinum-based combination therapy is still the standard for these patients. The target population of this study is limited to EGFR gene mutation-negative patients, for whom EGFR-TKI is not a treatment option and alternative treatment options need to be investigated.

Anaplastic lymphoma kinase (ALK) fusion gene is a gene mutation that is reported to be present in 4-5% of adenocarcinoma[10]. In PROFILE1007 study in ALK fusion gene-positive patients[11], the median PFS by chemotherapy (docetaxel [DTX] or PEM) was 3.0 months and the median PFS by an ALK inhibitor crizotinib was 7.7 months (HR=0.49 [0.37-0.64]), indicating a significant prolongation. Thus, ALK inhibitor is superior in efficacy to chemotherapy in ALK fusion gene-positive patients. However, it is not so in ALK fusion gene-negative patients. Therefore, platinum-based combination therapy is still the standard for these patients. The target population of this study is limited to ALK fusion gene-negative patients, for whom ALK inhibitors are not a treatment option and alternative treatment options need to be investigated.

This study will be conducted in patients negative both for EGFR gene mutation and ALK fusion gene, in whom, as stated above, EGFR-TKI and ALK inhibitors are not indicated, although the agents are highly effective to particular patient populations. For these patient populations, platinum-based combination therapy is still considered as the mainstay of treatment. We believe that exploring the most effective treatment method for these populations is highly significant in the improvement of overall treatment outcome for lung cancer patients.

2.3 Standard therapy for the target population

2.3.1 Platinum-based combination therapy

For the treatment of untreated advanced/recurrent non-squamous non-small cell lung cancer, systemic chemotherapy with anticancer agents is selected. Treatment outcome with chemotherapy for non-small cell lung cancer was improved with the introduction of cisplatin (CDDP) in 1980's. However, it was not demonstrated until a metaanalysis[12] in 1995 that chemotherapy in fact prolongs OS compared with best supportive care (BSC). Thereafter, combination therapies with platinum agents (CDDP, CBDCA) and the third generation anticancer drugs introduced in 2000's such as irinotecan (CPT-11), paclitaxel (PTX), DTX, GEM, and vinorelbine (VNR) were proved to be superior to the conventional regimens in terms of OS and other measures. Therefore, platinum-based combination therapy has been the standard therapy to date[13].

2.3.2 Pemetrexed-based combination therapy

PEM proved to be non-inferior to GEM in terms of OS in a phase III study (JMDB study)[3] that compared CDDP+PEM combination therapy with CDDP+GEM combination therapy as a first line in patients with advanced non-small cell lung cancer; MST was 10.3 months with CDDP+PEM combination therapy and 10.3 months with CDDP+GEM combination therapy (HR=0.94 [0.84-1.05]). PEM was significantly more effective than GEM in patients with non-squamous cancer; MST was 11.8 months with CDDP+PEM combination therapy and 10.4 months with CDDP+GEM combination therapy (HR=0.81 [0.70-0.94]). CDDP+PEM combination therapy is accompanied with a significantly lower incidence of Grade ≥3 neutrophil count decreased, anemia, platelet count decreased, as well as a lower frequency of

erythrocyte/platelet transfusion for adverse events. Therefore, the combination is considered to be the standard therapy for non-squamous non-small cell lung cancer. In a phase III study (PARAMOUNT study)[14] conducted overseas that compared the PEM maintenance therapy and placebo in SD or PD patients after induction therapy with CDDP+PEM, PFS from randomization, the primary endpoint, was 4.1 months in the PEM group and 2.8 months in the placebo group (HR=0.62 [0.49-0.79]), indicating a significant prolongation. A significant prolongation was also achieved for OS from randomization, with 13.9 months in the PEM group and 11.0 months in the placebo group (HR=0.78 [0.64-0.96]). The results of this study led to the recognition of the efficacy of PEM maintenance therapy after the first line CDDP+PEM therapy, and to its wide use in the current clinical practice.

PEM has been clinically available in Japan since 2009, and is recommended as an effective treatment for non-squamous non-small cell lung cancer by the Guideline for Diagnosis and Treatment of the Lung Cancer (2013 Revision)[6] based on the results of several studies[4][5] including the aforementioned JMDB study[3].

2.3.3 Bevacizumab-based combination therapy

BEV, a human monoclonal antibody against VEGF, selectively binds to VEGF that promotes neovascularization, thereby inhibiting the binding of VEGF to human vascular endothelial growth factor receptor (VEGFR). BEV thus induces the regression of blood vessels around tumors, decreasing the oxygen and nutrition supplies to the tumors, and eventually exerting its anti-tumor effect[15].

BEV also normalizes the abnormal growth of blood vessels around the tumor to reduce the intratumoral perfusion pressure, facilitating the intratumoral penetration of anticancer agents used in combination with BEV[16]. In a phase III study (E4599 study)[17] conducted mainly in the U.S.A that compared the efficacy and safety of CBDCA+PTX combination therapy, the standard first line therapy for non-small cell lung cancer, and the combination therapy with CBDCA+PTX and BEV (CBDCA+PTX+BEV combination therapy), significant prolongations of OS (the primary endpoint) and PFS (the secondary endpoint) were demonstrated: OS, 12.3 months in CBDCA+PTX+BEV group, and 10.3 months in CBDCA+PTX group, (HR=0.79 [0.67-0.92]); PFS, 6.2 months in CBDCA+PTX+BEV group, and 4.5 months in CBDCA+PTX group (HR=0.66 [0.57-0.77]). Furthermore, a phase III study (AVAiL study)[18] in Europe that compared CDDP+GEM combination therapy with CDDP+GEM+BEV combination therapy for efficacy and safety, a significant prolongation was confirmed for the primary endpoint, PFS: 6.7 months in CDDP+GEM+BEV group, and 6.1 months in CDDP+GEM group (HR=0.82 [0.68-0.98]).

With a purpose to test the reproducibility of E4599 study results, a phase II randomized comparative study (JO19907 study)[19] was conducted in Japan to compare CBDCA+PTX combination therapy and CBDCA+PTX+BEV combination therapy in patients with non-squamous local advanced/metastatic or post-operative recurrent non-small cell lung cancer. The study results indicated a significant prolongation for the primary endpoint, PFS, with 6.9 months in the CBDCA+PTX+BEV group versus 5.9 months in the CBDCA+PTX group HR=0.61[0.42-0.89]). A favorable result was also shown for the response rate, with 31.0% in the CBDCA+PTX group versus 60.7% in the CBDCA+PTX+BEV group (P=0.0013). These outcomes compare favorably with those observed in overseas clinical studies. Based on these results, BEV in combination with platinum-based combination therapy is now positioned as the standard therapy for the disease, recommended by the NCCN Clinical Guideline[20] in the U.S.A and the Guideline for Diagnosis and Treatment of the Lung Cancer (2013 Revision)[6] in Japan.

2.3.4 PEM+BEV Combination therapy

An overseas phase III study (AVAPERL study) demonstrated the effectiveness of CDDP+PEM+BEV combination therapy followed by PEM+BEV maintenance therapy; PFS from randomization was 7.4 months by combination therapy with PEM+BEV and 3.7 months by BEV monotherapy (HR=0.57 [0.44-0.75], ECCO/ESMO 2011[21]). Furthermore, OS from the start of induction therapy, the secondary endpoint, was more favorable for PEM+BEV maintenance therapy compared with BEV monotherapy; PEM+BEV combination therapy, 19.8 months; BEV monotherapy, 15.9 months (HR=0.88 [0.64-1.22], ASCO 2013[22]). This therapy using combined PEM and BEV from induction through maintenance is now considered one of the promising standard therapies. The results of an overseas phase III study (PointBreak study)[23], another attempt to combine PEM and BEV, were reported at Chicago Multidisciplinary Symposium in Thoracic Oncology in 2012. This study was intended to verify the superiority in OS of the study treatment, i.e., CBDCA+PEM+BEV induction therapy and PME+BEV maintenance therapy, over CBDCA+PTX+BEV combination therapy. Although a statistically significant prolongation was confirmed for PFS, no significant difference was noted for OS, the primary endpoint, between the groups; CBDCA + PEM + BEV combination therapy, 12.6 months, CBDCA + PTX + BEV combination therapy, 13.4 months (HR=1.00 [0.86 – 1.16]).

2.4 Rationale for the treatment plan

The results of above AVAPERL study[21] and PointBreak study[23] suggest that the regimen of induction therapy and maintenance therapy containing PEM and BEV can prolong survival compared with the standard therapy. In PointBreak study[23], PFS was prolonged but OS was not prolonged. The platinum agent used in combination is considered as one of the reasons for this outcome. The results of a phase II study[24] of PEM in combination with CDDP or CBDCA in patients with non-small cell lung cancer indicated PFS and OS were more favorable with PEM in combination with CDDP. The regimen used in PointBreak study[23] was a combination of PEM and CBDCA. If the used platinum agent had been CDDP, OS would have possibly been prolonged. AVAPERL study[21] on the other hand used a combination regimen of PEM and CDDP, and the results were a promising one. However, AVAPERL study was intended to compare the regimens for maintenance therapy, and was not designed to verify whether the CDDP+PEM+BEV combination therapy followed by PEM+BEV maintenance therapy investigated in this study was superior to the conventional standard therapy. Therefore, despite the fact that CDDP+PEM+BEV combination therapy is currently the most promising regimen that may prolong survival compared with the standard therapy, no report exists to verify the assumption. We therefore planned a randomized phase II study to compare the already-established standard therapy, CBDCA+PTX+BEV combination therapy, with CDDP+PEM+BEV combination therapy, and to examine the effectiveness and safety of CDDP+PEM+BEV combination therapy.

It is still undecided whether a phase III study with a primary endpoint of OS will be conducted to establish CDDP+PEM+BEV combination therapy as a new standard therapy, because it depends on the result of this study.

2.5 Rationale for sample size

In the first-line therapy for non-small cell lung cancer patients without mutations such as EGFR, a prolongation of approximately 2 months of median PFS is considered a clinically significant

difference that may lead to OS prolongation. Assuming from the results of E4599 study[17] and PointBreak study[23] that the median PFS in Arm A is approximately 5.6 to 6 months and the prolongation of median PFS in Arm B is approximately 2 months, the median PFS in Arm B will be approximately 8 months with a HR of 0.7 to 0.75. Given the mean of this HR, the expected true HR is 0.72. If HR=0.72 is true, it is then expected that the point estimate of HR in this study will be lower than 0.83 observed in PointBreak Study [23] at a probability of ≥80%. The value HR=0.83 is the HR for PFS by CBDCA+PEM+BEV therapy (PEM+BEV for maintenance therapy) in relation to PFS by CBDCA+PTX+BEV therapy (the same therapy as Arm A in this study). The HR is an appropriate index for this study, which is intended to screen the regimens with a superior outcome to the conventional therapy, because the sample size is sufficient to give a HR of 0.83 or less at a satisfactory probability when the true HR of Arm B against Arm A in this study is ≤0.72. With the above setting, the number of required events is approximately 170. In consideration of the annual drop-out rate and the 1:2 randomization, ≥210 patients need to be enrolled. Given that the combination therapy in Arm A is established therapy mentioned in the guidelines in and outside Japan based on the results of two Japanese and overseas studies, (E4599 study)[17] and (JO19907 study)[19], the randomization ratio is determined to be 1:2 with a purpose to increase the data accuracy in Arm B.

3. Criteria/Definition in This Study

3.1 Staging criteria (example)

UICC-TNM Classification (2009) will be used for staging.

Latent cancer	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a or T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a or T1b	N1	M0
	T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a or T1b	N2	M0
	T2a or T2b	N2	M0
	T3	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	Any T	N3	M0
	T4	N2	M0
Stage IV	AnyT	Any N	M1a or M1b

TNM clinical staging (cTNM)

T-primary tumor

TX: Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or by bronchial wash cytology but not visualized by imaging or bronchoscopy

T0: No evidence of primary tumor

Tis: Carcinoma in situ

T1: Tumor 3 cm or less in the greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (for example, not in the main bronchus)

T1a: Tumor 2.0 cm or less in the greatest dimension

T1b: Tumor >2.0 cm and 3 cm

T2: Tumor more than 3.0 cm but 7.0 cm or less or tumor more than 3 cm with any of the following features (T2a)

- Involves main bronchus, 2 cm or more distal to the carina.
- Invades visceral pleura
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T2a: Tumor more than 3 cm but 5 cm or less in the greatest dimension or 3 cm with pleural invasion (PL1, PL2, or PL3 if interlobar)

T2b: Tumor more than 5 cm but 7 cm or less in the greatest dimension

T3: Tumor more than 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung; or separate tumor nodule(s) in the same lobe

T4: Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or separate tumor nodule(s) in a different ipsilateral lobe

N-regional lymph node

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastases

N1: Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension

N2: Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)

N3: Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M-distant metastasis

MX: Distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis

M1a Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural (ipsilateral or contralateral) effusion, malignant pericardial effusion

M1b Distant metastasis (in extrathoracic organs)

*M1 will be described as follows according to the metastatic organs.

