ONO-4538 Phase 3 Study

A Multicenter, Randomized, Double-Blind Trial in Subjects with Non-Squamous Non-Small Cell Lung Cancer

Clinical Protocol

ONO PHARMACEUTICAL CO., LTD.

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SYNOPSIS

1 Study Objective

To compare the efficacy and safety of ONO-4538 in combination with carboplatin, paclitaxel, and bevacizumab (treatment administered to ONO-4538 group) to placebo in combination with carboplatin, paclitaxel, and bevacizumab (treatment administered to placebo group) in chemotherapy-naïve subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation in a multicenter, randomized, double-blind study.

2 Study Design

A multicenter, randomized, double-blind study

2.1 Overview of Study Design

This study is a multicenter, randomized, double-blind, placebo controlled phase 3 study in chemotherapy-naïve subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation. The study is intended to evaluate the superiority of the ONO-4538 group over the placebo group, with progression-free survival (PFS), based on the Independent Radiology Review Committee (IRRC) assessment, as the primary endpoint.

The study will consist of the screening period, treatment period, and follow-up period. In a double-blind fashion, subjects will be randomized in a 1:1 ratio into either the ONO-4538 group or the placebo group and stratified by PD-L1 expression level (≥ 50% vs 1% to 49% vs < 1% or indeterminate), ECOG Performance Status (0 vs 1), and gender (male vs female).

In the ONO-4538 group, ONO-4538, carboplatin, paclitaxel, and bevacizumab will be administered every 3 weeks. In the placebo group, placebo, carboplatin, paclitaxel, and bevacizumab will be administered every 3 weeks. Subjects will receive ONO-4538 360 mg or placebo in combination with carboplatin (AUC 6), paclitaxel (200 mg/m^2), and bevacizumab (15 mg/kg). In both groups, carboplatin and paclitaxel will be administered for up to 4 cycles and if deemed safe, treatment may continue for up to a maximum of 6 cycles. Even after the completion of treatment with carboplatin and paclitaxel, the investigational product (ONO-4538 or placebo) and bevacizumab will be administered intravenously on Day 1 of each cycle in both treatment groups until RECIST 1.1 defined PD, unacceptable toxicity, or withdrawal of consent. Upon completion of the investigational product and chemotherapy, subjects will enter the follow-up period.

In this study, one interim analysis of PFS among randomized subjects is planned for early stopping in case of superior efficacy, at the time when approximately 82.4% of the target number of events are observed.

An overview of the study design is shown in Figure 2-1.

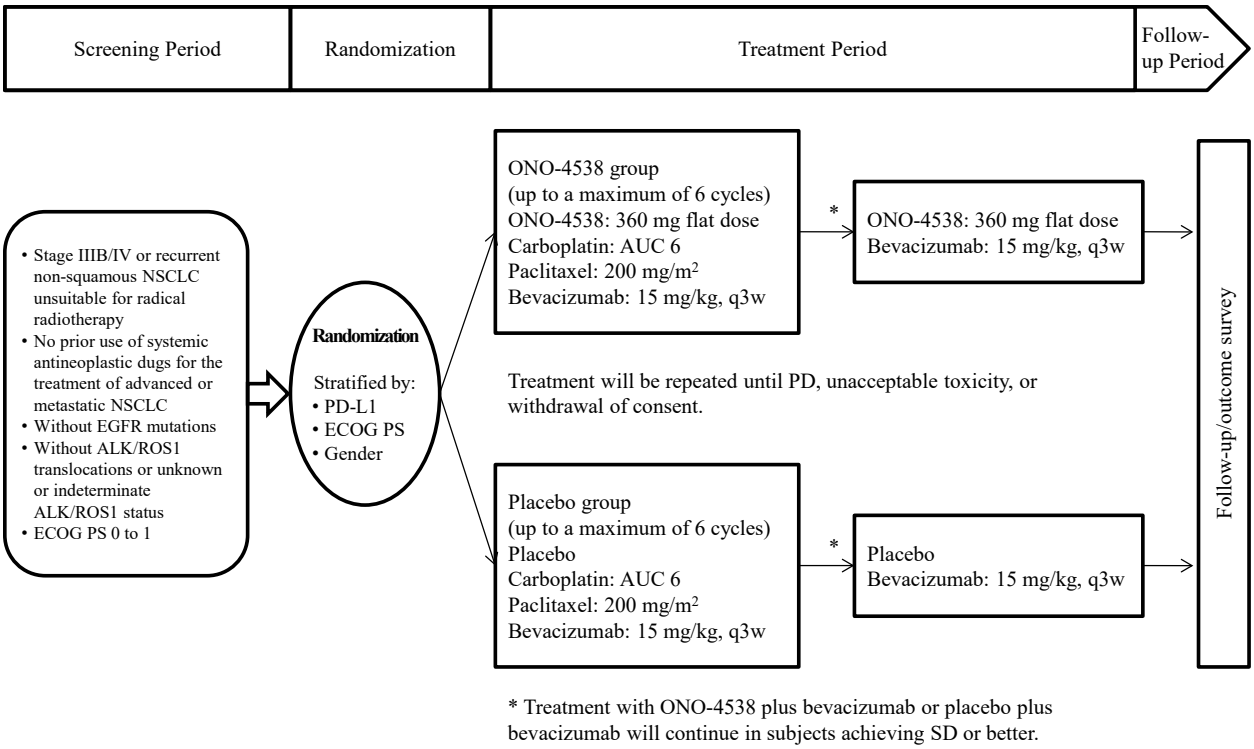

Figure 2-1: Study Design

3 Study Population

3.1 Study Subjects

Chemotherapy-naïve subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation

3.2 Inclusion Criteria

After subjects provide written informed consent before participating in the study, subjects must meet all of following inclusion criteria at the time of randomization. When it has been confirmed that the subject does not meet any of the following criteria from randomization to the first dose of the investigational product, the subject will be withdrawn from the study without receiving any investigational products.

1. Males and females
2. ≥ 20 years of age (at the time of informed consent)
3. Subjects with histologically- or cytologically-confirmed non-squamous non-small cell lung cancer
4. Subjects who received a diagnosis of stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation according to the UICC-TNM Classification (7th edition) with no prior systemic anticancer therapy (including EGFR, ALK and ROS1

inhibitors) given as primary therapy for advanced or metastatic disease.
Prior adjuvant or neoadjuvant chemotherapy is permitted provided the last administration of the prior regimen occurred at least 6 months prior to enrollment.

5. Subjects with at least one measurable lesion by radiographic tumor assessments per RECIST 1.1 criteria; radiographic tumor assessments performed within 28 days of randomization (target lesions may be located in a previously irradiated field if there is documented disease progression after the completion of radiation therapy.)
6. Subjects who are able to provide tumor tissue specimens. If no fresh specimens are available, these will be allowed as archival samples, but they must contain a minimum of 100 evaluable tumor cells. Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections must be submitted for investigational product assignment and biomarker evaluation. The tumor tissue sample may be fresh or archival if obtained within 6 months prior to enrollment, and there was no systemic therapy (eg, adjuvant or neoadjuvant chemotherapy) given after the sample was obtained.
   Tissue must be from a core needle biopsy, excisional biopsy, incisional biopsy, or forceps biopsy. EBUS-TBNA is acceptable if no tissue can be obtained through the above biopsy methods and tumor tissues may be collected by EBUS-TBNA. Fine needle biopsies, biopsies of bone lesions that do not have a soft tissue component, or decalcified bone tumor samples are not acceptable. In addition, cell block is not acceptable.
7. ECOG Performance Status of 0 or 1
8. Life expectancy ≥ 90 days by investigator assessment
9. Women of childbearing potential (including those who have no menses for medical reasons, such as chemotherapy-induced menopause)[#1] must agree to follow instructions for method(s) of contraception[#2] or maintain complete abstinence from the time of informed consent through at least 5 months after the last administration of the investigational product (ONO-4538 or placebo) or at least 6 months after the last administration of bevacizumab, whichever is longer. Women of childbearing potential must agree to discontinue breastfeeding from the time of informed consent through at least 5 months after the last administration of the investigational product or at least 6 months after the last administration of bevacizumab, whichever is longer.
10. Male subjects who have agreed to follow instructions for method(s) of contraception[#2] from the start of administration of the investigational product through at least 7 months after the last administration of the investigational product or at least 6 months after the last administration of bevacizumab, whichever is longer
11. Subjects with percutaneous oxygen saturation of ≥ 94% by pulse oximetry at rest, without oxygen supplementation, within 7 days prior to randomization
12. Latest laboratory values obtained within 7 days prior to randomization must meet the criteria listed below. These values should not reflect granulocyte-colony stimulating factor (G-CSF) or blood transfusion given within 14 days before the test day.
    - WBC ≥ 2000/mm^3
    - Neutrophils ≥ 1500/mm^3
    - Platelets ≥ 100000/mm^3
    - Hemoglobin ≥ 9.0 g/dL
    - AST (GOT) and ALT (GPT) ≤ 3.0 × upper limit of normal (ULN)
    - LDH ≤ 2.0 × ULN
    - Total bilirubin ≤ 1.5 × ULN

- Creatinine ≤ 1.5 mg/dL or creatinine clearance (observed values or estimates calculated by the Cockcroft-Gault formula) > 50 mL/min

13. Subjects who have been fully informed of the nature of the study through the informed consent form by the investigator and gave their consent for voluntary participation in the study

[#1]: Women of childbearing potential are defined as all premenopausal women who have reached menarche and who have not undergone sterilization (including hysterectomy, bilateral tubal ligation, or bilateral oophorectomy). Menopause is defined as amenorrhea for at least 12 successive months in the absence of significant causes. Women who use oral contraceptives or mechanical contraception such as intrauterine devices or barrier methods are regarded as having childbearing potential.

[#2]: Subjects must agree to dual contraception using any 2 of the following methods: vasectomy or condoms in male subjects or male partners, or tubal ligation, contraception pessaries, intrauterine devices, or oral contraceptives in female subjects or female partners.

3.3 Exclusion Criteria

The investigator cannot enroll subjects meeting any of the following criteria at the time of randomization. When subjects meet any of the following criteria between randomization to the first dose of the investigational product, subjects will be withdrawn from the study without receiving any investigational products.

1. Subjects with known EGFR mutations, including deletions in exon 19 and exon 21 (L858R) substitution mutations. All subjects must have been tested for EGFR mutation status. Non-squamous non-small cell lung cancer subjects with unknown or indeterminate EGFR status are excluded.
2. Subjects with known ALK or ROS1 translocations. Subjects with unknown or indeterminate ALK or ROS1 status will be eligible for randomization.
3. Complication or history of severe hypersensitivity reactions to antibody products or platinum-containing compounds
4. Subjects with current or prior ≥ Grade 2 peripheral neuropathy
5. Subjects with residual effects of adverse drug reactions associated with prior treatment or surgery that may have an impact on the safety assessment of the investigational product and/or chemotherapy at the investigator's discretion.
6. Subjects with autoimmune disease or known chronic or recurrent autoimmune disease. Subjects with type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement or skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are acceptable for enrollment.
7. Subjects with contraindications to carboplatin, paclitaxel, or bevacizumab
8. Subjects with current or prior interstitial lung disease or pulmonary fibrosis diagnosed based on radiographic tumor assessments or clinical findings. Subjects with radiation pneumonitis

with fibrosis, which is considered to be stable, and without recurrence are acceptable for enrollment.