Lung	PUL	Bone marrow	MAR
Bone	OSS	Pleura	PLE
Liver	HEP	Peritoneum	PER
Brain	BRA	Adrenal gland	ADR
Lymph node	LYM	Skin	SKI
Other	OTH		

3.2 Adverse event classification

Adverse events/reactions will be assessed according to NCI-CTCAE v4.0/Common Terminology Criteria for Adverse Events v4.0 Japanese JCOG Version.

3.3 Tumor response evaluation criteria

Tumor response will be evaluated per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

4. Eligibility criteria

4.1 Inclusion criteria

Patients who fulfill all of the following are eligible to enter the study. Both sexes will be included in the study.

(1) Patients who have been histologically and cytologically diagnosed with non-squamous non-small cell lung cancer (patient with mixed types will be categorized into the predominant histological type. However, those that include small cell cancer must not be registered)

(2) Patients with Stage IIIB/IV or post-operative recurrent cancer who have not been treated with chemotherapy and are not indicated for radical radiotherapy. Registration of patients who have undergone adjuvant chemotherapy and experienced relapse in ≥48 weeks after the last dose, and have not undergone the 1st line therapy after the relapse is permitted. Adjuvant chemotherapy with uracil/tegafur (UFT) will be excepted from the restriction on the time to recurrence.

(3) Patients who are negative for epidermal growth factor receptor (EGFR) mutation (Exon 19 deletion or Exon 21 L858R) and negative or unknown for anaplastic lymphoma kinase (ALK) fusion gene

(4) Patients with Performance Status (ECOG) 0-1

(5) Patients with measurable lesion per RECIST (ver.1.1)

(6) Patients aged between 20 and 74 years at the time of informed consent

(7) Patients with functional bone marrow, liver, and kidney as indicated by the following the indices of organ functions:

1)	Neutrophil count	≥1,500 /mm^3
2)	Platelet count	≥100,000 /mm^3
3)	Hemoglobin	≥9.0 g/dL
4)	AST/ALT	≤2.5-fold the upper limit of normal
5)	Total bilirubin	≤1.5 mg/dL
6)	Serum creatinine or estimated CCr	≤1.5 mg/dL or ≥50 ml/min
7)	Urinary protein	≤1+ or <1.0g/24 hours
8)	PT-INR	≤1.5 (except patients on prophylactic anticoagulation therapy)
9)	SpO2	≥90%

(8) Patients for whom the following periods of time has elapsed after the last therapy as of the scheduled date to start the study treatment

1) Radiotherapy
   - ≥2 weeks after the last radiation to parts other than the chest

2) Surgery/Procedure (including pleurodesis, thoracic drainage)
   - ≥4 weeks after the day of surgery
   - ≥2 weeks after the day of procedure (the day of pleurodesis, removal of thoracic drainage)
   - ≥4 weeks after the day of surgical procedure for brain metastasis

(9) Patients whose life expectancy is ≥90 days after the day of registration

(10) Patients who have been fully informed of the details of the study before registration and then provided written informed consent in person

4.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study.

(1) Patients who have been treated with pemetrexed, paclitaxel, or bevacizumab
(2) Patients who have experienced hemoptysis of ≥2.5 mL within 3 months or with such complication
(3) Patients who have previously received radical or palliative radiation therapy to the chest
(4) Patients whose radiographic examinations indicate apparent tumor infiltration to the pulmonary hilar vessels, heart and great vessels
(5) Patients with exposed tumor in the central airway up to the segmental bronchi (patients with suspected exposed tumor must undergo brochoscopy)
(6) Patients whose radiographic examinations indicate apparent cavity in the lung lesions
(7) Patients with clinically significant infections
(8) Patients with fever (≥38°C)
(9) Patients with serious complication (cardiovascular disease, interstitial pneumonia, poorly-controlled diabetes etc.)
(10) Uncontrolled ascites, pleural effusion, pericardial fluid
(11) Patients with active multiple primary cancer
    * Except carcinoma in situ considered to have been cured by local treatment or diseases equivalent to intramucosal carcinoma
(12) Patients with history of multiple primary cancer within 5 years
    * Except non-melanoma skin cancer or cervical cancer, thyroid gland cancer, early-stage gastric cancer, and early-stage colon cancer
(13) Patients with serious allergy to drugs
(14) Patients with active peptic ulcer
(15) Patients complicated with gastrointestinal perforation or such history within 1 year prior to the registration
(16) Patients with complication or history of intestinal diverticulitis, inflammatory intestinal disease (ulcerative colitis, Crohn’s disease etc.)
(17) Patients with active hepatic disease (viral hepatitis, alcoholic hepatitis, autoimmune hepatitis, hepatic cirrhosis)
(18) Patients complicated with arterial/venous thromboembolism, or with history of arterial thrombosis or serious venous thrombosis within 1 year
(19) Patients with poorly-controlled hypertension (roughly defined by systolic pressure of ≥150 mmHg or diastolic pressure of ≥100 mmHg despite treatment with oral antihypertensives)
(20) Patients who currently use or have recently (within 10 days prior to the start of bevacizumab) used aspirin (>325 mg/day) or clopidogrel (>75 mg/day). Patients who currently use or have recently (within 10 days prior to the start of bevacizumab) used oral or non-oral anticoagulants or thrombolytic agents. Prophylactic use of anticoagulants is allowed.
(21) Patients with symptomatic brain metastasis or who needs anti-edematous agents such as steroids to control the symptoms
(22) Pregnant women, breast-feeding women or patients who are not willing to use contraception

(23) Patients who have been considered ineligible for any other reason by the treating investigator for the safe conduct of the study

5. Patient registration

(1) Registration procedures

In this study, patients will be registered via a Web registration system.

(2) User ID and Password to be provided in advance

Patient registration requires the User ID and Password to log into the Web registration system. The treating investigator who conducts the registration will be provided with the individual User ID and Password by the Data Center after the approval by the ethics committee (EC) or institutional review board (IRB) and conclusion of the study agreement.

(3) Patient registration

The treating investigator will confirm that the patient meet all of the inclusion criteria and none of the exclusion criteria, and then access the Web registration system via Internet. Patient registration is open 24 hours except during system check or maintenance for system problems. Following the instruction of registration system, the treating investigator will enter the necessary items to register the patient.

Web registration help desk

Data Center

Data Science Division, Development Business Headquarters, EPS Corporation

Data Management Department

6-29 Shinogawamachi, Shinjuku-ku, Tokyo, 162-0814

TEL: 03-5684-7852 (main number)

Mail:prj-cleardc@eps.co.jp

Monday to Friday 9:00-17:00 (Except Saturdays/Sundays/Holidays and December 29 to January 4)

Contact for inquiries on patient inclusion criteria

Study Secretariat

Eri Sugiyama

Hibiki Udagawa

Koichi Goto

Department of Respiratory Medicine, National Cancer Center Hospital East

Mail: esugiyam@east.ncc.go.jp (Sugiyama)
hudagawa@east.ncc.go.jp (Udagawa)

6-5-1 Kashiwanoha, Kashiwa-shi, Chiba-ken, 277-8577 TEL: 04-7133-1111 (main number)

Monday to Friday 9:00-17:00 (Except Saturdays/Sundays/Holidays and December 29 to January 4)

(4) Issue and notification of registration

[1] After the registration, a registration number and the assigned group will be issued/notified.

[2] Registration will be complete when the registration number is issued on the registration

screen after the eligibility is confirmed. After the completion of registration, the registration result confirmation sheet will be printed to confirm the details and must be stored with the medical record etc.

(5) Cautions for registration

[1] Registration after the start of protocol treatment is not allowed with no exception. (significant violation)

[2] Data required for registration are essential and must be true. If any false data registration is found after the registration, the case will be handled as a significant violation. Handling of such patients will be determined by the Study Secretariat, Study Steering Committee, and the Data and Safety Monitoring Committee.

[3] Protocol treatment must not be started before the registration result is available. After the completion of registration, the assigned protocol treatment must be started within 14 days.

[4] If the entered data are insufficient, registration will not be accepted until sufficient entry is made.

[5] If any duplicate registration is found after the registration, the Study Secretariat should be immediately notified of it. In any case of duplicate registrations, the initial information of registration (registration number, assigned group) should be used.

[6] Except those who have withdrawn their consent and refused the use of their data for research, registrations of patients who have once been registered cannot be cancelled.

[7] The body surface area and planned dose of each drug calculated based on the height/weight at the time of registration are provided just for double-check of the values calculated by the treating investigator. The values must be calculated and confirmed at the study institution.

[8] “Day of registration” is the day when the registration result (registration number and assigned group) becomes available. For those who have been determined ineligible, the day will not be “day of registration” but “day of ineligibility determination”

(6) Randomization and allocation adjustment factor

In registration, patients will be randomly allocated to the treatment groups by the allocation program of the Web registration system.

For randomization, the minimization method will be used with the following items as the allocation adjustment factors in order to minimize possible biases between the treatment groups with regard to the factors: [1] PS(0/1), [2] Stage (IIIB/IV/post-operative recurrence), [3] brain metastasis (present/absent), and [4] study institution. The details of random allocation will not be disclosed to investigators of the participating institutions.

6. Protocol treatment

6.1 Protocol treatment

The below shows the manufacturers in Japan of each drug to be used in this study.

Carboplatin

Product name: PARAPLATIN (Bristol-Myers)
Product name: CARBOPLATIN (Nichi-Iko Pharmaceutical Co., Ltd.)
Product name: CARBOPLATIN “NK” (Mylan Seiyaku Ltd.)
Product name: CARBOPLATIN “TYK” (Taisho Pharmaceutical Co., Ltd)
Product name: CARBOPLATIN “Sawai” (Sawai Pharmaceutical Company Limited)
Product name: CARBOPLATIN “Sandoz” (Sandoz)

Paclitaxel

Product name: TAXOL (Bristol-Myers)
Product name: PACLITAXEL “NK” (Nippon Kayaku Co.,Ltd.)
Product name: PACLITAXEL “Mylan” (Mylan Seiyaku Ltd.)
Product name: PACLITAXEL “Sawai” (Sawai Pharmaceutical Company Limited)
Product name: PACLITAXEL “Sandoz” (Sandoz)

Bevacizumab

Product name: AVASTIN (Chugai Pharmaceutical Co., Ltd.)

Cisplatin

Product name: BRIPLATIN (Bristol-Myers)
Product name: RANDA (Nippon Kayaku Co., Ltd.)
Product name: CISPLATIN “Nichi-Iko” (Nichi-Iko Pharmaceutical Co., Ltd.)
Product name: CISPLATIN “MARUKO” (Nichi-Iko Pharma)
Product name: CISPLATIN “Mylan” (Mylan Seiyaku Ltd.)
Product name: PLATOSIN (Pfizer)

Pemetrexed

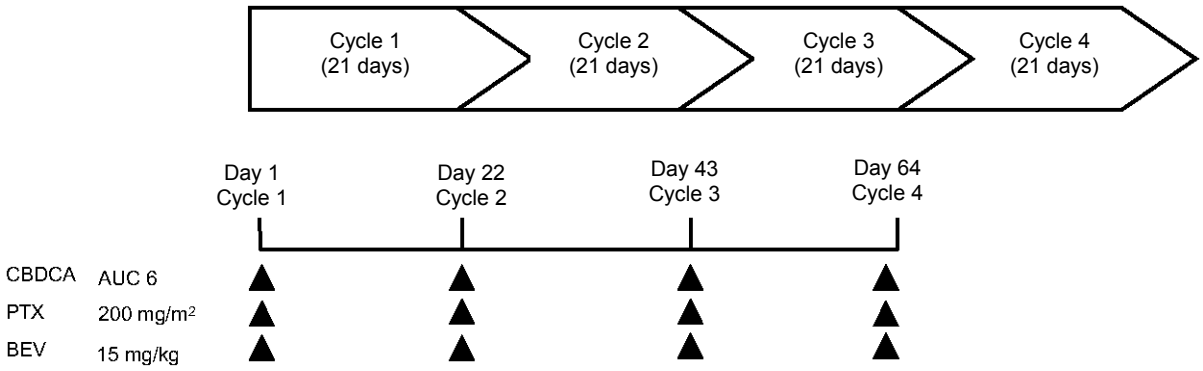
Product name: ALIMTA (Eli Lily Japan K.K.)

6.1.1 Arm A

(1) Induction therapy

A 21-day cycle of therapy with carboplatin+paclitaxel+bevacizumab will be repeated for 4 cycles. When a patient has finished 3 cycles of the induction therapy, the patient may start to receive the maintenance therapy in the subsequent cycle at the discretion of the treating investigator. Each drug should be administered according to its package insert. The dose of each drug after the initial dose will be re-calculated only if the weight of patients has been increased/decreased by ≥10% from that at the time of registration.

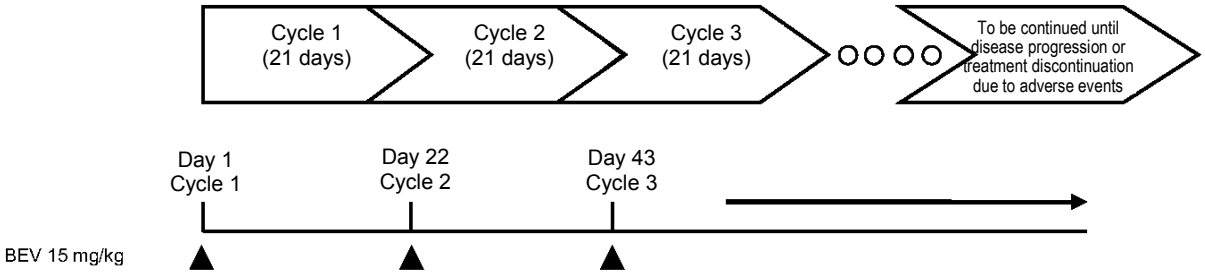
Drug	Dose	Administration schedule
Carboplatin (CBDCA)	AUC 6	Day 1
Paclitaxel (PTX)	200 mg/m^2	Day 1
Bevacizumab (BEV)	15 mg/kg	Day 1



(2) Maintenance therapy

After the induction therapy, a 21-day cycle of bevacizumab monotherapy will be continued until disease progression or treatment discontinuation due to adverse events.

Drug	Dose	Administration schedule
Bevacizumab (BEV)	15 mg/kg	Day 1



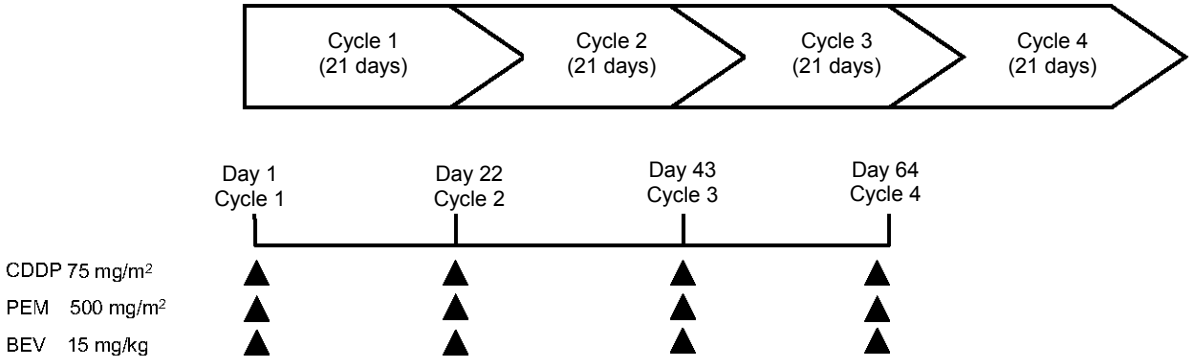
6.1.2 Arm B

(1) Induction therapy

A 21-day cycle of therapy with cisplatin+pemetrexed+bevacizumab will be repeated for 4 cycles.

When a patient has finished 3 cycles of the induction therapy, the patient may start to receive the maintenance therapy in the subsequent cycle at the discretion of the treating investigator. Each drug should be administered according to its package insert. The dose of each drug after the initial dose will be re-calculated only if the weight of patients has been increased/decreased by ≥10% from that at the time of registration.

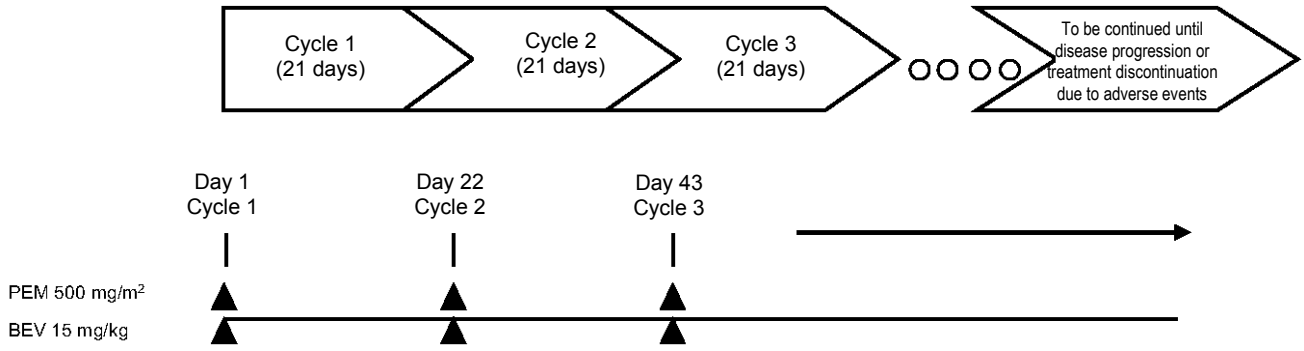
Drug	Dose	Administration schedule
Cisplatin (CDDP)	75 mg/m^2	Day 1
Pemetrexed (PEM)	500 mg/m^2	Day 1
Bevacizumab (BEV)	15 mg/kg	Day 1



(2) Maintenance therapy

After the induction therapy, a 21-day cycle of therapy with pemetrexed+bevacizumab will be continued until disease progression or treatment discontinuation due to adverse events.

Drug	Dose	Administration schedule
Pemetrexed (PEM)	500 mg/m^2	Day 1
Bevacizumab (BEV)	15 mg/kg	Day 1



[Supplementary Information] Therapy with cisplatin+pemetrexed+bevacizumab by short hydration method (Arm B)

Day 1			
Pre-hydration+antiemetics	1	Transfusion of glucose electrolyte solution 500 ml (containing KCl 10 mEq)	60 min
	2	5% glucose solution 50 ml	5 min
		Antiemetic (palonosetron 0.75 mg)	
		Dexamethasone 9.9 mg	
		Famotidine 20 mg	
	3	Transfusion of glucose electrolyte solution 500 ml (containing KCl 10 mEq, MgSO4 8 mEq) or physiological saline solution 500 ml+KCl 10mEq+MgSO4 8 mEq	60 min
PEM	4	Physiological saline solution 100 ml	10 min
		Pemetrexed 500 mg/m^2	
CDDP	5	Physiological saline solution 250 ml	60 min
		Cisplatin 75 mg/m^2	
BEV	6	Physiological saline solution 100 ml	90* min
		Bevacizumab 15 mg/kg	
Diuretics	7	Physiological saline solution 50 ml	5 min
		Furosemide 20 mg	
Post-hydration	8	Physiological saline solution 250 ml	30 min

Day 1-3
Add oral rehydration 1000 ml/day

KCl, potassium chloride; $MgSO_4$, magnesium sulfate

[Yakushiji N, Hiragushi S, Moritani Y: Safety evaluation of cisplatin short hydration regimen, Journal of Japanese Society of Hospital Pharmacists, 48, 753-756 2012. Partially adapted]

6.2 Induction therapy/maintenance therapy for Arm A

6.2.1 Criteria to start induction therapy for Arm A

Therapy should be started after it is confirmed that the subjective/objective symptoms including PS and laboratory values within 7 days prior to the start of therapy meet the eligibility criteria. If the criteria are not met, the start of therapy should be postponed until the criteria are met. If the therapy cannot be started in 14 days after the day of registration, the case will be considered to have discontinued the protocol treatment.

6.2.2 Criteria to start Cycle 2 and later cycles of induction therapy for Arm A

On the day or the day before the start of the subsequent cycle of each drug, it should be confirmed that all of the criteria to start carboplatin+paclitaxel (Table 1) and all the criteria to start bevacizumab (Table 2) are met before the therapy is started. If any of the criteria are not met, the start of therapy should be postponed until the criteria are met. If treatment with carboplatin+paclitaxel cannot be started within 43 days after the start of the previous cycle, the case will be considered to have discontinued the protocol treatment. If the criteria to start carboplatin+paclitaxel (Table 1) are met but the criteria to start bevacizumab (Table 2) are not met, administration of bevacizumab should be suspended and only carboplatin+paclitaxel should be administered. If all of the criteria to start bevacizumab (Table 2) are met on the day of planned subsequent dose, treatment with bevacizumab should be resumed. If the criteria to start carboplatin+paclitaxel (Table 1) are not met but only the criteria to start bevacizumab (Table 2) are met, bevacizumab monotherapy should not be administered and the therapy should be postponed until the criteria to start carboplatin+paclitaxel (Table 1) are met.

[Table 1] Criteria to start carboplatin+paclitaxel

PS	0-1
Neutrophil count	≥1,500 /mm^3
Platelet count	≥100,000 /mm^3
Fever	Not presenting with fever of ≥38°C
AST/ALT	≤2.5-fold the upper limit of normal
Total bilirubin	≤2.0 mg/dl
Creatinine	≤1.5 mg/dl
Pneumonitis	Absent
SpO2	≥90%
Other	Treatment may be postponed if determined necessary by the treating investigator for adverse events other than the above.

[Table 2] Criteria to start bevacizumab

Hemorrhage	No hemoptysis of ≥2.5 ml Other hemorrhage of Grade ≤1
Urinary protein	Grade ≤1
Blood pressure	No uncontrollable hypertension
Other	Treatment may be postponed if determined necessary by the treating investigator for adverse events other than the above.

6.2.3 Criteria for dose reduction and treatment discontinuation of induction therapy for Arm A

If any adverse event is reported in the previous cycle, the dose for the subsequent cycle should be modified or the therapy should be discontinued according to the criteria for carboplatin+paclitaxel dose reduction/treatment discontinuation (Table 3) and the criteria for discontinuation of bevacizumab (Table 4). Once reduced, doses will not be re-increased. The dose of bevacizumab will not be reduced except when the dose is modified due to weight changes. If bevacizumab cannot be administered for 2 consecutive cycles, bevacizumab should be discontinued, and combination therapy with carboplatin+paclitaxel will be administered thereafter. If carboplatin+paclitaxel cannot be administered within 43 days after the start of the previous cycle, the case will be considered to have discontinued the protocol treatment.

[Table 3] Criteria for carboplatin+paclitaxel dose reduction/treatment discontinuation

Item	Start	CBDCA (mg/m^2)	PTX (mg/m^2)
		AUC 6	200
[1] Grade 4 neutropenia	1st time	AUC 5	160
[2] Grade 4 platelet count decreased	2nd time	AUC 4	130
[3] Grade ≥3 platelet count decreased with hemorrhage [4] Grade ≥3 neutropenia with fever of ≥38°C [5] Grade ≥3 non-hematological toxicity (Except anorexia/nausea/vomiting/ hypertension, asymptomatic transient abnormalities in laboratory test) [6] The dose may be reduced due to adverse events other than the above if determined necessary by the treating investigator. The reason should be specified.	3rd time	Treatment discontinuation	

[Table 4] Criteria for discontinuation of bevacizumab

Item	BEV (mg/kg)
	15
[1] Grade ≥2 thromboembolism [2] Grade ≥3 hemorrhage (except hemoptysis) [3] Grade ≥2 hemoptysis (except hemoptysis controllable by oral medicines) [4] Grade ≥3 myocardial infarction, ventricular arrhythmia, sinus bradycardia, sinus tachycardia, heart failure [5] Gastrointestinal perforation [6] Adverse events other than the above requiring treatment discontinuation at the discretion of treating investigator	Treatment discontinuation

6.2.4 Criteria to start maintenance therapy for Arm A

Patients who have completed Cycle 4 of induction therapy with carboplatin+paclitaxel+bevacizumab and whose response has been confirmed to be SD or better at the latest evaluation of the lesion will start the maintenance therapy with bevacizumab in the subsequent cycle. Nevertheless, a patient who has finished 3 cycles of the induction therapy may start the maintenance therapy in the subsequent cycle at the discretion of the treating investigator. Before the maintenance therapy is started, it should be confirmed that all of the criteria to start bevacizumab (Table 2) are met, and the continuation of bevacizumab monotherapy is possible. If any of the criteria are not met, the start of maintenance therapy should be postponed until the criteria are met. If a patient meets the criteria for discontinuation of bevacizumab (Table 4), the case will be considered to have discontinued the protocol treatment.

6.2.5 Criteria to start Cycle 2 and later cycles of maintenance therapy for Arm A

The therapy should be started after it is confirmed that all of the criteria to start bevacizumab (Table 2) are met on the day or the day before the start of the subsequent cycle. If the criteria are not met, the start of therapy should be postponed until the criteria are met. If the therapy cannot be started within 43 days after the start of the previous cycle, the case will be considered to have discontinued the protocol treatment.

6.2.6 Criteria for dose reduction and treatment discontinuation of maintenance therapy for Arm A

The dose of bevacizumab will not be reduced except when the dose is modified due to weight change. If a patient meets the criteria for discontinuation of bevacizumab (Table 4), or if the subsequent cycle cannot be started within 43 days after the start of the previous cycle, the case will be considered to have discontinued the protocol treatment.

6.3 Induction therapy/maintenance therapy for Arm B

6.3.1 Criteria to start induction therapy for Arm B

Therapy should be started after it is confirmed that the subjective/objective symptoms including PS and laboratory values within 7 days prior to the start of therapy meet the eligibility criteria. If the criteria are not met, the start of therapy should be postponed until the criteria are met. If the therapy cannot be started in 14 days after the day of registration, the case will be considered to have discontinued the protocol treatment.