9. Subjects with active diverticulitis or symptomatic gastrointestinal ulceration
10. Subjects with multiple cancers (those with completely resected basal cell carcinoma, stage I squamous cell carcinoma, carcinoma in situ, intramucosal carcinoma, or superficial bladder cancer or with a history of other forms of cancer that has not recurred for at least 5 years are acceptable for enrollment.)
11. Subjects with brain or meningeal metastasis. Subjects with metastatic lesions can be enrolled if the metastases are adequately treated with radiotherapy and/or surgery and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) at least 14 days prior to randomization and subjects have no documented evidence of progression confirmed by CT/MRI.
12. Subjects with pericardial, pleural, or peritoneal effusion requiring treatment. In subjects who have recently undergone aspiration, the date of the procedure (or, in the case of drainage, the date of removal of the drain) must be at least 14 days prior to randomization, and there must not be any finding of aggravation of pericardial, pleural, or peritoneal effusion.
13. Subjects with uncontrollable cancer pain
14. Subjects who have a history of transient ischemic attack, cerebrovascular accident, thrombosis, or thromboembolism (pulmonary thromboembolism or deep venous thrombosis) within 180 days prior to randomization
15. Subjects with any of the following uncontrollable or significant cardiovascular disease:
    - Myocardial infarction occurring within 180 days prior to randomization;
    - Uncontrollable angina occurring within 180 days prior to randomization;
    - Congestive heart failure, defined as New York Heart Association (NYHA) functional Class III or IV;
    - Uncontrollable hypertension even if adequately treated (systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 90 mmHg lasting for 24 hours or longer); or
    - Arrhythmia requiring treatment.
16. Subjects who are receiving anticoagulants (except antiplatelet therapy including low-dose aspirin) or have a disease for which anticoagulant therapy is required
17. Subjects with uncontrollable diabetes
18. Subjects who have received systemic adrenocorticosteroids equivalent to prednisone > 10 mg/day (except for temporary use for examination, prophylaxis, or a similar purpose) or immunosuppressants within 28 days prior to randomization
19. Subjects who have received pleurodesis or pericardial adhesion within 28 days prior to randomization
20. Subjects who have had surgery under general anesthesia within 28 days prior to randomization
21. Subjects who have had surgery under local or surface anesthesia within 14 days prior to randomization
22. Subjects who have received radiotherapy within 28 days prior to randomization, who have received stereotactic irradiation for brain metastasis within 14 days prior to randomization or who have received chest radiotherapy or radiopharmaceuticals (except for use of radiopharmaceuticals for examination and diagnosis) within 56 days prior to randomization

23. Subjects who have received radiotherapy for pain relief within 14 days prior to randomization. Subjects who may require palliative radiotherapy within 4 weeks of randomization are strongly encouraged to receive palliative radiotherapy before randomization.
24. Subjects who have received any other unapproved drugs (including investigational treatments, unapproved combination drugs, and drugs with new dosage forms) within 28 days prior to randomization
25. Subjects with systemic infection requiring treatment
26. Prior treatment with ONO-4538 (MDX-1106 or BMS-936558), anti-PD-1 antibody, anti-PD-L1 antibody, anti-PD-L2 antibody, anti-CD137 antibody, anti-CTLA-4 antibody, or any other antibody therapy for regulation of T cells or drug therapies including cancer vaccines
27. Any positive test for HIV-1 antibody, HIV-2 antibody, HTLV-1 antibody, HBs antigen, or HCV antibody
28. Subjects who test positive for HBs antibody or HBc antibody and have detectable HBV-DNA levels despite testing negative for HBs antigen
29. Subjects who are pregnant, breastfeeding, or may be pregnant
30. Subjects who are judged to lack the ability to provide consent for reasons such as dementia
31. Subjects disqualified from participation in the study at the investigator's discretion
32. Subjects who have received a live/attenuated vaccine within 28 days prior to randomization

4 Investigational Product (ONO-4538 or Placebo) and Chemotherapy

4.1 Dose and Mode of Administration and Duration of Treatment

Subjects will be randomized in a 1:1 ratio into either the ONO-4538 group or the placebo group and then receive all drugs on the same day every 3 weeks. The subjects will be given the investigational product first and start to receive chemotherapy at least 30 minutes after completion of the investigational product infusion.

The dose and mode of administration and duration of treatment with the investigational product and chemotherapy are as follows.

4.1.1 Dose and Mode of Administration and Duration of Treatment with Investigational Product

The investigational product (ONO-4538 360 mg or placebo) will be administered intravenously over 30 minutes every 3 weeks. The investigational product will continue until the subject meets any of 7.1.4.1 Investigational Product Discontinuation Criteria.

No escalations or reductions in the dose of the investigational product will be allowed. Please refer to the current version of the Investigator's Brochure and pharmacy reference sheets for proper storage, handling, preparation, and administration of the investigational product.

4.1.2 Dose and Mode of Administration and Duration of Treatment with Chemotherapy

Subjects will receive carboplatin AUC 6, paclitaxel 200 mg/m^2, and bevacizumab 15 mg/kg every 3 weeks. When calculating doses, in principle, the dose (mg) will be rounded to one decimal place.

It is permissible for the initial dose of paclitaxel and bevacizumab to be calculated based on the body weight measured at the time of randomization, instead of that measured on the day of first dosing (predose). The dose will be adjusted in each cycle if the subject's weight changes by ≥ 10% compared to the weight used to calculate the initial dose. If the subject's weight changes by ≥ 10% compared to the weight used to calculate the initial dose on the day of dosing, dose adjustment is acceptable for future infusions. Thereafter, similar action will be taken for any further changes in the subject's weight (≥ 10% compared to the weight used to calculate the dose adjusted).

Carboplatin dose will be calculated using the Calvert formula as follows:

Carboplatin dose (mg) = Target AUC × [(Creatinine clearance (mL/min) + 25]

Creatinine clearance calculation is based on the Cockcroft/Gault formula and should include the most recent serum creatinine and most recent weight. If calculation of the creatinine clearance by the Cockcroft/Gault formula yields a result of > 125 mL/min, then a creatinine clearance should be calculated by an alternative formula per institutional standards or capped at 125 mL/min. The dose of carboplatin may be capped as per local standards.

The mode of administration should be based on the procedures specified by the study site and recommended procedures are described below.

Subjects will receive paclitaxel as a 180-minute IV infusion on Day 1 of each cycle (3 weeks). On Day 1 of each cycle, subjects will receive carboplatin as a 30-minute IV infusion at least 30 minutes after paclitaxel treatment completion. On Day 1 of each cycle, subjects will receive bevacizumab as an IV infusion at least 30 minutes after carboplatin treatment completion. The initial administration of bevacizumab will be given intravenously over 90 minutes, and if well tolerated, the duration of the second administration will be reduced to 60 minutes and to 30 minutes in subsequent cycles.

Carboplatin and paclitaxel will be administered for up to 4 cycles and if deemed safe, treatment may continue for up to a maximum of 6 cycles. Even after the completion of treatment with carboplatin and paclitaxel, bevacizumab will be administered intravenously on Day 1 of each cycle until RECIST 1.1 defined PD, unacceptable toxicity, or withdrawal of consent. Even where carboplatin and paclitaxel have been discontinued for reasons such as adverse events, bevacizumab may be continued if deemed safe.

5 Concomitant Treatments

5.1 Treatments Prohibited during the Study

The following treatments are prohibited during the study (from the time of informed consent through completion of protocol-specified final examination [except outcome survey]); except when the final examination at the completion of treatment period (the discontinuation) is completed and the treatment is medically unavoidable. For any drugs other than those mentioned below, please refer to the current version of the package inserts for chemotherapy administrated concomitantly in the study:

1. Immunosuppressive drugs

2. Adrenocorticosteroids equivalent to prednisone > 10 mg/day[Note 1)]
3. Antineoplastic drugs except chemotherapy assigned in the study (such as chemotherapy, molecular targeted therapy, and immunotherapy[Note 2]])
4. Surgery for malignant tumor
5. Radiotherapy (including chemoradiation)[Note 3)]
6. Radiopharmaceuticals[Note 4)]
7. Bisphosphonates and anti-RANKL antibodies[Note 5)]
8. Transplantation therapy
9. Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment with the investigational product and until 100 days after the last dose of the investigational product
10. Any other unapproved drugs (including investigational treatments, unapproved combination drugs, and drugs with new dosage forms)

Note 1): Subjects are permitted the local use of topical, intra-articular, intranasal, ocular, or inhalational adrenocorticosteroids or the temporary use of adrenocorticosteroids for the treatment or prophylaxis of contrast media allergy or adverse events. The Sponsor's Medical Monitor must be consulted for continued treatment with the investigational product or chemotherapy in subjects requiring systemic adrenocorticosteroids for treating drug-related adverse events and if necessary, the investigator will determine whether or not to continue treatment with the investigational product or chemotherapy after consultation with the Sponsor's Medical Monitor.

Note 2): Including local therapy with Picibanil.

Note 3): Radiotherapy to brain or meningeal metastasis in the screening period is permitted unless subjects meet 3.3 Exclusion Criteria 22. As for palliative radiotherapy, only procedures specified in 5.2.1 Palliative Radiotherapy are permitted.

Note 4): Use of radiopharmaceuticals for examination and diagnosis is permitted.

Note 5): Use of bisphosphonates and anti-RANKL antibodies is acceptable only when their administration is started prior to randomization and the same dosage and administration are maintained.

5.2 Permitted Therapy

5.2.1 Palliative Radiotherapy

Palliative radiotherapy for non-target lesions, except the chest lesion, is permitted only if clinically indicated. Radiographic tumor assessments should be performed wherever possible before starting palliative radiotherapy.

The potential for overlapping toxicities of radiotherapy and ONO-4538 is not currently known. As concurrent radiotherapy and ONO-4538 have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then the investigational product and chemotherapy should be withheld for at least 1 week before, during, and 1 week after radiation.

Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and adverse events related to radiotherapy should resolve to Grade 1 or less prior to resuming administration of the investigational product and chemotherapy.

5.2.2 Prophylactic Administration

Prophylactic medications for administration of the investigational product or chemotherapy should follow the procedures specified by the study site. Recommended medications and procedures for administration of the investigational product are described below.

5.2.2.1 Prophylactic Medications for Administration of Investigational Product

Prior prophylactic use of acetaminophen or diphenhydramine is recommended for subjects who are at risk of infusion-related reaction after administration of the investigational product.