6.3.2 Criteria to start Cycle 2 and later cycles of induction therapy for Arm B

On the day or the day before the start of the subsequent cycle of each drug, it should be confirmed that all of the criteria to start cisplatin+pemetrexed (Table 5) and the criteria to start bevacizumab (Table 2) are met before the therapy is started. If any of the criteria are not met, the start of therapy should be postponed until the criteria are met. If the therapy with cisplatin+pemetrexed cannot be started within 43 days after the start of the previous cycle, the case will be considered to have discontinued the protocol treatment. If the criteria to start cisplatin+pemetrexed (Table 5) are met but the criteria to start bevacizumab (Table 2) are not met, administration of bevacizumab should be suspended and cisplatin+pemetrexed should be administered. If all of the criteria to start bevacizumab (Table 2) are met on the day of

scheduled subsequent dose, treatment with bevacizumab should be resumed. If the criteria to start cisplatin+pemetrexed (Table 5) are not met and only the criteria to start bevacizumab (Table 2) are met, bevacizumab monotherapy should not be administered and the therapy should be postponed until the criteria to start cisplatin+pemetrexed (Table 5) are met.

[Table 5] Criteria to start cisplatin+pemetrexed

PS	0-1
Neutrophil count	≥1,500 /mm^3
Platelet count	≥100,000 /mm^3
Fever	Not presenting with fever of ≥38°C
AST/ALT	≤2.5-fold the upper limit of normal
Total bilirubin	≤2.0 mg/dl
Creatinine	≤1.5 mg/dl
Pneumonitis	Absent
SpO^2	≥90%
Other	Treatment may be postponed if determined necessary by the treating investigator for adverse events other than the above.

[Table 2 (repeated as information)] Criteria to start bevacizumab

Hemorrhage	No hemoptysis of ≥2.5 ml Other hemorrhage of Grade ≤1
Urinary protein	Grade ≤1
Blood pressure	No uncontrollable hypertension
Other	Treatment may be postponed if determined necessary by the treating investigator for adverse events other than the above.

6.3.3 Criteria for dose reduction and treatment discontinuation of induction therapy for Arm B

If any adverse event is reported in the previous cycle, the dose for the subsequent cycle should be modified or the therapy should be discontinued according to the criteria for cisplatin+pemetrexed dose reduction/treatment discontinuation (Table 6) and the criteria for discontinuation of bevacizumab (Table 4). Once reduced, the doses will not be re-increased. The dose of bevacizumab will not be reduced except when the dose is modified due to weight changes. If bevacizumab cannot be administered for 2 consecutive cycles, bevacizumab should be discontinued and combination therapy with cisplatin+pemetrexed will be administered thereafter.

[Table 6] Criteria for cisplatin+pemetrexed dose reduction/treatment discontinuation

Item	Start	CDDP (mg/m^2)	PEM (mg/m^2)
		75	500
[1] Grade 4 neutropenia	1st time	60	400
[2] Grade 4 platelet count decreased	2nd time	50	300
[3] Grade ≥3 platelet count decreased with hemorrhage [4] Grade ≥3 neutropenia with fever of ≥38°C [5] Grade ≥3 non-hematological toxicity (Except anorexia/nausea/vomiting/ hypertension, asymptomatic transient abnormalities in laboratory test) [6] The dose may be reduced due to adverse events other than the above if determined necessary by the treating investigator. The reason should be specified.	3rd time	Treatment discontinuation	

[Table 4 (repeated as information)] Criteria for discontinuation of bevacizumab

Item	BEV (mg/kg)
	15
[1] Grade ≥2 thromboembolism [2] Grade ≥3 hemorrhage (except hemoptysis) [3] Grade ≥2 hemoptysis (except hemoptysis controllable by oral medicines) [4] Grade ≥3 myocardial infarction, ventricular arrhythmia, sinus bradycardia, sinus tachycardia, heart failure [5] Gastrointestinal perforation [6] Adverse events other than the above requiring treatment discontinuation at the discretion of treating investigator	Treatment discontinuation

6.3.4 Criteria to start maintenance therapy for Arm B

Patients who have completed Cycle 4 of induction therapy with cisplatin+pemetrexed+bevacizumab and whose response has been confirmed to be SD or better at the latest evaluation of the lesion will start the maintenance therapy with pemetrexed+bevacizumab in the subsequent cycle. Nevertheless, a patient who has finished 3 cycles of the induction therapy may start to receive the maintenance therapy in the subsequent cycle at the discretion of the treating investigator. When the subsequent cycle is started, it should be confirmed that all of the criteria to start cisplatin+pemetrexed (Table 5) and the criteria to start bevacizumab (Table 2) are met and the continuation of therapy with pemetrexed+ bevacizumab is possible. If the criteria are not met, the start of therapy should be postponed until the criteria are met. If the criteria to start cisplatin+pemetrexed (Table 5) are met but the criteria to start bevacizumab (Table 2) are not met, therapy will be conducted only with pemetrexed. If the criteria to start cisplatin+pemetrexed (Table 5) are not met and only the criteria to start bevacizumab (Table 2) are met, bevacizumab monotherapy should not be started and the therapy should be postponed until the criteria to start cisplatin+pemetrexed (Table 5) are met. Neverthelss, if the criteria for cisplatin+pemetrexed dose reduction/treatment discontinuation (Table 6) are met when the dose of pemetrexed is 300 mg/m^2, bevacizumab monotherapy will be started. If the dose of pemetrexed is reduced in the induction therapy, the maintenance therapy should be started at the reduced dose, which should not be re-increased. If the criteria for discontinuation of bevacizumab (Table 4) are met, pemetrexed monotherapy will be started.

6.3.5 Criteria to start Cycle 2 or later cycles of maintenance therapy for Arm B

On the day or the day before the start of the subsequent cycle, it should be confirmed that all of the criteria to start cisplatin+pemetrexed (Table 5) and the criteria to start bevacizumab (Table 2) are met before the therapy is started. If the criteria to start cisplatin+pemetrexed (Table 5) are met but the criteria to start bevacizumab (Table 2) are not met, therapy will be conducted only with pemetrexed. If the criteria to start cisplatin+pemetrexed (Table 5) are not met but only the criteria to start bevacizumab (Table 2) are met, therapy only with bevacizumab should not be conducted and the therapy should be postponed until the criteria to start cisplatin+pemetrexed (Table 5) are met. If pemetrexed cannot be administered within 43 days after the start of the previous cycle, the case is considered to have discontinued the protocol treatment. Nevertheless, if in the case of pemetrexed discontinuation the patient meets all the criteria to start bevacizumab (Table 2) and none of the criteria for discontinuation of bevacizumab (Table 4), the case will not be considered to have discontinued the protocol treatment, and bevacizumab monotherapy will be administered thereafter.

6.3.6 Criteria for dose reduction and treatment discontinuation of maintenance therapy for Arm B

If any adverse event is reported in the previous cycle, the dose for the subsequent cycle should be modified or the therapy should be discontinued according to the criteria for cisplatin+pemetrexed dose reduction/treatment discontinuation (Table 6) and the criteria for discontinuation of bevacizumab (Table 4). Once reduced, the doses will not be re-increased. If bevacizumab cannot be administered for 2 consecutive cycles, bevacizumab should be discontinued, and pemetrexed monotherapy will be administered thereafter. If the subsequent cycle of pemetrexed cannot be started within 43 days after the start of the previous cycle, the case will be considered to have discontinued the protocol treatment. Nevertheless, if in the case of pemetrexed discontinuation, all of the criteria to start bevacizumab (Table 2) are met

but none of the criteria for discontinuation of bevacizumab (Table 4) are met, the case will not be considered to have discontinued the protocol treatment, and bevacizumab monotherapy will be administered thereafter.

6.4 Scope of protocol treatment

A protocol treatment refers to a treatment provided according to Section 6 Protocol Treatment. The acceptable scope of protocol treatment in the case of treatment changes is shown in the below table.

[Supplementary Information] Protocol treatments acceptable as induction therapy (Arm A, Arm B)

Changes of treatment	Treatment after the change	Acceptability as protocol treatment
Suspend bevacizumab	Arm A) Therapy with carboplatin+paclitaxel Arm B) Therapy with cisplatin+pemetrexed	Yes
Arm A) Suspend carboplatin+paclitaxel Arm B) Suspend cisplatin+pemetrexed	Bevacizumab monotherapy	No
Discontinue bevacizumab	Arm A) Therapy with carboplatin+paclitaxel Arm B) Therapy with cisplatin+pemetrexed	Yes
Arm A) Discontinue carboplatin+paclitaxel Arm B) Discontinue cisplatin+pemetrexed	Bevacizumab monotherapy	No

[Supplementary Information] Protocol treatments acceptable as maintenance therapy (Arm B)

Changes of treatment	Treatment after the change	Acceptability as protocol treatment
Suspend bevacizumab	Pemetrexed monotherapy	Yes
Suspend pemetrexed	Bevacizumab monotherapy	No
Discontinue bevacizumab	Pemetrexed monotherapy	Yes
Discontinue pemetrexed	Bevacizumab monotherapy	No

6.5 Prohibited concomitant medication/therapy

Concomitant use of the following medications/therapy is prohibited throughout the study because they are likely to have impact on the study.

(1) Anti-tumor treatment other than the protocol treatment

Chemotherapy, hormonal therapy, immunotherapy, antibody therapy, radiotherapy, thermotherapy, surgical treatment etc.

Bisphosphonates and anti-RANKL antibody for symptomatic treatment of bone metastasis are allowed.

(2) Investigational drug or unapproved drug

6.6 Criteria to discontinue protocol treatment

Criteria to discontinue protocol treatment for Arm A and Arm B

If a patient meets any of the following criteria, the treating investigator should discontinue the protocol treatment for the patient. For both Arms, subsequent treatment after the protocol treatment discontinuation is not specified.

1) Disease progression
2) Death
3) Treatment discontinuation according to the criteria for treatment postponement, interruption, dose reduction or treatment discontinuation
4) The patient is found after the registration not to be eligible for the study. This does not apply to patients found after the registration to be ALK fusion gene-positive provided that it was unknown at the time of registration whether the patient had ALK fusion gene.
5) Patient's request to discontinue the treatment
6) Criteria for dose reduction are met for 3 times or more
7) The following drugs cannot be administered within 43 days after the start of the previous cycle
   - Arm A induction therapy: carboplatin+paclitaxel
   - Arm A maintenance therapy: bevacizumab
   - Arm B induction therapy: cisplatin+pemetrexed
   - Arm B maintenance therapy: pemetrexed. Nevertheless, if therapy with bevacizumab is feasible, the case will not be considered to have discontinued the protocol treatment, and bevacizumab monotherapy will be continued. If therapy with bevacizumab is not feasible, the case will be considered to have discontinued the protocol treatment.
8) Post-study treatment for non-small cell lung cancer is to be started
9) Grade 4 non-hematological toxicity except asymptomatic transient abnormalities in laboratory test
10) Grade ≥2 pneumonitis (to be distinguished from lung infection)
11) Any other cases considered inappropriate to continue the study by the treating investigator

6.7 Post-study treatment

After protocol treatment discontinuation due to adverse events, no post-study treatment is to be administered until disease progression in principle.

6.8 Handling for treatment discontinuation

(1) In the case of any finding that meets the criteria to discontinue protocol treatment (Section 6.6), the subsequent treatment should be discontinued, and the examinations specified for treatment discontinuation should be performed. This should be entered in EDC, and the discontinuation should be communicated.

(2) Patients in whom disease progression has not been documented at the time of discontinuation due to adverse events should not receive post-study treatment until disease progression. Disease progression found during the post-study observation period should be entered in EDC, and the discontinuation of the study should be communicated.

(3) For patients who have received none of the study drugs, protocol-specified examinations/observation are not required.

Any adverse reaction that has not resolved or returned to the pre-treatment grade on the day of study completion should be followed as far as possible until the adverse reaction resolves or returns to the pre-treatment grade. However, in the case where post-study treatment for non-small cell lung cancer is started or any other cause of the adverse reaction is identified, the adverse reaction should be followed up until the treating investigator considers that the influence of the study has been eliminated, the safety of the patient is sufficiently ensured, and no further follow-up is required.

6.9 Day of protocol treatment discontinuation/completion

The day of protocol treatment discontinuation/completion is defined as the day of death if the patient died during the protocol treatment. Otherwise, it is the day when the treating investigator decides to discontinue the protocol treatment.

7. Expected adverse reactions

For the details of each study drug to be used in this study, the latest package insert should be referred.

(Pharmaceutical and Medical Devices Agency http://www.info.pmda.go.jp/info/iyaku_index.html)

8. Examinations/Laboratory Tests/Evaluations Schedule

Table 9 shows the observation/examination schedule. For the induction therapy, 1 cycle consists of 21 days. The drugs will be administered on Day 1 of each cycle, which will be repeated for 4 cycles*. Thereafter, the drugs will be administered on Day 1 of each cycle as the maintenance therapy, which will be repeated until discontinuation due to disease progression or adverse events.

*When a patient has finished 3 cycles, the patient may start to receive the maintenance therapy in the subsequent cycle at the discretion of the treating investigator

8.1 Patient's informed consent

The day of written informed consent, and the day of re-consent will be recorded at the following timings.