6 Time and Events Schedule and Observations

6.1 Screening Period

Following the subject's written consent to participate in the study, examination and assessment will start in the screening period. After obtaining informed consent, the investigator will proceed to enrollment and select subjects eligible for the study who have satisfied all of 3.2 Inclusion Criteria and do not meet any of 3.3 Exclusion Criteria in the randomization process. Table 6-1 (Synopsis) shows assessments and tests in the screening period and the time and events schedule.

6.2 Treatment Period

6.2.1 Investigational Product (ONO-4538 or placebo)

ONO-4538 360 mg or placebo will be administered intravenously over 30 minutes every 3 weeks. The investigational product will continue until the subject meets any of 7.1.4.1 Investigational Product Discontinuation Criteria. In the protocol synopsis, Table 6-1 shows assessments and tests in the treatment period and the time and events schedule.

6.2.2 Chemotherapy

Subjects will receive carboplatin AUC 6, paclitaxel 200 mg/m^2, and bevacizumab 15 mg/kg every 3 weeks. Carboplatin and paclitaxel will be administered for up to 4 cycles and if deemed safe, treatment may continue for up to a maximum of 6 cycles. Even after the completion of treatment with carboplatin and paclitaxel, bevacizumab will be administered intravenously on Day 1 of each cycle until RECIST 1.1 defined PD, unacceptable toxicity, or withdrawal of consent. In the protocol synopsis, Table 6-1 shows the assessments and tests in the treatment period and the time and events schedule.

6.3 Follow-up Period

Subjects meeting any of 7.1.4 Treatment Discontinuation Criteria will be evaluated at the completion of the treatment period (at discontinuation) and enter the follow-up period. In the protocol synopsis, Table 6-1 shows the assessments and tests in the follow-up period and the time and events schedule.

6.4 Time and Events Schedule and Observations

Table 6-1: Time and Events Schedule

Parameter	Screening Period[1]		Treatment Period							Follow-up Period	
			Cycle 1				Cycle 2 and Subsequent Cycles		Completion of Treatment Period[2] (at Discontinuation)	28 Days after Completion of Treatment Period[2,3]	Follow-up
Study Day			1		8	22	1	22			
			Predose	Postdose							
Time Window (days)	-60 to -1	-7 to -1			5 to 11	19 to 25	1	±3	±3	±7	-
Informed Consent	○[4]										
Enrollment	○										
Randomization[5]		○[4]									
Demographics/Inclusion and Exclusion Criteria		○									
Investigational Product Administration[6]			○				○[7]				
Carboplatin, Paclitaxel, and Bevacizumab Administration[6]			○				○[7]				
Viral Test	○										
Pregnancy Test[8]		○	○				○[9]		○	○	
ECOG Performance Status		○			○	○	○[7,9]	○	○	○	
Vital Signs/Body Weight/Height[10]		○	○	○[11]	○[11]	○	○[7,9]	○	○	○	
Chest X-ray[12]		○						○	○	○	
12-lead ECG		○						○[13]	○	○	
Hematology/Blood Chemistry/Urinalysis		○			○	○	○[7,9]	○	○	○	
Immunological/Hormonal Examinations[14]		○						○[15]	○	○	
Serum Drug Concentration[16]			○	○[17]		○	○[18]	○[19]		○[20]	●[21]
Anti-ONO-4538 Antibody[16]			○			○		○[19]		○[20]	●[21]
Exploratory Biomarker Analyses											
Tumor Markers[24]		As needed									
Tumor Tissues	○[25]									●[26]	
Radiographic Tumor Assessment (CT/MRI, etc.)[27]		○[28]					○[29]		○	○[30]	○[30]
Concomitant Therapies/Adverse Events				←→							○[31]
Outcome Research											○[32]
QoL/Healthcare Resource Utilization		○	○[33]						○		○[33]

○, required; ●, optional

1. Recent test results obtained within 1 year, 28 days, and 28 days prior to randomization will be used, respectively, for viral test, radiographic tumor assessments (except chest X-ray), and immunological/hormonal examinations. Images obtained within 28 days prior to randomization will be used for radiographic tumor assessments performed to determine the presence or absence of brain metastases and bone metastases.
2. If the last examination is within the time window for completion of the treatment period (at discontinuation) or 28 days after completion of the treatment period, previous test results may be used except when medically indicated. However, an examination must be performed if at least 2 days (vital signs), 15 days (radiographic tumor assessments except chest X-ray), and 8 days (other tests) have elapsed since the last examination. An examination will be performed as needed if medically indicated.
3. If subsequent anticancer therapy for non-squamous non-small cell lung cancer is started out of clinical necessity by 28 days after completion of the treatment period, the assessment scheduled for 28 days after completion of the treatment period will be performed before start of subsequent anticancer therapy.
4. An initial dose should be administered within 60 days after informed consent. The re-enrollment of a subject who failed to proceed to randomization is permitted. If re-enrolled, the subject needs to be re-consented in writing.
5. Subjects will be randomized through the IWRS. An initial dose should be administered within 3 days after randomization.
6. Subjects will receive the investigational product and chemotherapy at least 18 days after the previous dose, namely on or after Day 19.
7. Data obtained on Day 22 in the previous cycle may be used for ECOG Performance Status, vital signs, body weight, hematology, serum chemistry, and urinalysis, except when medically indicated. However, an examination must be performed if at least 2 days (vital signs) and 8 days (other tests) have elapsed since the last examination. An examination will be performed as needed if medically indicated.
8. Women of childbearing potential will undergo a serum or urine pregnancy test. The same procedures should be used as much as possible throughout the study. In Cycle 2 and subsequent cycles, a pregnancy test will be performed within 7 days prior to administration of the investigational product.
9. An examination will be performed before administration of the investigational product. A pregnancy test will be performed only in odd cycles.
10. Height will be measured only during the screening period.
11. No weight determination is required.
12. For any symptoms/signs or laboratory data indicative of respiratory disease, chest X-ray may be performed as needed in addition to scheduled examinations during the study (from the time of informed consent through completion of the protocol-specified final examination [except outcome survey]).
13. Only applicable to Cycles 2, 6, and 8.
14. SP-D and KL-6 measurement is optional.
15. An examination will be performed only in even cycles.
16. Measurement will continue up to Cycle 16, but not be required for the subject who discontinued the investigational product but remained in the treatment period.
17. Samples will be collected immediately before the end of infusion of the investigational product.
18. Only applicable to Cycle 7. Samples will be collected immediately before the end of infusion of the investigational product.
19. Applicable to Cycles 2, 6, 8, 12, and 16.
20. Measurement will be performed only in subjects who entered the follow-up period by Cycle 16.
21. Measurement will also be performed, wherever possible, 6 to 12 weeks after the last administration of the investigational product. For the subject who discontinued only the investigational product, the measurement may be performed during the treatment period.

[redacted]

24. Tumor markers must be measured continuously wherever possible in subjects who have tumor marker levels exceeding the upper limit of normal. Tumor markers will be measured as needed.
25. Tissue samples will be submitted for PD-L1 IHC testing performed by the central laboratory during the screening period. Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections must be submitted for investigational product assignment and biomarker evaluation prior to

randomization. The tumor tissue sample may be fresh or archival if obtained within 6 months prior to enrollment, and there was no systemic therapy (eg, adjuvant or neoadjuvant chemotherapy) given after the sample was obtained. The PD-L1 status will be determined before randomization and used for IWRS-based assignment.

26. After the end of efficacy assessment, tumor tissues will be collected.
27. A chest, abdominal, and pelvic CT scan will be performed to determine antitumor activity. The same procedures will be used for antitumor activity assessment throughout the study. The antitumor activity is assessed according to the RECIST 1.1 criteria.
28. Subjects will be examined for brain metastases by head CT/MRI scan (images obtained within 28 days prior to randomization will be used). According to clinical symptoms, FDG-PET (or bone scintigraphy) must be performed to determine the presence or absence of bone metastases.
29. The first tumor assessment will take place 6 weeks after the first day of treatment (+ 7 days). Subsequent tumor assessments will be performed every 6 weeks (± 7 days) for the first 12 months (until Week 48) and after Week 48, assessments will be conducted every 12 weeks (± 7 days) until PD. According to clinical symptoms, radiographic tumor assessment results will be used to determine the presence or absence of brain metastases and bone metastases.
30. For subjects whose overall response is a CR, PR, or SD per RECIST 1.1 criteria and who terminated the treatment period for safety reasons or disease progression, radiographic tumor assessments should be continued wherever possible until start of subsequent anticancer therapy for non-squamous non-small cell lung cancer or the outcome is assessed as PD or recurrence. Subjects whose PD is not confirmed by the IRRC will be required to continue radiographic tumor assessments according to the protocol-specified schedule, and their subsequent tumor images must be submitted to the IRRC (if clinically feasible). If thoracentesis, pericardiocentesis, or abdominal paracentesis is considered, for example due to clinical symptoms, a CT scan should be performed wherever possible before these treatments.
31. All adverse events and concomitant treatments will be investigated for up to 100 days after the last administration of the investigational product or chemotherapy, whichever comes later. When drug-related adverse events or adverse events leading to discontinuation are reported at the start of follow-up, concomitant treatments administered for these events should be investigated at appropriate intervals until no further follow-up is required because the events have resolved or are resolving, or the symptoms become stable. The presence or absence of subsequent anticancer therapy for non-squamous non-small cell lung cancer, the date of starting such therapy, and details of the therapy should also be investigated wherever possible during the follow-up.
32. Outcome survey (date and cause of death will be investigated if the subject has died) can be conducted by phone or letter, which will be performed approximately every 3 months or as needed depending on the incidence of events. Any new information on survival status should be entered on the eCRF accordingly. The presence or absence of subsequent anticancer therapy for non-squamous non-small cell lung cancer, the date of starting such therapy, and details of the therapy should also be investigated wherever possible.
33. QoL and healthcare resource utilization assessments will be performed every 6 weeks (± 7 days) for the period from the first day of Cycle 1 through completion of the treatment period. To minimize potential bias, QoL assessments should be, in principle, conducted prior to any study procedures in each study visit. QoL assessments will also be performed before administration of the investigational product. In follow-up study visits, EQ-5D will be collected every 3 months for the first year of the follow-up period, and every 6 months thereafter.

7 Endpoints

7.1 Efficacy Endpoint - Primary Endpoint

Progression-free survival (as assessed by the Independent Radiology Review Committee [IRRC])

7.2 Efficacy Endpoint - Secondary Endpoints

1. Overall survival
2. Progression-free survival (as assessed by the study site's investigator)
3. Objective response rate (as assessed by the IRRC and study site's investigator)
4. Disease control rate (as assessed by the IRRC and study site's investigator)
5. Duration of response (as assessed by the IRRC)
6. Time to response (as assessed by the IRRC)
7. Best overall response (as assessed by the IRRC and study site's investigator)
8. Maximum percentage of change in the sum of diameters of target lesions (as assessed by the IRRC)

7.3 Safety Endpoints

1. Adverse events
2. Laboratory tests
3. Vital signs
4. Chest X-ray
5. 12-lead ECG
6. ECOG Performance Status

7.4 Patient Reported Outcomes

1. QoL questionnaire (EQ-5D)
2. Questionnaire to assess disease-related symptoms (LCSS)

7.5 Other Tests

Healthcare resource utilization

7.6 Biomarkers

[redacted]

3. Tumor markers (as needed)

[redacted]

5. Tumor tissues

7.7 Pharmacokinetic Assessment

Serum ONO-4538 concentration

7.8 Immunogenicity Assessment

Anti-ONO-4538 antibody

8 Interim Analysis

One interim analysis for PFS per IRRC will be performed in the ITT population to determine whether to stop the study early for superiority based on the stratified log-rank test with allocation factors (PD-L1 expression level, ECOG PS, and gender) as stratification factors when approximately 82.4% (n = 280) of the target number of PFS events over the entire study (n = 340) have occurred. To control the overall type I error rate at no more than 5% (two-sided), the significance levels used in the interim and final analyses will be calculated by the Lan-DeMets α spending function (O'Brien-Fleming type) based on the actual number of events. When the planned interim analysis is performed when exactly 280 PFS events have been reported, the nominal two-sided significance levels for the interim and final analyses are calculated as shown in Table 8-1.

Whether the study is to be stopped for superiority based on the interim analysis will be decided by the IDMC. The details of the interim analysis are separately specified in the IDMC procedural manual and the interim analysis plan.

Table 8-1: Criteria for Success at Interim and Final Analyses

Analysis	Timing	Nominal two-sided significance level
Interim analysis	280 events	2.70%
Final analysis	340 events	4.22%[a)]

[a)]: In the final analysis using the ITT and the PD-L1 1% Positive Set, Hochberg's method will also be used to adjust multiplicity.

9 Planned Sample Size

The target sample size is approximately 265 subjects per group, and approximately 530 subjects in total for the entire study.

10 Planned Study Period

Mar-2017 to Jul-2022

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Table 1: List of Abbreviations

Term	Definition
ADCC	antibody-dependent cell cytotoxicity
ALP	alkaline phosphatase
ALT (GPT)	alanine aminotransferase (glutamic pyruvic transaminase)
ANA	antinuclear antibody
AST (GOT)	aspartate aminotransferase (glutamic oxaloacetic transaminase)
AUC	area under the plasma concentration-time curve
BOR	best overall response
BUN	blood urea nitrogen
CD	cluster of differentiation (antigen)
CDC	complement-dependent cytotoxicity
CHO	Chinese hamster ovary
CMV	cytomegalovirus
CR	complete response
CRP	C-reactive protein
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
CV	coefficient of variation
DCR	disease control rate
DNA	deoxyribonucleic acid
DNP-Ficoll	2,4-dinitrophenyl-conjugated Ficoll
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDG-PET	fluorodeoxyglucose positron emission tomography
GAD	glutamic acid decarboxylase
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HBc	hepatitis B virus core protein
HBs	hepatitis B virus surface protein
HBsAg	hepatitis B virus surface antigen

Term	Definition
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
HTLV-1	human T-cell leukemia virus type 1
ICOS	inducible costimulator
IDMC	Independent Data Monitoring Committee
IFN-γ	interferon-gamma
IgA	immunoglobulin A
IRRC	Independent Radiology Review Committee
ITT	Intention-to-Treat
IWRS	Interactive Web Response System
K_D	dissociation constant
KL-6	sialylated carbohydrate antigen
LAG-3	lymphocyte activation gene 3
LDH	lactate dehydrogenase
LKM	liver kidney microsome
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MLR	mixed lymphocyte reaction
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NE	not evaluable
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival

Term	Definition
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 1
PD-L2	programmed cell death-ligand 2
Performance Status	general performance status
PK	pharmacokinetics
PFS	progression-free survival
PPK	population pharmacokinetics
PR	partial response
PT	preferred term
QoL	quality of life
RA	rheumatoid factor
RANKL	receptor activator of NF-κB ligand
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAF	Safety Set
SD	stable disease
SOC	system organ class
SP-D	pulmonary surfactant protein D
SpO_2	percutaneous oxygen saturation
SSA	Sjogren syndrome A
SSB	Sjogren syndrome B
TSH	thyroid-stimulating hormone
TTR	time to response
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
Vss	volume of distribution at steady state
γ-GTP	gamma-glutamyl transpeptidase

1 PRODUCT DEVELOPMENT BACKGROUND

1.1 Introduction

Lung cancer remains the leading cause of cancer-related deaths worldwide and approximately 1,589,900 deaths in 2012 from lung cancer are reported.[1] Non-small cell lung cancer is the major histological subtype of lung cancer accounting for 85% of all lung cancers. Of these, approximately 70% are non-squamous and approximately 30% are squamous.[2]

Clinical practice guidelines recommend the use of platinum-based chemotherapy with a third- or later-generation anticancer drug as standard of care for chemotherapy-naïve subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation. The use of platinum-based chemotherapy with a third- or later-generation anticancer drug and bevacizumab combination therapy is also one of the therapies recommended.[3] However, clinical benefit of the use of platinum-based chemotherapy with a third- or later-generation anticancer drug as standard of care has a median Progression Free Survival (PFS) of 4.5 to 6.2 months, and a median Overall Survival (OS) of 10.3 to 12.3 months.[4 5] Therefore, conventional therapies are not effective for treating stage IIIB/IV or recurrent non-small cell lung cancer unsuitable for radical radiation, and there is an urgent need for development of novel therapeutic drugs in these patient populations.

ONO-4538 is a human monoclonal antibody to human programmed cell death-1 (PD-1, also known as cluster of differentiation 279 [CD279]) produced by ONO PHARMACEUTICAL CO., LTD. (ONO PHARMA) and Medarex, Inc. (current Bristol-Myers Squibb [BMS]). Programmed cell death-1 is a 55-kDa type I transmembrane protein and belongs to the CD28 subfamily known as a costimulatory receptor for T cells, including CD28, CTLA-4, ICOS, and BTLA, within the immunoglobulin superfamily. Programmed cell death-1 is primarily expressed on activated T cells and B cells. Programmed cell death-1 is also expressed on the memory T cell subset with varying levels of expression. Two specific ligands for PD-1 have been identified: programmed cell death-ligand 1 (PD-L1, also known as B7-H1 or CD274) and programmed cell death-ligand 2 (PD-L2, also known as B7-DC or CD273). Binding of PD-L1 and PD-L2 to PD-1 in mice and humans results in the down-regulation of T cell activation.[6 to 8]

ONO-4538 is approved in a number of countries including Japan (Jul-2014), the United States (US, Dec-2014), South Korea (Mar-2015), the European Union (EU, Jun-2015), and Taiwan (May-2016).

In CA209017 (in subjects with stage IIIB/IV or recurrent squamous non-small cell lung cancer after failure of prior platinum-based chemotherapy), ONO-4538 demonstrated superior OS compared with docetaxel. The median overall survival (OS) was 9.2 months in the ONO-4538 group and 6 months in the docetaxel group (hazard ratio [HR] = 0.59).[9] In CA209057 (in subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer after failure of prior platinum-based chemotherapy), ONO-4538 also demonstrated superior OS compared with docetaxel. The median OS was 12.2 months in the ONO-4538 group and 9.4 months in the docetaxel group (HR = 0.73).[10] In CA209026, a phase III study of ONO-4538 versus investigator's choice chemotherapy as first-line therapy for stage IV or recurrent PD-L1+ (≥ 1%) non-small cell lung cancer, the study did not meet the primary endpoint (PFS in PD-L1 strongly

positive [≥ 5%] subjects) with a median PFS of 4.2 months in the ONO-4538 group and 5.9 months in the chemotherapy group (HR = 1.15).[11]

Chemotherapy has been reported to not only directly inhibit tumor proliferation but also reinstate anticancer immunosurveillance.[12] The immune response eliminating the tumor is made robust when chemotherapy results in tumor cell death with a resultant increase in tumor antigen delivery to antigen-presenting cells.[13 14] Chemotherapy may also disrupt immune system regulatory networks to reinstate anticancer immunosurveillance by decreasing the number of T-regulatory cells.[12 15] Antiangiogenic agents have been shown to induce antitumor activity by impairing vascular endothelial growth factor (VEGF) signal-mediated immune evasion in cancer, in addition to angiogenesis.[16 to 19]

Based on findings described above, the potential for synergistic antitumor activity to disturb cancer-immune evasion system via multiple mechanisms by combining an antiangiogenic agent-based chemotherapy and immune checkpoint inhibitor in addition to chemotherapy induced cytotoxic antitumor activity could be offered.

ONO-4538-04, a phase 1 study in subjects with untreated NSCLC in Japan, evaluated safety and tolerability of ONO-4538 plus platinum-based chemotherapy. The combination therapy showed a tolerable safety profile, in addition to some promising activity evaluated for exploratory endpoint in this study.[20]

From the above, the study is to evaluate the efficacy and safety of ONO-4538 in combination with chemotherapy, including platinum-based drugs, in chemotherapy-naïve subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation.

1.2 Summary of Major Findings from Nonclinical and Clinical Studies

1.2.1 Nonclinical Overview

ONO-4538 is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. The drug substance is ONO-4538 aqueous solution and is a clear to opalescent colorless to pale yellow liquid, light (few) particulates may be present. The drug product is an aqueous solution, containing 100 mg of ONO-4538 per vial, and must be stored at 2°C to 8°C and protected from light (for details, refer to the Investigator's Brochure).

ONO-4538 has been shown to bind specifically to PD-1 and bind with high affinity to human and monkey PD-1 with K_D of 3.06 nmol/L and 3.92 nmol/L, respectively. ONO-4538 inhibits the binding of PD-1 to its ligands (PD-L1 and PD-L2), resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release *in vitro* in a mixed lymphocyte reaction (MLR). When ONO-4538 was investigated by restimulating human peripheral blood mononuclear cells (PBMCs) from a cytomegalovirus (CMV)-exposed donor with CMV antigen, ONO-4538 augmented IFN-γ secretion by priming in a dose-dependent manner. In monkeys inoculated with HBsAg, SKMel, and DNP-Ficoll, ONO-4538 increased specific antibody titers to SKMel cells.

In several syngeneic murine tumor models, an anti-mouse PD-1 antibody (4H2) delayed tumor growth and the results demonstrate that an anti-PD-1-antibody inhibiting PD-1 binding to its ligands exhibits antitumor activity.

Therefore, ONO-4538 inhibits the binding of PD-1 to its ligands and enhances antigen-specific T-cell activation, resulting in an augmented immune response to cancer and antitumor activity.