1) Before screening
2) At the time of re-consent

8.2 Subject registration

Eligibility with regard to inclusion criteria and exclusion criteria

Whether eligibility with regard to inclusion criteria/exclusion criteria has been assessed, and the eligibility with regard to each of the inclusion criteria/exclusion criteria will be recorded at screening.

8.3 Demographic investigation/height/weight

The following items will be investigated and recorded at screening: date of birth, sex, height, weight, day of the first diagnosis (day of diagnosis of recurrence in the case of post-operative recurrence), histopathological classification, presence/absence of primary lesion, clinical stage, presence/absence of smoking habit, smoking history, smoking amount, medical history*, concurrent diseases, prior treatment for non-small cell lung cancer (surgical treatment, radiotherapy, neoadjuvant/adjuvant chemotherapy), whether EGFR gene mutation was tested, and the EGFR gene mutation test result, whether ALK fusion gene was tested, the ALK fusion gene test method and test result (if the test has been performed)

*Those considered by the treating investigator likely to have influence on the evaluation in this study

8.4 Vital signs, Performance Status (PS)

(1) Blood pressure, pulse rate, body temperature, SpO_2

Systolic/diastolic pressure, pulse rate, body temperature, date of test will be recorded at the following timings.

[1] Within 7 days prior to the treatment start

[2] During treatment: On the day or the day before the start of each cycle

[3] At the time of treatment discontinuation

(2) PS

PS, and the date of evaluation will be recorded at the following timings.

[1] Within 7 days prior to the treatment start

[2] During treatment: On the day or the day before the start of each cycle

[3] At the time of treatment discontinuation

8.5 Laboratory tests

(1) Hematology

The following items will be tested and recorded: white blood cell count, red blood cell count, hemoglobin, platelet count, neutrophil count, date of sampling.

[1] Within 7 days prior to the treatment start

[2] During treatment: On the day or the day before the start of each cycle

[3] At the time of treatment discontinuation

(2) Blood biochemistry

The following items will be tested and recorded: albumin, total bilirubin, AST, ALT, ALP, electrolyte (Na, K, Ca), BUN, serum creatinine, date of sampling

[1] Within 7 days prior to the treatment start

[2] During treatment: On the day or the day before the start of each cycle

[3] At the time of treatment discontinuation

(3) Urinalysis (qualitative)

The following items will be tested and recorded:protein, glucose, urobilinogen, occult blood, date of sampling

[1] Within 7 days prior to the treatment start

[2] During treatment: On the day or the day before the start of each cycle

[3] At the time of treatment discontinuation

8.6 Evaluation/observation of tumor lesion

(1) Target lesion

The following items will be investigated and recorded: detailed location of lesion, date of test, measurement method, size.

[1] Within 28 days prior to the treatment start

[2] During treatment: Every 6 weeks up to Week 36 (acceptable window ±1 week), every 9 weeks thereafter (acceptable window ±1 week)

[3] At the time of treatment discontinuation

(2) Non-target lesion

The following items will be investigated and recorded: presence/absence of non-target lesion(s), detailed location of the lesion(s), number of non-target lesions within the organ, date of test, examination method

[1] Within 28 days prior to the treatment start

[2] During treatment: Every 6 weeks up to Week 36 (acceptable window ±1 week), every 9 weeks thereafter (acceptable window ±1 week)

[3] At the time of treatment discontinuation

(3) New lesion

The following items will be investigated and recorded during the study: presence/absence of new lesion, detailed location of the lesion, date of test, examination method

(4) Tumor response evaluation

The following items will be evaluated and recorded during the study: response of the target lesion, non-target lesion, overall response

8.7 Best overall response

Best overall response will be evaluated on the day of study completion.

8.8 Adverse events

The following items will be investigated for adverse events listed in (1) to (10) in Section 10 (Adverse Event Reporting) at the following timings.

(1) Name of adverse event, date of onset, severity, worst severity, date of resolution/remission, actions for each regimen, treatment for the event, causal relationship with each regimen, outcome

(2) Investigation period: Course of the event up to the study completion for adverse events that occur between the treatment start and 28 days after the last dose of study drug (course up to the start of post-study treatment for non-small cell lung cancer if such treatment is started)

8.9 Drug Administrations

(1) The following items will be investigated and recorded: day of administration in each cycle, administered doses, presence/absence of suspension, dose reduction, postponement of treatment, discontinuation of a drug and the reasons, and presence/absence of protocol treatment discontinuation as well as the reason.

(2) Investigation period: between the start of treatment and 28 days after the last dose of study drug

8.10 Concurrent therapy

(1) The following items will be investigated and recorded: name of concurrent drug/regimen, treatment period, reason for concurrent therapy

(2) Investigation period: between the start of treatment and 28 days after the last dose of study drug

8.11 Study completion

The reason for study discontinuation will be investigated and recorded at the time of study discontinuation.

8.12 Survival outcome investigation

8.12.1 Survival outcome investigation (until the end of observation period)

If a patient is alive on the day of study completion, the treating investigator will confirm the patient's survival on a regular basis thereafter, and enter the data according to the EDC entry manual. If the patient has been dead, the treating investigator will investigate the day and cause of death. The presence/absence of post-study treatment for non-small cell lung cancer and its details should also be investigated as far as possible.

8.12.2 Survival outcome investigation (April 2018)

Survival outcome will be investigated as far as possible for all subjects who are alive at the day of study completion by the method instructed by the Study Secretariat.

The date of last survival confirmation, date of death, cause of death, post-study treatment will be investigated.

After the end of follow-up period, no observations/examinations or reports (including reports of adverse events) will be necessary. In April 2018, the final survival outcome will be investigated.

[Table 9] Observation/examination schedule

Acceptable window of visit	Before treatment start		Induction therapy (for 4 cycles)				Maintenance therapy (until discontinuation due to disease progression or adverse events)	At the time of treatment discontinuation[c)]
			Cycle 1	Cycle 2	Cycle 3	Cycle 4		
	Within 28 days	Within 7 days	The day before the start or Day 1	The day before the start or Day 1	The day before the start or Day 1	The day before the start or Day 1	Each Cycle The day before the start or Day 1	
General condition								
Blood pressure, pulse rate, body temperature, SpO_2		●		●	●	△	●	●
PS		●		●	●	△	●	●
Laboratory test								
Hematoloy		●		●	●	△	●	●
Blood biochemistry		●		●	●	△	●	●
Urinalysis		●		●	●	△	●	●
Radiography								
Chest/abdominal CT	●		●Every 6 weeks up to Week 36 (acceptable window ±1 week), every 9 weeks thereafter (acceptable window ±1 week)					●
Head CT/MRI	●		○					
Bone RI/PET	●		○					
Abdominal sonography	○		○					
Adverse event								
Observation of adverse events[b)]			○ During the study					

a) Treatment for Arm A or Arm B: One cycle consists of 21 days. On Day 1 of each cycle, the drug will be administered by intravenous drip infusion. The drug should be administered after the patient is confirmed to meet none of the criteria for treatment postponement/suspension/discontinuation.

b) Adverse event: Between the start of treatment and 28 days after the last dose of study drug, or up to the day when treatment discontinuation is decided if it is decided beyond 28 days after the last dose
In the case of protocol treatment discontinuation due to adverse events, post-study treatment should not be administered until disease progression. The adverse event should be followed up until the start of post-study treatment for non-small cell lung cancer, in case it is started.

c) Observations and examinations to be conducted at the time of treatment discontinuation. Before any post-study treatment for non-small cell lung cancer is started, all these observations and examinations should be conducted.

●: Mandatory ○: As necessary according to the routine care △: May be omitted if the maintenance therapy is started without conducting Cycle 4

[Evaluation/observation of tumor lesion]

- Target and non-target lesions should be examined using the same methodology (CT, MRI etc.) and under the same conditions (same slice thickness and contrast medium etc.) as those at the screening unless there is any special reason. Presence/absence of new lesions should also be confirmed preferably by the same method as at the screening.
- The treating investigator should measure and evaluate the target lesions as well as evaluate non-target lesions promptly after the radiographic images are available.

9. Data Collection

9.1 EDC system

Electronic Data Capture (EDC) system will be used in this study to prepare and submit the case report forms. Prior to the use of EDC system, the treating investigator should obtain the individual User ID and Password from the Data Center after the approval by EC or IRB and conclusion of the study agreement, and then register patients and prepare and submit case report forms.

9.2 Preparation of case report form (CRF)

Case report forms should be completed, submitted, modified and read only via EDC system. The treating investigator should enter the data according to the entry manual by the designated deadline.

10. Adverse Event Reporting

10.1 Adverse events that need reporting, serious adverse events, emergency report

10.1.1 Adverse events that need reporting

In this study, the following adverse events that occur during the study, i.e., between the start of treatment and 28 days after the last dose of study drug (or the day when treatment discontinuation is decided if it is decided beyond 28 days after the last dose) should be captured.

(1) Hemorrhage (gastrointestinal tract, lung/upper respiratory tract, urinary system, genitals, central nervous system, and others)
(2) Thromboembolism (arterial, venous)
(3) Perforation (gastrointestinal tract, lung/upper respiratory tract, urinary system, genitals, and others)
(4) Fistula (gastrointestinal tract, lung/upper respiratory tract, urinary system, genitals, and others)
(5) Hypertension
(6) Urinary protein
(7) Complication due to delayed wound healing
(8) Congestive heart failure
(9) Reversible posterior leukoencephalopathy syndrome
(10) Pneumonitis (to be differentiated from lung infections)
(11) Grade ≥3 adverse events except (1) to (10)

If any of the adverse events listed above has occurred, the treating investigator should enter the necessary information into EDC. In addition, the treating investigator should follow up the adverse event for outcome during the study as far as possible and enter the information into EDC.

10.1.2 Serious adverse event

(1) If a serious adverse event has occurred, the principal investigator at the study institution must promptly report it in accordance with the reporting procedure. The principal investigator has the responsibility to submit the following reports in compliance with the rules of the study institution: reporting adverse reactions to the Minister of Health, Labour and Welfare in accordance with the Pharmaceutical Affairs Act; reporting serious adverse events to the head of study institution or regulatory authorities in accordance with the Ethical Guidelines for Clinical Research, and communication of such events to the drug marketing company.

Serious adverse event

[1] Result in death
[2] Life-threatening
[3] Inpatient hospitalization or prolongation of existing hospitalization
[4] Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
[5] Congenital anomaly in the subsequent generations
[6] Other events or reactions considered medically significant

(2) In the case of an unexpected serious adverse event considered to be (definitely, probably, or possibly) related to the protocol treatment during the study, the head of the study institution where the event has occurred should report it to the Minister of Health, Labour and Welfare and make public the EC's/IRB's opinion on the event.

10.1.3 Emergency report

In this study, serious adverse events need emergency reporting.

(1) Seriousness is defined by
[1] Result in death
[2] Life-threatening
[3] Inpatient hospitalization or prolongation of existing hospitalization
[4] Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
[5] Congenital anomaly in the subsequent generations
[6] Other events or reactions considered medically significant

(2) In case a serious adverse event has occurred, the treating investigator should promptly inform the principal investigator of the study institution. If the principal investigator cannot be reached, the treating investigator should act on behalf of the principal investigator.

(3) In case a serious adverse event has been found, the principal investigator of the study institution should promptly report it to the head of the study institution. The principal investigator should enter the necessary information to EDC and submit the first report to the research representative and the Study Secretariat within 72 hours after the adverse event is found.

(4) The principal investigator of the study institution should also enter a detailed course of the event to EDC and make additional reports to the research representative and the Study Secretariat.

(5) In case the principal investigator of a study institution is informed by the research representative of any serious adverse event in any other study institution, the principal investigator should forward the information as a “serious adverse event related to clinical research” to the head of the study institution in compliance with the rule of the study institution.

10.1.4 Adverse events that need reporting by Study Secretariat to Data and Safety Monitoring Committee and study institutions

[1] All deaths during the protocol treatment or within 30 days after the day of last protocol treatment

[2] Grade 4 adverse event

[3] Unexpected Grade 1-3 adverse event requiring hospitalization for ≥24 hours or prolongation of existing hospitalization*

* “Hospitalization for ≥24 hours or prolongation of existing hospitalization” refers to only hospitalization for ≥24 hours/prolongation of existing hospitalization medically required to treat adverse events. Reporting is not required for the following hospitalizations.

- Hospitalization/prolongation of existing hospitalization to observe the course after the resolution/remission of adverse events
- Hospitalization/prolongation of existing hospitalization to lessen the burden for patients who must travel over a long distance to visit the institution
- Any other hospitalization/prolongation of hospitalization that is medically unnecessary

[4] Other adverse events considered medically significant

* This does not apply to events that meet any of the following.

a) Any adverse event (including death) that has occurred beyond 31 days after the day of last protocol treatment and for which causal relationship to the treatment can be ruled out (ie, unlikely related, or not related).

b) Myelodysplastic syndromes (MDS), secondary tumor

c) The following adverse events that need not reporting

Adverse reactions that need not reporting

In this study, adverse events that have established treatment and are thus unlikely to become life-threatening, when the characteristics of the responsible treatment and the condition are taken into consideration, will be exempted from the review by the Data and Safety Monitoring Committee. Specifically, the following adverse events not leading to death need not a review by the Data and Safety Monitoring Committee. Such adverse events will need assessment in the monitoring report.

System organ class (CTCAE ver 4.0)	AE term
Blood and lymphatic system disorders	Anaemia, hypocellular marrow
Gastrointestinal disorders	Constipation
General disorders and administration site conditions	Fever
Laboratory test	ALP increased, CD4 lymphocyte decreased, high cholesterol, CPK increased, forced expiratory volume decreased, lipase decreased, lymphocyte count decreased, neutrophil count decreased, platelet count decreased, serum amylase increased, leukopenia
Metabolism and nutrition disorders	Obesity, anorexia, hyperuricemia, hypoalbuminemia, hypertriglyceridaemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia

Renal and urinary disorders	Chronic kidney disease
Respiratory, thoracic and mediastinal disorders	Sleep apnea
Skin and subcutaneous tissue disorders	Hypohidrosis

10.2 Responsibilities of the data center, Study Secretariat, Data and Safety Monitoring Committee and the research representative

10.2.1 Decisions on the suspension of registration and the necessity of emergency notice to study institutions

When receiving an emergency report of adverse events from the principal investigator of a study institution, the Study Secretariat will forward the report to the research representative, determines the significance of the event and expected extent of influence, and take actions as necessary including the suspension of patient registration (to be communicated to the Data Center and all the participating institutions) and an emergency notice to the participating institutions. Communication by telephone to the Data Center and the study institutions is acceptable, according to the degree of emergency, which should however be followed by a written report (FAX, post, e-mail) as promptly as possible (referred to as emergency notice).

10.2.2 Reporting to Data and Safety Monitoring Committee

If the research representative determines that an adverse event needs an emergency notice, he should immediately report it to Data and Safety Monitoring Committee in writing and request the committee to review the appropriateness of the research representative's opinion on the event and the actions taken for the adverse event.

10.2.3 Notification to investigators at study institutions

If the research representative has reported an adverse event to Data and Safety Monitoring Committee, he should notify all the principal investigators of the opinion/advice of Data and Safety Monitoring Committee.

If the research representative did not report the adverse event to Data and Safety Monitoring Committee, he will notify the reporting principal investigator of his decision in writing.

10.2.4 Review of adverse events at periodic monitoring

At each periodic monitoring, the research representative should carefully review periodic monitoring reports prepared by the Data Center and confirm there is no missing report from the study institutions. The research representative should also confirm that all the reported adverse events have been listed in the periodic monitoring reports. The presence/absence of missing report of adverse events should be specified in the periodic monitoring report, eg, in the group review report field.

10.2.5 Review at Data and Safety Monitoring Committee

Data and Safety Monitoring Committee will review/examine the reports on adverse events, advise the research representative about future actions including the necessity of protocol revision, and report the assessment result, including the recommended action to be taken, to the EC/IRB.

11. Response Evaluation and Definition of Endpoints

11.1 Efficacy endpoints

In this study, tumor response in individual patients will be evaluated per RECIST (version 1.1).

(1) Primary endpoint

Progression free survival (PFS) by central radiographic assessment

Time from the day of registration to the day when progressive disease is determined or death by any cause, whichever is earlier. There will be two types of PFS: PFS determined by the treating investigator (investigator's PFS) and PFS by central radiographic assessment (Independent Review Committee PFS; IRC PFS). IRC PFS will be the primary endpoint.

1) "Progression" includes both radiographic overall response of progressive disease (PD) and clinical progression irrespective of radiographic assessment. For a radiographic progression, the day of radiographic examination will be the day of progression. For a clinical progression irrespective of radiographic assessment, the day of clinical assessment will be the day of progression. In the case where the response is PD according to the response evaluation criteria but the tumor diameter has become very small, and the clinical assessment is "clearly not progression," the radiographic assessment according to the response evaluation criteria must prevail (in such a case, however, clinical assessment should be prioritized in deciding on whether to continue the protocol treatment).
2) Surviving patients without progression will be censored on the day when the absence of clinical progression is confirmed (ie, the day of last confirmed survival). It is not essential to confirm the progression-free status by radiographic examination or biopsy. Progression-free status clinically confirmed at an out-patient visit will be acceptable, but confirmation only via telephone will not be acceptable. If any information of progression is obtained from the medical institution to which the patient has been transferred or referred, the medical information memorandum with the evidence of progression should be obtained and retained. Communication only via telephone is not acceptable in this case as well.
3) If there are patients who have discontinued protocol treatment due to toxicity or their refusal to continue and received post-study treatment thereafter, two methods of censoring will be used for the analyses: one censored on the day when protocol treatment is discontinued or post-study treatment is started and the other not censored.
4) When it is difficult to radiographically determine progression with a single assessment of tumor lesions (which is to be described as "suspected radiographic progression"), continuation of protocol treatment is allowed until the next scheduled tumor assessment for re-testing. If re-testing indicates progression, the day of previous examination that indicated suspected progression on the image should be the day of PFS event. In the case of clinical progression irrespective of radiographic assessment, the day when progression is determined will be the day of PFS event.
5) If a definitive diagnosis of recurrence or new lesions has been made based on pathological biopsy, the day of PFS event will be the day of clinical diagnosis for patients with also a clinical diagnosis of recurrence or new lesions, and the day of

pathological diagnosis for patients with only a diagnosis based on pathological biopsy.

Secondary cancer, metachronal double cancer or metachronal multiple cancer will not be considered as a PFS event or a cause of censoring. Patients with such a condition will be considered to be progression-free until any PFS event occurs.

(2) Secondary endpoint

1) Overall survival: OS

Time from the day of registration to the day of death by any cause.

[1] Surviving patients will be censored on the day of last confirmed survival. Survival confirmed via telephone is acceptable. Such confirmation should be documented in the medical record.

[2] Patients lost to follow up will be censored on the day of last confirmed survival before the patient is lost to follow up.

2) Response rate (RR)

A responder is defined by an eligible subject with a measurable lesion whose best overall response is CR or PR. The response rate refers to the proportion of responders in the analysis set.

3) Disease control rate

A patient with disease control is defined by an eligible subject with a measurable lesion whose best overall response is CR, PR or SD. The disease control rate refers to the proportion of patients with disease control in the analysis set.

4) Duration of response

Time from the day when the response is reported to be CR or PR to the day of confirmed PD. If a patient has died without documented PD, the period of duration will end with the day of death regardless of the cause.

5) Time to treatment failure (TTF)

Time from the day of registration to the day of confirmed PD, the day of death by any cause, or the day of protocol treatment discontinuation, whichever is earlier.

[1] The day of protocol treatment discontinuation is the day when the discontinuation of treatment is decided.

[2] “Progression” includes both radiographic overall response of PD (progressive disease) and clinical progression irrespective of radiographic assessment.

[3] For patients with radiographic progression, the day of PFS event is not the day of radiography indicating “suspected radiographic progression” but the day of subsequent radiographic assessment when a definitive diagnosis is made. For patients with clinical progression or recurrence irrespective of radiographic assessment, the day of PFS event will be the day when clinical progression or recurrence is determined.

[4] If a definitive diagnosis of recurrence has been made based on pathological biopsy, the day of OS event will be the day of clinical diagnosis for patients with a clinical diagnosis of recurrence made before the biopsy, and the day of pathological diagnosis for patients without a clinical diagnosis of recurrence.

[5] Patients on the protocol treatment with no progression will be censored on the day of last confirmed survival. Patients with no confirmed progression after the

completion of protocol treatment will be censored on the last day when the absence of progression is confirmed (last confirmed date of progression-free survival).

Secondary cancer, metachronal double cancer or metachronal multiple cancer will not be considered as a OS event or a cause for censoring. Such a patient will be considered to be progression-free until any event occurs.

6) Incidence of adverse events

Using the number of all treated patients as the denominator, the frequency of the worst grade episodes of the following adverse events will be calculated for each arm. Grades of the adverse events will be determined according to NCI-CTCAE v4.0/Common Terminology Criteria for Adverse Events v4.0 Japanese JCOG Version.

(1) Hemorrhage (gastrointestinal tract, lung/upper respiratory tract, urinary system, genitals, central nerve, and others)
(2) Thromboembolism (arterial, venous)
(3) Perforation (gastrointestinal tract, lung/upper respiratory tract, urinary system, genitals, and others)
(4) Fistula (gastrointestinal tract, lung/upper respiratory tract, urinary system, genitals, and others)
(5) Hypertension
(6) Urinary protein
(7) Complication due to delayed wound healing
(8) Congestive heart failure
(9) Reversible posterior leukoencephalopathy syndrome
(10) Pneumonitis (to be differentiated from lung infections)
(11) Grade ≥3 adverse events except (1) to (10)

Only the above-listed adverse events will be documented in the clinical course page. Incidence of other adverse events will not be calculated in principle unless many cases of a specific adverse event are reported.

11.2 Evaluation method

(1) The schedule of lesion observation/evaluation is provided in Table 9 Observation/Examination schedule.
(2) Tumor response will be evaluated in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) version1.1.
(3) Target and non-target lesions should be examined using the same methodology (CT, X-ray, MRI etc.) and under the same conditions (same slice thickness and contrast medium etc.) as those at the screening unless there is any special reason. The presence/absence of new lesions should also be confirmed preferably by the same method as used at the screening to confirm the absence of lesions.

11.3 Central Radiographic Assessment

Central radiographic assessment will be performed, independently from efficacy evaluation by the treating investigator, in accordance with separately specified procedures. Response

Evaluation Criteria in Solid Tumors (RECIST) version1.1 will also apply to central radiographic assessment so that the evaluation method will be standardized. Central Radiographic Assessment Support Organization will obtain the efficacy evaluation materials (CT, MRI etc.) for all treated subjects from the study institutions. Central radiographic assessment will follow the documented procedures that will be separately provided.

Central Radiographic Assessment Support Organization

Name: Micron, Inc.

Contact: Nihonbashi Nishikawa Building,1-5-3, Nihonbashi, Chuo-ku, Tokyo, 103-0027

12. Identification of Source Data/Direct Access to Source Documents

12.1 Identification of Source Data

For the following items entered only in EDC, the data in EDC will serve as the source data.

(1) Comment by the treating investigator

(2) Administration status: Reason for treatment discontinuation, reason for treatment suspension/dose reduction, reason for treatment postponement

(3) Examination of tumor lesions: Target lesion (detailed location of the lesion, long axis [short axis for lymph node metastasis], non-target lesion [detailed location of the lesion], new lesion [presence/absence of lesion, detailed location of the lesion], tumor response, best overall response

(4) Adverse event: Seriousness, severity of adverse events etc.,
Assessment of causal relationship, outcome, day of resolution/remission

(5) Study discontinuation: Reason for treatment discontinuation, reason for study discontinuation, report of death (causal relationship with the drugs)

(6) Assessment of abnormal changes in laboratory tests

12.2 Direct Access to Source Documents

If case of any monitoring or audit or inspection by the EC/IRB and the regulatory authorities, the head of study institution and the treating investigator should allow the monitors and auditors, upon their request, directly access to all the study-related documents including source documents.

Necessary measures should be taken to preserve the subject's confidentiality during the act of direct access to source documents.

13. Statistical Analysis

13.1 Handling of subjects

Subjects registered in this study will be analyzed for efficacy and safety based on the following analysis sets. If any subject is found to be incompliant with the study protocol, the research representative and the Study Steering Committee will decide whether the subject should be included in the analysis sets before the analysis is performed.

(1) Safety analysis set

Subjects who have received the protocol treatment at least once after treatment allocation will be included in the safety analysis set and analyzed for safety. Subjects who have received the protocol treatment that is different from their allocated treatment will be counted in the arm of their actual treatment.

(2) Full analysis set (FAS)

The FAS consists of patients of the safety analysis set excluding the following patients.

- Subjects who have not been cytologically or histologically confirmed to have non-squamous non-small cell lung cancer.
- Subjects who have not undergone any post-dose efficacy evaluation at all. However, subjects who have died of any cause will be included in the FAS. Subjects who have received the protocol treatment that is different from their allocated treatment will be counted in the arm of their allocated treatment.

13.2 Handling of individual data

Handling of individual data obtained in this study will be determined by the research representative after discussion with the Study Steering Committee and the person responsible for statistical analysis.

13.3 Analysis method

Analyses will be performed by the person responsible for statistical analysis in accordance with the statistical analysis plan that will be finalized before the database lock. The research representative will discuss with the Study Steering Committee and the person responsible for statistical analysis and determine the analysis plan. The below explains the analysis policy.

13.3.1 Subject characteristics

Subject characteristics will be calculated and summarized for each arm.

13.3.2 Efficacy

(1) Primary endpoint: Progression-free survival by central radiographic assessment

Between-group comparison of PFS will be performed in the FAS by a log-rank test. The estimated treatment effect in terms of PFS will be presented with the hazard ratio and 95% confidence interval by Cox proportional hazard model. A survival function will be estimated by Kaplan-Meier method. The median PFS and its 95% confidence interval will be calculated. A graphic presentation will be prepared to visually compare the treatment groups.