Following single intravenous administration of ONO-4538 to conscious monkeys, ONO-4538 did not affect clinical signs, body temperature, heart rate, blood pressure, and electrocardiogram at concentrations up to 50 mg/kg. No drug-related findings were observed in standard clinical evaluations of neurologic, cardiovascular, and respiratory functions conducted in monkeys as part of the repeated-dose toxicity studies for up to 13 weeks with ONO-4538.

In monkeys receiving 1, 10, and 50 mg/kg IV single doses of ONO-4538, the AUC of serum ONO-4538 increased in an approximately dose-proportional manner. The Vss was similar to plasma volume, suggesting that ONO-4538 is mainly distributed in circulating blood. The serum ONO-4538 concentrations were lower in anti-ONO-4538-positive monkeys than in monkeys with no detectable anti-ONO-4538 antibodies. In a reproductive and developmental toxicity study in pregnant monkeys, ONO-4538 was detected in the serum of offspring, suggesting the placental transfer of maternal ONO-4538 to the fetus.

In a single-dose intravenous toxicity study with monkeys, no deaths or ONO-4538-related adverse effects were noted at the maximum dose level, 10 mg/kg.

In repeated-dose intravenous toxicity studies with monkeys, no adverse events associated with ONO-4538 were observed when administered by weekly IV injections at the maximum dose (50 mg/kg) for 4 weeks and by IV injections twice weekly for 13 weeks, and the no-observed-adverse-effect level was determined to be 50 mg/kg. In these studies, irritation was not observed at the injection sites at ONO-4538 concentrations up to 10 mg/mL.

In an enhanced pre- and postnatal development study in pregnant monkeys, increases in third trimester embryonic or fetal losses or offspring mortality were reported at doses of 10 mg/kg or higher but ONO-4538 caused no teratogenicity and did not affect the growth, behavior, and immune function of offspring.

In studies to assess the cross-reactivity of ONO-4538 in normal monkey and human tissues, ONO-4538 demonstrated reactivity to the cell membranes of monkey and human lymphocytes, in which expression of PD-1 had been reported. As an instance of unexpected reactivity, there was cytoplasmic staining of endocrine cells in the pituitary gland in monkeys and humans. However, ONO-4538 is an antibody preparation and does not penetrate cell membranes, suggesting that it would not have a direct action on the cytoplasm of endocrine cells in the pituitary gland. In 4- and 13-week repeated-dose intravenous toxicity studies with monkeys, no clinical signs of toxicity were observed with respect to pituitary hormones and organ weights of the pituitary gland or in histologic pathology findings.

ONO-4538 showed no antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) effects on activated human CD4 T cells in the presence of effector cells (human PBMCs were used) or human complements. ONO-4538 did not induce cytokine production in human whole blood.

1.2.2 Clinical Overview and Summary of Known and Potential Risks and Benefits

The pharmacokinetics (PK) of ONO-4538 was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of ONO-4538 every 2 or 3 weeks. The geometric mean (CV%) clearance (CL) was 9.5 mL/h (49.7%), the geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and the geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of ONO-4538 were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3-fold. The exposure of ONO-4538 increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. Additionally, ONO-4538 has a low potential for drug-drug interactions. The clearance of ONO-4538 increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of ONO-4538: age (29 to 87 years), gender, race, baseline LDH, PD-L1. A PPK analysis suggested no difference in the CL of ONO-4538 based on age, gender, race, solid tumor type, baseline tumor size, and hepatic impairment.

Although ECOG Performance Status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment influenced ONO-4538 CL, the effect was not clinically meaningful. PPK analysis suggested that ONO-4538 CL in subjects with cHL was lower by approximately 32% relative to subjects with NSCLC; however, the lower CL in cHL subjects was not considered to be clinically relevant as ONO-4538 exposure was not a significant predictor for safety risks in these patients.

ONO-4538 has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several-type cancers, including NSCLC, melanoma, RCC, cHL, small-cell lung cancer, gastric cancer, urothelial cancer, hepatocellular cancer, and colorectal cancer. ONO-4538 as monotherapy demonstrated a statistically significant improvement in OS as compared with the standard of care in subjects with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or squamous cell carcinoma of the head and neck in confirmatory trials. ONO-4538 in combination with ipilimumab demonstrated a statistically significant improvement in PFS and a high rate of objective response over ipilimumab alone in subjects with unresectable or metastatic melanoma in confirmatory trials.

Across studies conducted to date, the safety experience with ONO-4538 based on experience in approximately 12,300 subjects is accumulated as a monotherapy or in combination with other therapeutics. Drug-related adverse events have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, gastrointestinal toxicity, dermatologic toxicity (including rash), and hepatotoxicity. For ONO-4538 monotherapy and combination therapy, the majority of these adverse events have been managed successfully with supportive care and, in more severe cases, therapy as instructed in the management guidelines.

In several ongoing clinical studies, the safety of ONO-4538 in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and molecular targeted drugs is being explored.

For details, refer to the Investigator’s Brochure for ONO-4538.

2 STUDY ADMINISTRATIVE STRUCTURE AND RESPONSIBILITIES (IF APPLICABLE)

Please refer to Supplement 1 “Study Administrative Structure.”

Any amendments to Supplement 1 will be made separately from the study protocol.

3 STUDY OBJECTIVES

To compare the efficacy and safety of ONO-4538 in combination with carboplatin, paclitaxel, and bevacizumab (treatment administered to ONO-4538 group) to placebo in combination with carboplatin, paclitaxel, and bevacizumab (treatment administered to placebo group) in chemotherapy-naïve subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation in a multicenter, randomized, double-blind study.

3.1 Primary Objectives of the Study

- To compare the PFS, based on the Independent Radiology Review Committee (IRRC) assessment, in chemotherapy-naïve subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation, regardless of PD-L1 status, between the ONO-4538 group and the placebo group.
- To compare the PFS, based on the IRRC assessment, in chemotherapy-naïve subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation with tumor PD-L1+ expression (≥ 1%).

3.2 Secondary Objective of the Study

To evaluate the efficacy and safety in the ONO-4538 group compared to those in the placebo group, from a range of viewpoints, in chemotherapy-naïve subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation.

4 STUDY POPULATION

4.1 Study Subjects

Chemotherapy-naïve subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation

4.2 Inclusion Criteria

After subjects provide written informed consent before participating in the study, subjects must meet all of following inclusion criteria at the time of randomization. When it has been confirmed that the subject does not meet any of the following criteria from randomization to the first dose of the investigational product, the subject will be withdrawn from the study without receiving any investigational products.

1. Males and females
2. ≥ 20 years of age (at the time of informed consent)
3. Subjects with histologically- or cytologically-confirmed non-squamous non-small cell lung cancer
4. Subjects who received a diagnosis of stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation according to the UICC-TNM Classification (7th edition) with no prior systemic anticancer therapy (including EGFR, ALK and ROS1 inhibitors) given as primary therapy for advanced or metastatic disease
   Prior adjuvant or neoadjuvant chemotherapy is permitted provided the last administration of the prior regimen occurred at least 6 months prior to enrollment.
5. Subjects with at least one measurable lesion by radiographic tumor assessments per RECIST 1.1 criteria; radiographic tumor assessments performed within 28 days of randomization (target lesions may be located in a previously irradiated field if there is documented disease progression after the completion of radiation therapy.)
6. Subjects who are able to provide tumor tissue specimens. If no fresh specimens are available, these will be allowed as archival samples, but they must contain a minimum of 100 evaluable tumor cells. Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections must be submitted for investigational product assignment and biomarker evaluation. The tumor tissue sample may be fresh or archival if obtained within 6 months prior to enrollment, and there was no systemic therapy (eg, adjuvant or neoadjuvant chemotherapy) given after the sample was obtained.
   Tissue must be from a core needle biopsy, excisional biopsy, incisional biopsy, or forceps biopsy. EBUS-TBNA is acceptable if no tissue can be obtained through the above biopsy methods and tumor tissues may be collected by EBUS-TBNA. Fine needle biopsies, biopsies of bone lesions that do not have a soft tissue component, or decalcified bone tumor samples are not acceptable. In addition, cell block is not acceptable.
7. ECOG Performance Status of 0 or 1
8. Life expectancy ≥ 90 days by investigator assessment
9. Women of childbearing potential (including those who have no menses for medical reasons, such as chemotherapy-induced menopause)[#1] must agree to follow instructions for method(s) of contraception[#2] or maintain complete abstinence from the time of informed consent through at least 5 months after the last administration of the investigational product (ONO-4538 or placebo) or at least 6 months after the last administration of bevacizumab, whichever is longer. Women of childbearing potential must agree to discontinue breastfeeding from the time of informed consent through at least 5 months after the last administration of the investigational product or at least 6 months after the last administration of bevacizumab, whichever is longer.

10. Male subjects who have agreed to follow instructions for method(s) of contraception[#2] from the start of administration of the investigational product through at least 7 months after the last administration of the investigational product or at least 6 months after the last administration of bevacizumab, whichever is longer
11. Subjects with percutaneous oxygen saturation of ≥ 94% by pulse oximetry at rest, without oxygen supplementation, within 7 days prior to randomization
12. Latest laboratory values obtained within 7 days prior to randomization must meet the criteria listed below. These values should not reflect granulocyte-colony stimulating factor (G-CSF) or blood transfusion given within 14 days before the test day.
    - WBC ≥ 2000/mm^3
    - Neutrophils ≥ 1500/mm^3
    - Platelets ≥ 100000/mm^3
    - Hemoglobin ≥ 9.0 g/dL
    - AST (GOT) and ALT (GPT) ≤ 3.0 × upper limit of normal (ULN)
    - LDH ≤ 2.0 × ULN
    - Total bilirubin ≤ 1.5 × ULN
    - Creatinine ≤ 1.5 mg/dL or creatinine clearance (observed values or estimates calculated by the Cockcroft-Gault formula) > 50 mL/min
13. Subjects who have been fully informed of the nature of the study through the informed consent form by the investigator and gave their consent for voluntary participation in the study

[#1]: Women of childbearing potential are defined as all premenopausal women who have reached menarche and who have not undergone sterilization (including hysterectomy, bilateral tubal ligation, or bilateral oophorectomy). Menopause is defined as amenorrhea for at least 12 successive months in the absence of significant causes. Women who use oral contraceptives or mechanical contraception such as intrauterine devices or barrier methods are regarded as having childbearing potential.

[#2]: Subjects must agree to dual contraception using any 2 of the following methods: vasectomy or condoms in male subjects or male partners, or tubal ligation, contraception pessaries, intrauterine devices, or oral contraceptives in female subjects or female partners.

4.2.1 Rationale

1. No restrictions need to be placed on the gender of study participants.
2. The age at which the subject can legally decide whether or not to participate in the study.
3. To enroll subjects with histology for which the chemotherapy to be investigated in the study (carboplatin, paclitaxel, and bevacizumab combination therapy) is the standard of care.
4. To select subjects who are eligible for systemic drug therapy.
5. To select subjects with evaluable efficacy data per RECIST 1.1 criteria.
6. To select subjects whose PD-L1 status can be evaluated.

7. To register subjects with good performance status.
8. To register subjects in whom the efficacy and safety of the investigational product can be evaluated properly.
9, 10. Safety in fetuses and infants has not been established.
11. To register subjects without cardiopulmonary insufficiency.
12. To register subjects without any damage to vital organs.
13. To select subjects who have the ability to provide consent.

4.3 Exclusion Criteria

The investigator cannot enroll subjects meeting any of the following criteria at the time of randomization. When subjects meet any of the following criteria between randomization to the first dose of the investigational product, subjects will be withdrawn from the study without receiving any investigational products.

1. Subjects with known EGFR mutations, including deletions in exon 19 and exon 21 (L858R) substitution mutations. All subjects must have been tested for EGFR mutation status. Non-squamous non-small cell lung cancer subjects with unknown or indeterminate EGFR status are excluded.
2. Subjects with known ALK or ROS1 translocations. Subjects with unknown or indeterminate ALK or ROS1 status will be eligible for randomization.
3. Complication or history of severe hypersensitivity reactions to antibody products or platinum-containing compounds
4. Subjects with current or prior ≥ Grade 2 peripheral neuropathy
5. Subjects with residual effects of adverse drug reactions associated with prior treatment or surgery that may have an impact on the safety assessment of the investigational product and/or chemotherapy at the investigator's discretion.
6. Subjects with autoimmune disease or known chronic or recurrent autoimmune disease. Subjects with type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement or skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are acceptable for enrollment.
7. Subjects with contraindications to carboplatin, paclitaxel, or bevacizumab
8. Subjects with current or prior interstitial lung disease or pulmonary fibrosis diagnosed based on radiographic tumor assessments or clinical findings. Subjects with radiation pneumonitis with fibrosis, which is considered to be stable, and without recurrence are acceptable for enrollment.
9. Subjects with active diverticulitis or symptomatic gastrointestinal ulceration
10. Subjects with multiple cancers (those with completely resected basal cell carcinoma, stage I squamous cell carcinoma, carcinoma in situ, intramucosal carcinoma, or superficial bladder cancer or with a history of other forms of cancer that has not recurred for at least 5 years are acceptable for enrollment.)

11. Subjects with brain or meningeal metastasis. Subjects with metastatic lesions can be enrolled if the metastases are adequately treated with radiotherapy and/or surgery and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) at least 14 days prior to randomization and subjects have no documented evidence of progression confirmed by CT/MRI.
12. Subjects with pericardial, pleural, or peritoneal effusion requiring treatment. In subjects who have recently undergone aspiration, the date of the procedure (or, in the case of drainage, the date of removal of the drain) must be at least 14 days prior to randomization, and there must not be any finding of aggravation of pericardial, pleural, or peritoneal effusion.
13. Subjects with uncontrollable cancer pain
14. Subjects who have a history of transient ischemic attack, cerebrovascular accident, thrombosis, or thromboembolism (pulmonary thromboembolism or deep venous thrombosis) within 180 days prior to randomization
15. Subjects with any of the following uncontrollable or significant cardiovascular disease:
    - Myocardial infarction occurring within 180 days prior to randomization;
    - Uncontrollable angina occurring within 180 days prior to randomization;
    - Congestive heart failure, defined as New York Heart Association (NYHA) functional Class III or IV;
    - Uncontrollable hypertension even if adequately treated (systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 90 mmHg lasting for 24 hours or longer); or
    - Arrhythmia requiring treatment.
16. Subjects who are receiving anticoagulants (except antiplatelet therapy including low-dose aspirin) or have a disease for which anticoagulant therapy is required
17. Subjects with uncontrollable diabetes
18. Subjects who have received systemic adrenocorticosteroids equivalent to prednisone > 10 mg/day (except for temporary use for examination, prophylaxis, or a similar purpose) or immunosuppressants within 28 days prior to randomization
19. Subjects who have received pleurodesis or pericardial adhesion within 28 days prior to randomization
20. Subjects who have had surgery under general anesthesia within 28 days prior to randomization
21. Subjects who have had surgery under local or surface anesthesia within 14 days prior to randomization
22. Subjects who have received radiotherapy within 28 days prior to randomization, who have received stereotactic irradiation for brain metastasis within 14 days prior to randomization or who have received chest radiotherapy or radiopharmaceuticals (except for use of radiopharmaceuticals for examination and diagnosis) within 56 days prior to randomization
23. Subjects who have received radiotherapy for pain relief within 14 days prior to randomization. Subjects who may require palliative radiotherapy within 4 weeks of randomization are strongly encouraged to receive palliative radiotherapy before randomization.
24. Subjects who have received any other unapproved drugs (including investigational treatments, unapproved combination drugs, and drugs with new dosage forms) within 28 days prior to randomization
25. Subjects with systemic infection requiring treatment

26. Prior treatment with ONO-4538 (MDX-1106 or BMS-936558), anti-PD-1 antibody, anti-PD-L1 antibody, anti-PD-L2 antibody, anti-CD137 antibody, anti-CTLA-4 antibody, or any other antibody therapy for regulation of T cells or drug therapies including cancer vaccines
27. Any positive test for HIV-1 antibody, HIV-2 antibody, HTLV-1 antibody, HBs antigen, or HCV antibody
28. Subjects who test positive for HBs antibody or HBc antibody and have detectable HBV-DNA levels despite testing negative for HBs antigen
29. Subjects who are pregnant, breastfeeding, or may be pregnant
30. Subjects who are judged to lack the ability to provide consent for reasons such as dementia
31. Subjects disqualified from participation in the study at the investigator's discretion
32. Subjects who have received a live/attenuated vaccine within 28 days prior to randomization

4.3.1 Rationale

1, 2.	In consideration of effective standard of care.
3 to 8.	In consideration of subject safety.
9 to 12.	To exclude potential influences on efficacy and safety assessments in the study.
13 to 16.	In consideration of subject safety.
17 to 23.	To exclude potential influences on efficacy and safety assessments in the study.
24.	To eliminate the effects of an investigational product with undetermined therapeutic efficacy.
25.	In consideration of subject safety.
26.	To exclude potential influences on efficacy and safety assessments in the study.
27, 28.	To ensure the safety of subjects and those who collect or measure blood samples.
29.	Safety in fetuses and infants has not been established.
30.	To protect the human rights of the subject.
31.	In consideration of unsuitable conditions other than those mentioned in 1 to 30 and 32.
32.	To exclude potential influences on safety assessments in the study.

5 STUDY PROCEDURES

5.1 Study Design

5.1.1 Study Design

This study is a multicenter, randomized, double-blind, placebo controlled phase 3 study in chemotherapy-naïve subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation. The study is intended to evaluate the superiority of the

ONO-4538 group over the placebo group, with PFS, based on an IRRC assessment, as the primary endpoint.

The study will consist of the screening period, treatment period, and follow-up period. In a double-blind fashion, subjects will be randomized in a 1:1 ratio into either the ONO-4538 group or the placebo group and stratified by PD-L1 expression level (≥ 50% vs 1% to 49% vs < 1% or indeterminate), ECOG Performance Status (0 vs 1), and gender (male vs female).

In the ONO-4538 group, ONO-4538, carboplatin, paclitaxel, and bevacizumab will be administered every 3 weeks. In the placebo group, placebo, carboplatin, paclitaxel, and bevacizumab will be administered every 3 weeks. Subjects will receive ONO-4538 360 mg or placebo in combination with carboplatin (AUC 6), paclitaxel (200 mg/m^2), and bevacizumab (15 mg/kg). In both groups, carboplatin and paclitaxel will be administered for up to 4 cycles and if deemed safe, treatment may continue for up to a maximum of 6 cycles. Even after the completion of treatment with carboplatin and paclitaxel, the investigational product (ONO-4538 or placebo) and bevacizumab will be administered intravenously on Day 1 of each cycle in both treatment groups until RECIST 1.1 defined PD, unacceptable toxicity, or withdrawal of consent. Upon completion of the investigational product and chemotherapy, subjects will enter the follow-up period.

In this study, one interim analysis of PFS among randomized subjects is planned for early stopping in case of superior efficacy, at the time when approximately 82.4% of the target number of events are observed.

An overview of the study design is shown in Figure 2-1.

5.1.1.1 Rationale for study design

Clinical practice guidelines recommend the use of platinum-based chemotherapy with a third- or later-generation anticancer drug as standard of care for chemotherapy-naïve subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation. The use of platinum-based chemotherapy with a third- or later-generation anticancer drug and bevacizumab combination therapy is also one of the therapies recommended.[3] However, clinical benefit of the use of platinum-based chemotherapy with a third- or later-generation anticancer drug as standard of care has a median PFS of 4.5 to 6.2 months, and a median OS of 10.3 to 12.3 months[4 5]. Therefore, conventional therapies are not effective for treating stage IIIB/IV or recurrent non-small cell lung cancer unsuitable for radical radiation, and there is an urgent need for development of novel therapeutic drugs in these patient populations.

Phase 1 studies (ONO-4538-04 and CA209012) are in progress to evaluate the safety and efficacy of ONO-4538 in combination with chemotherapy including platinum-based drugs in chemotherapy-naïve subjects with advanced non-small cell lung cancer.

In ONO-4538-04, ONO-4538 10 mg/kg was administered in combination with cisplatin and gemcitabine (Arm A), cisplatin and pemetrexed (Arm B), or carboplatin, paclitaxel, and bevacizumab (Arm C). In CA209012, ONO-4538 10 mg/kg was administered in combination with cisplatin and gemcitabine or cisplatin and pemetrexed. ONO-4538 10 mg/kg or 5 mg/kg was also given concomitantly with carboplatin and paclitaxel. In ONO-4538-04, the response rate was 50% (3/6 subjects) in Arm A, 50% (3/6) in Arm B, and 100% (6/6) in Arm C. The

median PFS was 6.28 months in Arm A, 9.63 months in Arm B, and not reached in Arm C.[20] In CA209012, the response rate was 33% (4/12 subjects) in the cisplatin/gemcitabine group (ONO-4538 10 mg/kg), 47% (7/15) in the cisplatin/pemetrexed group (ONO-4538 10 mg/kg), 47% (7/15) in the carboplatin/paclitaxel group (ONO-4538 10 mg/kg), and 43% (6/14) in the carboplatin/paclitaxel group (ONO-4538 5 mg/kg).[21] In ONO-4538-04 and CA209012, administration of ONO-4538 in combination with chemotherapy resulted in a comparable or higher response rate compared to those cited in previous reports on chemotherapy, and the duration of response also tended to be longer.

In CA209012, efficacy was also evaluated by PD-L1 expression and was observed in subjects with both PD-L1 expressing and non-expressing tumors. At the 1% expression level, the response rate was 48% and 43% for expressors and non-expressors, respectively. The 1-year overall survival was 70% and 76% for expressors and non-expressors, respectively. Thus, the efficacy was consistent between expressors and non-expressors.