(2) Secondary endpoints

1) Overall survival

This will be analyzed in the same manner as PFS.

2) Response rate, disease control rate

The estimate and its 95% confidence interval will be calculated. The confidence interval will be calculated by Clopper-Pearson method.

3) Duration of response

A survival function will be estimated by Kaplan-Meier method. The median duration of response and its 95% confidence interval will be calculated for each treatment group.

4) Time to treatment failure

This will be analyzed in the same manner as PFS.

13.3.3 Safety

Adverse events will be coded using the MedDRA terminology. The number of subjects/events will be counted by SOC/PT. Of these, events for which causal relationship cannot be ruled out will be counted separately as adverse reactions. Changes in laboratory test will be tabulated mainly using the data summary.

13.4 Target sample size

Target sample size: 210 (70 in Arm A, 140 in Arm B)

[Rationale]

In the first-line therapy for non-small cell lung cancer patients without mutations such as EGFR, a prolongation of approximately 2 months of median PFS is considered a clinically significant difference that may lead to OS prolongation. Assuming from the results of E4599 study[17] and PointBreak study[23] that the median PFS in Arm A is approximately 5.6 to 6 months and the prolongation of median PFS in Arm B is approximately 2 months, the median PFS in Arm B will be approximately 8 months with a HR of 0.7 to 0.75. Given the mean of this HR, the expected true HR is 0.72. If HR=0.72 is true, it is then expected that the point estimate of HR in this study is lower than 0.83 observed in PointBreak Study [23] at a probability of ≥80%. The value HR=0.83 is the HR for PFS by CBDCA+PEM+BEV therapy (PEM+BEV for maintenance therapy) in relation to CBDCA+PTX+BEV therapy (the same therapy as Arm A in this study). The HR is an appropriate index for this study, which is intended to screen the regimens with a superior outcome to the conventional therapy, because the sample size is sufficient to give a HR of 0.83 or less at a satisfactory probability when the true HR of Arm B against Arm A in this study is ≤0.72. With the above setting, the number of required events is approximately 170. In consideration of the annual drop-out rate and the 1:2 randomization, ≥210 patients need to be enrolled. Given that the combination therapy in Arm A is established therapy mentioned in the guidelines in and outside Japan based on the results of two Japanese and overseas studies, (E4599 study)[17] and (JO19907 study)[19], the randomization ratio is determined to be 1:2 with a purpose to increase the data accuracy in Arm B.

13.5 Interim analysis

No interim efficacy analysis is planned in this study.

14. Ethical issues

14.1 Statement for compliance with regulatory requirements

This study will be conducted in compliance with the latest Declaration of Helsinki, study protocol, Ethical Guidelines for Clinical Research and ICH-GCP.

14.2 Patient protection

All the investigators involved in this study will conduct the study in compliance with the Declaration of Helsinki.

14.3 Informed consent

14.3.1 Written information

Prior to registration, the treating investigator will provide patients in person with written information approved by the EC (or IRB) and verbally explain the following in detail.

1) This study is a clinical trial.
2) Name of target disease and its stage
3) The study design and rationale (significance, number of patients to be registered, necessity, objective etc.)
4) Details of protocol treatment

   Name of the drugs, administration method, doses to be administered, treatment cycle, overall duration of protocol treatment etc.
5) Expected efficacy and adverse reactions of protocol treatment
6) Cost and compensation

   Treatment to be provided is the same as the treatment of general practice in the sense that the costs incurred by the treatment will be covered by the healthcare insurance; any health damage will be compensated in the same way as with the treatment of general practice
7) The presence/absence of other treatment options and the details in the case the patient does not participate in this study
8) Benefit and disadvantage
9) Planned period of participation and planned number of participants
10) Refusal and withdrawal of consent

    Patients are free to refuse to consent prior to the participation in the study and to withdraw consent that has once been provided, and receives no disadvantage by doing so
11) Human rights protection

    Subjects' personal information will be protected when the result of the study is published.
12) Direct access to documents such as medical records
13) Conflict of interest (research fund and possible conflict of interest)
14) Secondary use of data

    Possible secondary use of data in a manner that precludes any link with the subject's identification

15) Ethical review of clinical study
16) What the patient is required to observe during the study
17) Liberty of asking questions
    The contact information of the treating investigator, the principal investigator of the study institution, and the research representative (or the Study Secretariat) is provided in writing, and patients are free to ask questions about the study and the details of treatment.
18) Name, title, contact information of the treating investigator
19) Other

14.3.2 Consent

Patients should be fully informed of the study and provided with opportunities to ask questions and sufficient time to consider whether or not to participate in the study. Informed consent may be provided on the following day or later if necessary. Written voluntary informed consent should be obtained from patients in person after it is confirmed that patients fully understand the study. The treating investigator will promptly hand the copy of sealed or signed informed consent form to patients and retain the original with the medical records.

14.4 Protection of personal information and subject identification

The study institutions should not reveal the name of subjects to the Data Center. Identification of and inquiries on the registered subjects will be made using the registration number to be issued at the time of registration, date of birth, and subject identification number. Information, such as the name of patients, by which the third parties may directly identify patients without illicit access to staffs or database of the institutions will not be registered to the database of the Data Center. Case data will be exchanged only via EDC in principle between the institutions and the Data Center.

14.4.1 Purpose of personal information use, items to be used, and how it is used

1) Purpose of use

   In this study, subjects' personal information may be used with a purpose of appropriate monitoring among others.

2) Items to be used

   As minimum items required to identify and inquire about subjects, the following will be used: subject identification number (issued by each study institution), the month of birth

   This means that information other than the above, such as the name of patients, will not be disclosed by the study institutions to the Data Center and the research organization of the study. If any such information is inadvertently disclosed, the information should be destroyed regardless of the recording medium, or retained after the information is made unreadable by an appropriate measure such as masking.

3) How it is used

   Personal information of subjects and medical information will be collected and entered into EDC by the treating investigator. Personal information must not be exchanged via e-mail.

14.4.2 Secondary use of data

Data obtained from this study may be used for secondary purposes (e.g., meta analyses) in a manner that precludes any link with the patient's identification only if such use is reviewed and approved by the EC/IRB of the institution.

14.4.3 Structure for protection of personal information

In case the personal information is used, necessary security measures should be taken in accordance with the rules of each study institution in order to minimize the risk of information leakage.

14.4.4 Request of personal information disclosure

If a patient requests the disclosure of private information retained by the Data Center, the treating investigator of the patient will be responsible to answer, in principle.

14.5 Adherance to the study protocol

The treating investigator participating in this study should adhere to the study protocol unless it compromises the safety of patients or human rights.

14.6 Approval by ethics committee/institutional review board

14.6.1 Approval for study participation

Before a study institution can participate in this study, the study protocol and written information for patients should be approved by the EC of the institution or an IRB.

14.6.2 Annual renewal of IRB approval

Whether or not the approval of the study protocol and written information to patients by the ECe or IRB should be renewed annually should follow the rules of each participating institution. Submission of written approval of annual renewal by the IRB is not required.

14.7 Protocol amendment

14.7.1 Classification of protocol amendments

If the protocol is to be amended, the application of protocol amendment should be submitted to the Data and Safety Monitoring Committee for their approval prior to its activation.

Any protocol changes after the approval by the Study Steering Committee will be categorized by the Data and Safety Monitoring Committee to either amendment or revision, which will be processed differently. All the applications by the investigators to the committee will be termed “application for amendment.” The addition of supplemental explanation that does not fall under the category of protocol amendment or revision will be classified as a memorandum. The definition and procedure of each category is described below.

(1) Amendment

Amendments are partial changes of the protocol that may possibly increase the risks for participants in this study or that are related to the primary endpoints of this study. This requires the approval by the Data and Safety Monitoring Committee and each study institution.

(2) Revision

In difference from amendments, revisions are the changes of the protocol which are not likely to increase the risks for participants in this study or that are not related to the primary endpoints of this study. A protocol revision requires the approval by the Data and Safety Monitoring Committee. Prior to the application to the Data and Safety Monitoring Committee, the approval by the research representative and the Study Steering Committee is required.

(3) Memorandum

It is not a change in the protocol but supplemental explanation distributed by the research representative to persons involved in the study to reduce the variability of interpretations of the protocol stipulations or to call attention. Memorandums may be prepared in any format. Memorandum requires the approval by the research representative and the Study Steering Committee prior to its distribution, and reporting to the Data and Safety Monitoring Committee prior to or promptly after the distribution. Memorandum need not be described on the cover page of the protocol.

14.7.2 IRB approval for protocol amendment/revision

If the study protocol or written information to patients is revised with the approval of the Data and Safety Monitoring Committee during the study, the revised study protocol or written information must be approved by the EC or IRB. If the changes made falls under the category of revision but not the amendment, the necessity of the approval by the EC or IRB depends on the rules of each institution. If the amendment is approved by the IRB, the principal investigator of the study institution should send the copy of the written approval by IRB to the Study Secretariat. The written approval by IRB will be retained by the principal investigator while its copy will be retained by the Study Secretariat.

15. Conflict of Interest and Source of Funds

15.1 Conflict of Interest

Planning, conduct, and publication of this study and the analysis of the results arising from this study will be decided by the study organization including the research representative. The sponsor and funder of this study, i.e., Chugai Pharmaceutical, will not be involved in such decisions. The study organization will independently make these decisions. The independence of investigators from Chugai Pharmaceutical is described in the Clinical Trial Agreement (concluded on September 25, 2013) between Chugai Pharmaceutical and the clinical research organization (CRO), i.e., EPS Corporation, and the Research Agreement (concluded on March 13, 2014) between EPS Corporation and the research representative. EPS Corporation conducts this study and is not independent from the investigators. The investigators should properly manage their conflict of interest, complying with the management policy of academic societies and the institutions they belong to, and appropriately disclose it upon request of academic societies or medical journals where the outcome of this study will be published.

15.2 Source of funds and financial relationship

The sponsor of this study is Chugai Pharmaceutical Co, Ltd. This study will be conducted, under the funding of Chugai Pharmaceutical Co, Ltd. based on the outsourcing contract,

based on the agreement between the clinical research organization (CRO), ie, EPS Corporation, and the individual investigators. EPS Corporation will provide participating institutions with the research fund (to be separately specified) according to the number of registered subjects. In this study, the sponsor and funder of this study, Chugai Pharmaceutical Co, Ltd., will not be involved in data collection/management/analysis, or have any influence on the result of this study.

16. Research Cost and Compensation

16.1 Cost for study treatment

This study will be conducted within the scope of usual healthcare insurance coverage. Observation/examinations and the use of drugs during the study will be covered by the health insurance of subjects.

16.2 Compensation for health damage

In case of any health damage attributable to the conduct of this study, the treating investigator and participating institution should take necessary actions to provide appropriate treatment and care. Such treatment will be covered by the health insurance. No monetary compensation will be made.

17. Rights on the Research Outcomes

Rights on the research outcomes arising from this study will be entitled to Chugai Pharmaceutical Co., Ltd. and the research representative. Before Chugai Pharmaceutical Co., Ltd. can use the research outcome, however, the research representative should be informed. The intellectual property right of the drugs manufactured/marketed by Chugai Pharmaceutical Co., Ltd. belongs to Chugai Pharmaceutical Co., Ltd.

18. Monitoring

18.1 Central monitoring

Central monitoring is meant to confirm whether the study has been conducted safely and in compliance with the protocol and that the data have been accurately collected based on the data entered in the case report forms that have been collected via EDC. Central monitoring will be performed twice a year in principle (to be considered since the registration of first subject). Periodic monitoring reports should be prepared and submitted to the research representative. Periodic monitoring reports will be reviewed by the Study Steering Committee and used as a tool to review problems and provide feedbacks.

1) Accrual status: number of registered patients, cumulative, by period, by group, and by institution
2) Patient eligibility: Ineligible patients/possibly ineligible patients by group/institution
3) Pre-treatment demographics by group
4) Patients on protocol treatment, patients who discontinued treatment, reason for discontinuation
5) Protocol deviation by group/institution
6) Serious adverse event by group/institution
7) Adverse event/adverse reaction by group
8) Overall survival, progression-free survival for all registered subjects

18.2 On-site monitoring

On-site monitoring is meant to confirm by source data verification whether the study has been conducted safely and in compliance with the protocol and that the data have been accurately collected. The frequency and written procedure of on-site monitoring will be specified in the Monitoring Procedure to be separately defined.

18.3 Protocol deviation/violation

Protocol deviation refers to administration of drugs, laboratory tests or toxicity/efficacy evaluation that has not been performed in compliance with the requirements specified in the protocol. Violations/deviations will be classified by the Study Steering Committee. The handling of such cases in terms of data collection/analysis will also be determined by the Study Steering Committee.

1) Violation

Protocol deviation that is clinically inappropriate and meets two or more of the following.

[1] Has an influence on the endpoints of the study
[2] Attributable to the treating investigator/institution
[3] Intentional or systematic
[4] Hazardous or a significant extent of deviation

2) Deviation

Deviation that does not fall under (1) violation or (3) acceptable deviation.