As for safety, adverse events observed in the combination-therapy groups seem to be manageable in all studies. Although most of immune-related adverse events occurred more frequently in subjects receiving ONO-4538 plus chemotherapy than in those treated with ONO-4538 alone, no adverse events leading to death were observed.

Thus, to evaluate the efficacy and safety of ONO-4538 in combination with carboplatin, paclitaxel, and bevacizumab, one of the standards of care, in chemotherapy-naïve subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation, a randomized, double-blind study is to be conducted by using placebo in combination with carboplatin, paclitaxel, and bevacizumab as a comparator.

5.1.2 Planned Sample Size

The target sample size is approximately 265 subjects per group, and approximately 530 subjects in total for the entire study.

5.1.2.1 Rationale

This study is intended to evaluate the superiority of the ONO-4538 group over the placebo group, with PFS as the primary endpoint, in randomized or PD-L1+ (≥ 1%) chemotherapy-naïve subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation. Subjects will be randomized in a 1:1 ratio into either the ONO-4538 group or the placebo group and stratified by PD-L1 expression level (≥ 50% vs 1% to 49% vs < 1% or indeterminate), ECOG Performance Status (0 vs 1), and gender (male vs female).

In this study, one interim analysis of PFS among randomized subjects is planned for early stopping in case of superior efficacy, at the time when approximately 82.4% of the target number of events are observed. To adjust the multiplicity of tests, a significance level for interim and final analyses will be calculated using the Lan-DeMets α spending function (O'Brien-Fleming). The Hochberg method will be used to adjust the multiplicity of tests associated with final analysis in randomized subjects and PD-L1+ (≥ 1%) subjects.

Given that PFS followed an exponential distribution in the placebo group and followed a piecewise exponential distribution with consideration for time to ONO-4538 response in the ONO-4538 group in both PD-L1+ (≥ 1%) subjects and PD-L1− (< 1%) subjects, the hazard ratio of the ONO-4538 group to the placebo group was assumed to be 1.0 for the first 2 months and 0.60 thereafter (the median PFS was 7.0 months in the placebo group and 10.3 months in the ONO-4538 group). Since past clinical study data on ONO-4538 reported that the proportion of PD-L1+ (≥ 1%) subjects to NSCLC subjects was in the range of 52% to 70%[9 21 to 24], the proportion of PD-L1+ (≥ 1%) subjects to randomized subjects was assumed to be 55%. To detect a statistically significant difference via the log-rank test in either randomized subjects or PD-L1+ (≥ 1%) subjects with a two-sided significance level of 5% and a statistical power of approximately 90%, 340 events were required.

Assuming an accrual period of 24 months and a minimum follow-up of 16 months, 530 subjects may be required to observe the required number of events taking into account the number of censored subjects. Therefore, the target sample size was set at 530 subjects. The required number of events and the target sample size in the protocol were calculated by simulation with SAS statistical analysis software (version 9.4).

<Rationale for 7.0-month PFS (median) in the placebo group>

Based on the report that the PFS ranges from 6.2 to 6.9 months in subjects treated with carboplatin, paclitaxel, and bevacizumab in studies in chemotherapy-naïve subjects with non-squamous non-small cell lung cancer,[5 25] PFS was set at 7.0 months in the placebo group.

<Rationale for a period of 2 months to ONO-4538 response>

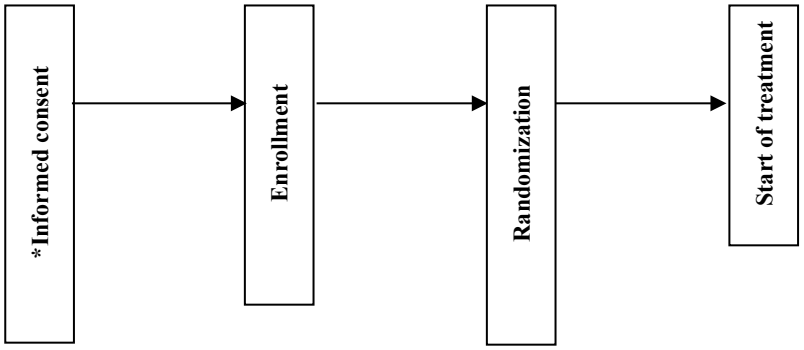
The time to ONO-4538 response was determined by referring to the results from the phase 3 study evaluating the efficacy and safety of ONO-4538 monotherapy in chemotherapy-naïve subjects with non-small cell lung cancer (CA209026).[11]

5.1.3 Planned Study Period

Mar-2017 to Jul-2022

5.2 Enrollment of Subjects

Subjects will be enrolled in the study according to the following procedures:



*: See 12 Subject Informed Consent.

After providing written informed consent, subjects will be enrolled in the study through the Interactive Web Response System (IWRS) (enrollment). Specific procedures for using the IWRS will be provided separately to each study site. The investigator or a person designated by the investigator will enroll the subjects according to predetermined procedures. The following data are required for subjects enrolled after informed consent:

- Date of informed consent
- Date (including year) of birth
- Gender.

After completion of enrollment, subjects who have met all the eligibility criteria will be randomized. Eligible subjects will start to receive the investigational product within 3 days after randomization.

If subjects failed to proceed to randomization, the investigator will inform that the study has been discontinued in these subjects before randomization via the IWRS. If subjects considered eligible at randomization discontinue the study before receiving the investigational product for any reasons, the investigator will inform that the study has been discontinued in these subjects before treatment via the IWRS. The re-enrollment of a subject who failed to proceed to randomization is permitted. However, the re-enrollment of a subject who has received subsequent anticancer therapy for non-squamous non-small cell lung cancer is not acceptable.

The following data are required for the randomization of subjects:

- Subject identification code
- Date (including year) of birth
- ECOG Performance Status (0 vs 1)
- Gender (male vs female).

5.3 Method of Assigning Subjects

Subjects will be randomized in a 1:1 ratio into either the ONO-4538 group or the placebo group and stratified by the following:

- PD-L1 expression level (≥ 50% vs 1% to 49% vs < 1% or indeterminate)
- ECOG Performance Status (0 vs 1)
- Gender (male vs female).

5.4 Blinding/Unblinding

The Sponsor, subjects, investigators, and study site's staff will be blinded to the investigational product assignment.

5.4.1 Maintenance of Blinding

The study will be conducted in a double-blind fashion and the Sponsor will provide drugs that are indistinguishable in appearance and maintain blinding through the IWRS. The Sponsor will not collect the remaining investigational products before key code breaking unless the investigational products have been sealed by the investigational product administrator.

5.4.2 Unblinding

In this study, unblinding is acceptable for the relevant subject in any of the following circumstances:

1. It becomes urgently necessary to know which investigational product is being used for reasons such as the occurrence of a serious adverse event; or
2. The overall response is PD as assessed by both the investigator and IRRC or the protocol-specified final examination (except follow-up) is terminated and subsequent anticancer therapy is administered.
3. The sponsor will request breaking the emergency code for the subject via IWRS, if requested to report on the type of investigational product allocation for the subject by the regulatory authorities, co-developing company, or the like, for the reasons of the onset of serious adverse events etc. In such case, the procedure should define that the code-breaking result will not be informed to the investigator and study staff.

In this study, the treatment assignment will be unblinded through the IWRS. For the method of unblinding, refer to IWRS Procedures.

In principle, the study site's staff will not be informed of PD-L1 analysis results.

5.5 Endpoints

5.5.1 Efficacy Endpoints

5.5.1.1 Primary Endpoint

The primary endpoint of this study is PFS as assessed by the IRRC.

5.5.1.1.1 Rationale

The PFS is defined as the time from randomization to tumor growth or death and is used as a measure of drug efficacy during the period when the underlying disease does not worsen. The primary objective of drug therapy for chemotherapy-naïve subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation is not to cure the disease but to control symptoms and prevent progression. Therefore, prolonged PFS may become an indicator of clinical benefit. PFS is not affected by subsequent anticancer therapy given after completion of the study, which enables proper assessment of prevention of progression by drug therapy. On the other hand, OS enables assessment of survival benefit, based on the subject's status (alive/dead), but if the OS is selected as a primary endpoint, it may be difficult to evaluate the efficacy of ONO-4538 due to the influence of subsequent anticancer therapy, including immune checkpoint inhibitor given after completion of the study.

From the above, PFS as assessed by the IRRC was selected as the primary endpoint of the study.

5.5.1.2 Secondary Endpoints

1. OS
2. PFS (as assessed by the study site's investigator)
3. Objective response rate (as assessed by the IRRC and study site's investigator)
4. Disease control rate (as assessed by the IRRC and study site's investigator)
5. Duration of response (as assessed by the IRRC)
6. Time to response (as assessed by the IRRC)
7. Best overall response (as assessed by the IRRC and study site's investigator)
8. Maximum percentage of change in the sum of diameters of target lesions (as assessed by the IRRC)

5.5.1.2.1 Rationale

These endpoints were selected to evaluate the efficacy of ONO-4538 group for non-squamous non-small cell lung cancer from a range of viewpoints.

5.5.2 Safety Endpoints

1. Adverse events
2. Laboratory tests
3. Vital signs
4. Chest X-ray

5. 12-lead ECG
6. ECOG Performance Status

5.5.2.1 Rationale

These endpoints were selected to evaluate the safety of ONO-4538 group from a range of viewpoints.

5.5.3 Patient Reported Outcomes

1. QoL questionnaire (EQ-5D)
2. Questionnaire to assess disease-related symptoms (LCSS)

5.5.4 Other Tests

Healthcare resource utilization

5.5.5 Biomarkers

[redacted]

3. Tumor markers (as needed)

[redacted]

5. Tumor tissues

5.5.6 Pharmacokinetic Assessment

Serum ONO-4538 concentration

5.5.7 Immunogenicity Assessment

Anti-ONO-4538 antibody

6 INVESTIGATIONAL PRODUCT

An investigational product, also known as the investigational medicinal product in some regions, is defined as the pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with marketing authorization but used or combined (formulated or packaged) differently from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area in accordance with local regulations. It is the responsibility of the investigator to ensure that the investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel in accordance with local regulations.

In this study, the investigational product is ONO-4538 or placebo corresponding to ONO-4538.

6.1 Handling and Dispensing of Investigational Product

As described below, investigational products will be dispensed to each study site.

Product Description and Dosage Form	Carton (content)	Appearance	Storage Conditions (per label)
ONO-4538 or placebo solution for injection	4 vials (100 mg or 0 mg/10 mL)	Clear to opalescent colorless to pale yellow liquid. May contain a few fine particles	Protect from freezing and light. Store at 2°C to 8°C

The investigator should ensure that the investigational product is stored in accordance with the environmental conditions (temperature, light, etc.) as determined by the Sponsor. If concerns regarding the quality or appearance of the investigational product arise, the investigational product should not be dispensed and the Sponsor should be contacted immediately. All drugs for basic treatment not supplied by the Sponsor (carboplatin, paclitaxel, and bevacizumab) should be stored in accordance with the instructions in the package inserts.