If many deviations of a particular type are reported, it is desirable to describe the deviations in the publication of the study.

Deviations will be classified into one of the following.

[1] Deviation that is undesirable and should be reduced
[2] Deviation (unavoidable) that does not deserve proactive effort of reduction
[3] Deviation (clinically appropriate) for which the decision by the treating investigator/institution is approvable.

3) Acceptable deviation

The scope of acceptable deviations will be determined by the Study Steering Committee after the study is completed.

19. Quality Control and Quality Assurance in the Study

19.1 Quality control

The accuracy, consistency, completeness, and reliability of data will be controlled in the following manners.

(1) To help understand the study protocol accurately and to standardize the assessment/evaluation, the principal investigator of the institution should explain the study protocol to the treating investigators on starting the study.
(2) The eligibility of subjects will be confirmed by the Web registration system to exclude those who do not meet the inclusion criteria or meet the exclusion criteria.
(3) Efficacy will be evaluated by central radiographic assessment to eliminate the variability of determination/evaluation.
(4) Central monitoring will be performed to confirm whether the study has been conducted safely and in compliance with the protocol and that the data have been accurately collected based on the data entered in the case report forms that have been collected via EDC.
(5) On-site monitoring at the study institutions will be performed to confirm that the study has been conducted appropriately in compliance with the study protocol, ICH-GCP, and related laws and regulations as well as to confirm the accuracy of data.

19.2 Quality assurance

As part of quality assurance for the study, the auditor will assess whether the study has been conducted in compliance with the study protocol and ICH-GCP in accordance with the written Audit Procedure specified by the Contract Research Secretariat, independently/separately from monitoring and quality control activities for the study.

20. Data Handling and Record Retention

20.1 Preparation/change/correction of case report form

Case report forms will be prepared for all registered subjects. The treating investigator should complete, change, or correct the case report forms in accordance with the EDC Entry Manual.

20.2 Storage and management of electronic data

The Data Center will retain the electronic data entered to case report forms using electronic data processing systems, and perform the following.

1) Document data correction (date of correction, person who has made the correction) if any correction is made to the electronic data.
2) Maintain the security of the systems.
3) Appropriately back up the data.

20.3 Record retention

Records should be retained in accordance with the standard operation procedure of the EC (or IRB).

20.3.1 Treating investigator and study institution

The treating investigator and the study institution should retain documents or records related to the conduct of the study under the instruction of the head of the institution.

20.3.2 Contract research organization (CRO)

The contract research organization will retain documents or records related to the study.

21. Study Organization

21.1 Research representative

Name: Koichi Goto
Title: Head of Department of Respiratory Medicine, National Cancer Center Hospital East
Contact: 6-5-1 Kashiwanoha, Kashiwa-shi, Chiba-ken, 277-8577
TEL: 04-7133-1111 (main number)

21.2 Study Steering Committee

Akira Inoue
Clinical Research, Innovation and Education Center, Tohoku University Hospital

Yoshiko Urata
Department of Respiratory Medicine, Hyogo Cancer Center

Yuki Yamane
Department of Respiratory Medicine, Saitama Cancer Center

Kiyotaka Yo
Department of Respiratory Medicine, National Cancer Center Hospital East

Hiroshige Yoshioka
Department of Respiratory Oncology, Kansai Medical University Hospital

21.3 Person responsible for statistical analysis

Takeharu Yamanaka
Department of Biostatistics, Yokohama City University

21.4 Data and Safety Monitoring Committee (in Japanese alphabetical order)

Chair

Yuichi Takiguchi
Medical Oncology, Chiba University Hospital

Member

Masahiro Tsuboi
Department of Thoracic Surgery, National Cancer Center Hospital East

Takayuki Yoshino
Department of Gastrointestinal Oncology, National Cancer Center Hospital East

21.5 Study secretariat (in Japanese alphabetical order)

Hibiki Udagawa
Department of Respiratory Medicine, National Cancer Center Hospital East

Koichi Goto
Department of Respiratory Medicine, National Cancer Center Hospital East

Eri Sugiyama
Department of Respiratory Medicine, National Cancer Center Hospital East

21.6 Contract Research Secretariat

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

Study secretariat assistant Responsible person: Kaoru Okabe
Clinical Coordinating Department, clinical Coordinating Center

Data Center Responsible person: Manami Tsuchiya
Data Management Department, Data Science Division,
Development Business Headquarters

Monitoring Responsible person: Junko Seki
Clinical Coordinating Department, Clinical Coordinating Center

Audit Responsible person: Katsumi Hirano

Quality Assurance Department

Statistical Analysis Responsible person: Yoshihiro Hikichi

Statistics Analysis Department 1, Data Science Division,
Development Business Headquarters

Medical writing Responsible person: Etsuro Kuramoto

Medical Writing Department, Clinical Development and Regulatory Affairs Center,
Development Business Headquarters

21.7 Central Radiographic Assessment Support Organization

Micron, Inc.

Nihonbashi Nishikawa Building,1-5-3, Nihonbashi, Chuo-ku, Tokyo, 103-0027

21.8 Sponsor

Chugai Pharmaceutical Co., Ltd.

1-1 Nihonbashi-Muromachi 2-chome, Chuo-ku, Tokyo 103-8324

TEL: 03-3273-0866

21.9 Participating institutions

Study (medical) institution	Department	Principal investigator
Hokkaido Hospital	Department of Respiratory Medicine	Toshiyuki Harada
Hokkaido University Hospital	Internal Medicine I	Jun Sakakibara
Iwate Medical University Hospital	Department of Respiratory/ Allergic/Connective tissue disorder medicine	Makoto Maemondo
Sendai Kousei Hospital	Department of Respiratory Medicine	Atsushi Nakamura
Miyagi Cancer Center	Department of Respiratory Diseases	Kana Watanabe
Hirosaki National Hospital	Department of Respiratory Diseases	Hideyuki Nakagawa
Fukushima Medical University Hospital	Department of Respiratory Medicine	Kenya Kanazawa
Chiba Cancer Center	Department of Respiratory Medicine	Masato Shingyoji
Center Hospital of the National Center for Global health and Medicine	Department of Respiratory Medicine	Yuichiro Takeda
Juntendo University Hospital	Department of Respiratory Medicine	Ryo Koyama
Japan Anti-Tuberculosis Association Fukujuji Hospital	Department of Respiratory Medicine	Kozo Yoshimori
National Hospital Organization Tokyo National Hospital	Department of Respiratory Medicine	Atsuhisa Tamura

Kanagawa Cardiovascular and Respiratory Center	Department of Respiratory Medicine	Akimasa Sekine
Yokohama Municipal Citizen's Hospital	Department of Respiratory Medicine	Yukiko Nakamura
Kitasato University Kitasato Institute Hospital	Department of Respiratory Medicine	Noriyuki Masuda
Kyoto Katsura Hospital	Department of Respiratory Medicine, Respiratory Center	Takashi Nishimura
National Hospital Organization Kanazawa Medical Center	Department of Respiratory Diseases	Toshiyuki Kita
University of Fukui Hospital	Department of Respiratory Medicine	Tamotsu Ishizuka
National Hospital Organization Kinki-Chuo Chest Medical Center	Internal Medicine	Shinji Atagi
Japanese Red Cross Kobe Hospital	Department of Respiratory Medicine	Keisuke Sugimoto
National Public Service Mutual Aid Association Otemae Hospital	Department of Respiratory Medicine	Shinichiro Iida
Okayama University Hospital	Department of Respiratory/ Allergic Diseases	Katsuyuki Hotta
National Hospital Organization Iwakuni Medical Center	Department of Respiratory Medicine	Shoichi Kuyama
National Hospital Organization Yamaguchi-Ube Medical Center	Department of Medical Oncology	Tadashi Maeda
National Hospital Organization Matsue Medical Center	Department of Respiratory Medicine	Shuichi Yano
National Hospital Organization Kyushu Medical Center	Department of Respiratory Medicine	Masao Ichiki
National Hospital Organization Kyushu Medical Center	Department of Respiratory Surgery	Sadanori Takeo
Asahikawa Medical University Hospital	Respiratory Disease Center	Yoshinobu Ohsaki
Saitama Cardiovascular and Respiratory Center	Department of Respiratory Medicine	Noboru Takayanagi
Japanese Red Cross Nagoya Daiichi Hospital	Department of Respiratory Medicine	Shiro Nomura
Graduate School of Medical Sciences Medical School, Nagoya City University	Department of Oncology/Immunology	Akio Niimi
Tosei General Hospital	Department of Respiratory/ Allergic Medicine	Tomoki Kimura
Osaka Police Hospital	Department of Respiratory Diseases	Kiyoshi Komuta
National Hospital Organization Toneyama National Hospital	Department of Respiratory Medicine	Masahide Mori
Matsuyama Red Cross Hospital	Department of Respiratory Medicine	Takanori Kanematsu
Hospital of the University of occupational and Environmental Health	Department of Surgery 2	Fumihiro Tanaka
Nagasaki Prefecture Shimabara Hospital	Department of Respiratory Medicine	Akitoshi Kinoshita
Graduate School of Medical and Dental Sciences, Kagoshima University	Department of Respiratory Medicine	Keiko Mizuno

Tohoku University Hospital	Department of Respiratory Medicine	Akira Inoue
National Cancer Center Hospital East	Department of Respiratory Medicine	Koichi Goto
Hyogo Cancer Center	Department of Respiratory Medicine	Miyako Satouchi
Jichi Medical University Hospital	Department of Respiratory Medicine	Ayako Takigami
Osaka University Hospital	Department of Respiratory Medicine	Hiroshi Kida
Saitama Cancer Center	Department of Respiratory Medicine	Yuki Yamane
Matsunami General Hospital	Department of Respiratory Medicine	Takashi Niwa
Showa University Hospital	Department of Medical Oncology	Yasutsuna Sasaki
Niigata University Medical & Dental Hospital	Department of Respiratory Medicine (Internal Medicine II)	Satoshi Watanabe
Shikoku Cancer Center	Department of Respiratory Medicine	Daijiro Harada
Kurashiki Central Hospital	Department of Respiratory Medicine	Toshihide Yokoyama
St. Marianna University School of Medicine	Department of Respiratory Medicine	Naoki Furuya
Hokkaido University	Department of Medical Oncology	Ichiro Kinoshita
Kanagawa Cancer Center	Department of Respiratory Medicine	Harumi Saito
Matsusaka Municipal Hospital	Department of Respiratory Medicine	Osamu Hataji
Niigata Cancer Center Hospital	Department of Respiratory Medicine	Hiroshi Tanaka
Aichi Cancer Center Hospital	Department of Respiratory Medicine	Tatsuya Yoshida

22. Publication of Research Outcome

The research representative will discuss the authorships and the target journals/academic societies with the participating principal investigators in accordance with the arrangement by the study organization.

22.1 Arrangement of authorship for publication/presentation at academic societies

22.1.1 Publication

The authors of literatures on this study will be determined based on the extent of contribution to this study and have to be approved by the Study Steering Committee.

All the co-authors should be those who have reviewed the literature prior to publication and agreed on its contents. If a co-author does not agree on the contents even after discussion, the research representative is allowed to exclude the co-author.

22.1.2 Presentation at academic societies

The presenter will be determined based on the extent of contribution to this study and have to be approved by the Study Steering Committee. In respect of presentation at academic societies, however, the Study Secretariat will be responsible for the preparation and the contents of presentations. In principle, the Study Secretariat will be solely responsible for the communication with the Data Center. No presenter, except the Study Secretariat, is allowed to receive the data collection/analysis result directly from the person responsible for statistical analysis or the Data Center without permission of the Study Secretariat and the representative of the Data Center.

22.1.3 Target journals and academic societies for publication

The research outcome will be presented at influential Japanese/international academic societies.

The reports of such presentation at academic societies will be summarized as literatures and submitted to specialized journals.

23. Planned Number of Registered Patients/Registration Period/Follow-Up Period

Planned sample size: 2 arms: 210 patients (Arm A, 70 patients; Arm B, 140 patients)

Planned study period: May 2014 to April 2018 (48 months)
(Only survival outcome will continue to be investigated after the end of follow-up period)

After the end of follow-up period, no observations/examinations and reports (including reports of adverse events) will be necessary. In April 2018, the final survival outcome will be investigated by the method instructed by the Study Secretariat

Planned registration period: May 2014 to April 2016 (24 months)

Planned follow-up period: 22 months after the registration of last patient

Planned time to investigate the final survival outcome April 2018

24. Special Note

24.1 Independence of Study

The sponsor of this study, Chugai Pharmaceutical Co., Ltd., will not be involved in **the following** so that the independence of the study is ensured:

1) Registration to clinical research information databases
2) Procedures related to the Ethics Committees of participating institutions and contracts
3) Direct verification/audit to the participating institutions
4) Safety information reporting to the Ethics Committee
5) Access to the database of this study
6) Data management and analytical tasks
7) Tasks related to the Data and Safety Monitoring Committee
8) Preparation of the clinical study report
9) Payment of the research cost to the participating institutions

25. Reference

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26. Appendix

- Package insert
- Informed consent form
- Declaration of Helsinki (translated by Japan Medical Association)

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