The investigator must maintain investigational product documentation that includes all processes required to ensure the drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

It is the responsibility of the investigator and study site to prepare supplies required for preparation and administration of the investigational product (eg, filters, diluents, intravenous drip infusion bags, administration sets) and pre-medications.

For details of preparation and administration and storage of the investigational product, refer to the current version of the Investigator's Brochure, pharmacy reference sheets and/or relevant package inserts and summary of product characteristics.

6.2 Investigational Product Management and Return of Unused Investigational Product

6.2.1 Storage and Management of Investigational Product

It is the responsibility of the investigator to ensure that a current disposition record of the investigational products (those inventoried and dispensed) is maintained at each study site. Records or logs must comply with applicable regulations and guidelines and should include:

- Quantity received and placed in storage area
- Quantity in inventory
- Label identification number or batch number
- Quantity dispensed to and returned by each subject, including subject identification codes
- Quantity transferred to another area/facility for dispensing or storage
- Quantity used for the reasons other than the study procedures (eg, lost, damaged)
- Quantity disposed of at the site (if applicable)
- Amount returned to the Sponsor
- Dates of confirmation by person responsible for investigational product dispensing/accountability and this person's initials, as per the Delegation of Authority Form.

The Sponsor will provide forms to facilitate inventory control if the study site does not have an established system that meets these requirements.

6.2.2 Destruction of Investigational Product

For this study, partially used investigational product vials may be destroyed on site.

Any unused investigational products may not be destroyed unless the investigational product containers must be immediately destroyed as required for safety, or to comply with local regulations (eg, cytotoxics or biologics). On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures must comply with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to the Sponsor upon request.
- Records are maintained that allow for traceability of each container, including the date of disposal, quantity disposed, and identification of the person who disposed of the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor, must be documented.
- Accountability and disposal records should be complete, up-to-date, and available for the Sponsor to review throughout the study period.

If conditions for destruction cannot be met, the responsible Sponsor's Study Monitor will make arrangements for return of the investigational product.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

6.2.3 Return of Investigational Product

If the investigational product is not to be destroyed upon completion or termination of the study, all unused investigational product vials that were supplied by the Sponsor, together with cartons, must be returned to the Sponsor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

7 STUDY TREATMENT

7.1 Investigational Product and Chemotherapy

7.1.1 Dose and Mode of Administration and Duration of Treatment

Subjects will be randomized in a 1:1 ratio into either the ONO-4538 group or the placebo group and then receive all drugs on the same day every 3 weeks. The subjects will be given the investigational product first and start to receive chemotherapy at least 30 minutes after completion of the investigational product infusion.

The dose and mode of administration and duration of treatment with the investigational product and chemotherapy are as follows.

7.1.1.1 Dose and Mode of Administration and Duration of Treatment with Investigational Product

The investigational product (ONO-4538 360 mg or placebo) will be administered intravenously over 30 minutes every 3 weeks. The investigational product will continue until the subject meets any of 7.1.4.1 Investigational Product Discontinuation Criteria.

No escalations or reductions in the dose of the investigational product will be allowed. Please refer to the current version of the Investigator's Brochure and pharmacy reference sheets for proper storage, handling, preparation, and administration of the investigational product.

7.1.1.1.1 Rationale

In this study, ONO-4538 is to be administered intravenously as repeated doses of 360 mg every 3 weeks. The rationale is explained below.

In phase 1 studies of ONO-4538 monotherapy (ONO-4538-01 and CA209003), intravenous ONO-4538 when administered repeatedly every 2 weeks has been well tolerated at doses up to 20 mg/kg in Japanese subjects and 10 mg/kg in non-Japanese subjects. However, given that chemotherapy is to be administered in combination with ONO-4538 generally once every 3 weeks, use of the same dosing regimen for chemotherapy (ie, repeated intravenous

administration every 3 weeks) might be preferable in an actual clinical setting and for greater convenience for subjects. Based on the above, the Japanese phase 1 study (ONO-4538-04) of ONO-4538 in combination with chemotherapy evaluated the safety of ONO-4538 10 mg/kg in combination with carboplatin, paclitaxel, and bevacizumab in chemotherapy-naïve subjects with advanced non-small cell lung cancer. As for safety profiles, ONO-4538 does not exacerbate the adverse drug reactions to chemotherapy and it has been well tolerated. Thus, ONO-4538 was considered to be administered once every 3 weeks in this study.

Taking convenience into consideration, recent studies of ONO-4538 examined the fixed dose regimen (mg) of ONO-4538 not adjusted for body weight and clinical trials with ONO-4538 360 mg (once every 3 weeks) are currently ongoing. A population pharmacokinetic model, which included data from 187 Japanese patients with malignant tumor (median weight, 59.1 kg; range, 34.1 to 93.4 kg), was used to predict steady-state serum ONO-4538 concentrations following repeated intravenous administration of ONO-4538 360 mg every 3 weeks in 1000 Japanese patients with malignant tumor. Predicted values (medians [90% prediction intervals]) of concentration at the end of infusion (Ceoi), trough concentration (Cmin), and average concentration (Cavg) are shown in Table 7.1.1-1. These values were considered not to exceed steady-state exposure obtained with 10 mg/kg given as repeated intravenous administration every 2 weeks, a regimen that has been shown to be tolerable in ONO-4538-01 and CA209003. Furthermore, these values were also considered not to be below steady-state exposure obtained with 3 mg/kg given as repeated intravenous doses every 2 weeks, a regimen that had proven to be effective in other tumor types. ONO-4538 is a human monoclonal antibody and very unlikely to cause drug interactions with combined chemotherapy. Thus, 360 mg was considered to be used as the dose of ONO-4538 in this study.

Based on the above, ONO-4538 is to be administered as repeated intravenous doses of 360 mg every 3 weeks.

Table 7.1.1-1: Predicted Steady-State Exposure of ONO-4538

Dosing Regimen	Ceoi [µg/mL]	Cmin [µg/mL]	Cavg [µg/mL]
360 mg Q3W	185 (91.5–392)	69.6 (22.6–213)	99.0 (46.1–224)
3 mg/kg Q2W	116 (56.8–239)	59.6 (17.6–161)	75.3 (33.6–152)
10 mg/kg Q2W	386 (195–791)	197 (71.5–514)	252 (125–519)

Median (90% prediction interval)
Q3W, dosing every 3 weeks; Q2W, dosing every 2 weeks

7.1.1.2 Dose and Mode of Administration and Duration of Treatment with Chemotherapy

Subjects will receive carboplatin AUC 6, paclitaxel 200 mg/m^2, and bevacizumab 15 mg/kg every 3 weeks. When calculating doses, in principle, the dose (mg) will be rounded to one decimal place.

It is permissible for the initial dose of paclitaxel and bevacizumab to be calculated based on the body weight measured at the time of randomization, instead of that measured on the day of first

dosing (predose). The dose will be adjusted in each cycle if the subject's weight changes by ≥ 10% compared to the weight used to calculate the initial dose. If the subject's weight changes by ≥ 10% compared to the weight used to calculate the initial dose on the day of dosing, dose adjustment is acceptable for future infusions. Thereafter, similar action will be taken for any further changes in the subject's weight (≥ 10% compared to the weight used to calculate the dose adjusted).

Carboplatin dose will be calculated using the Calvert formula as follows:

Carboplatin dose (mg) = Target AUC × [(Creatinine clearance (mL/min) + 25]

Creatinine clearance calculation is based on the Cockcroft/Gault formula and should include the most recent serum creatinine and most recent weight. If calculation of the creatinine clearance by the Cockcroft/Gault formula yields a result of > 125 mL/min, then a creatinine clearance should be calculated by an alternative formula per institutional standards or capped at 125 mL/min. The dose of carboplatin may be capped as per local standards.

The mode of administration should be based on the procedures specified by the study site and recommended procedures are described below.

Subjects will receive paclitaxel as a 180-minute IV infusion on Day 1 of each cycle (3 weeks). On Day 1 of each cycle, subjects will receive carboplatin as a 30-minute IV infusion at least 30 minutes after paclitaxel treatment completion. On Day 1 of each cycle, subjects will receive bevacizumab as an IV infusion at least 30 minutes after carboplatin treatment completion. The initial administration of bevacizumab will be given intravenously over 90 minutes, and if well tolerated, the duration of the second administration will be reduced to 60 minutes and to 30 minutes in subsequent cycles.

Carboplatin and paclitaxel will be administered for up to 4 cycles and if deemed safe, treatment may continue for up to a maximum of 6 cycles. Even after the completion of treatment with carboplatin and paclitaxel, bevacizumab will be administered intravenously on Day 1 of each cycle until RECIST 1.1 defined PD, unacceptable toxicity, or withdrawal of consent. Even where carboplatin and paclitaxel have been discontinued for reasons such as adverse events, bevacizumab may be continued if deemed safe.

7.1.1.2.1 Rationale

To standardize the dose and mode of administration, the dosing regimens of carboplatin, paclitaxel, and bevacizumab are based on local standards, such as package inserts and clinical practice guidelines used in countries participating in this study.

7.1.2 Dosing Criteria

Dosing criteria are defined as follows:

Discontinuation: The investigational product and/or chemotherapy should not be resumed.

Delay: The dosing interval should be prolonged or protocol-specified dosing should be delayed.

Skip: A planned dose of any chemotherapy is skipped to the subsequent dosing schedule.

Subjects must receive the investigational product and chemotherapy on the same day. If subjects fail to meet any of the criteria listed in 7.1.2.1 Dosing Criteria for Investigational Product or 7.1.2.2 Dosing Criteria for Chemotherapy, investigational product and chemotherapy will be, in principle, delayed. If subjects meet any of the criteria listed in 7.1.4.1 Investigational Product Discontinuation Criteria or 7.1.4.2 Chemotherapy Discontinuation Criteria, the investigational product or chemotherapy will be discontinued.

Radiographic tumor assessments will be performed to determine antitumor activity, even if dosing is delayed, every 6 weeks until Week 48. Thereafter, assessments will be performed every 12 weeks.

7.1.2.1 Dosing Criteria for Investigational Product

1. No Grade ≥ 3 drug-related adverse event (adverse drug reaction). Any ≥ Grade 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay if approved by the Sponsor's Medical Monitor.
2. No Grade 1 or 2 drug-related interstitial lung disease (such as interstitial pneumonia, organizing pneumonia, pneumonitis, and pulmonary infiltration), or Grade 2 drug-related diarrhea or colitis. If subjects resume treatment with the investigational product after the interstitial lung disease has resolved, CT scan images should be submitted and treatment may be resumed only if approved by the Sponsor's Medical Monitor. If an interstitial lung disease recurs after treatment is resumed, the investigational product should be discontinued.
3. No Grade ≥ 2 drug-related increase in creatinine.
4. No Grade ≥ 2 drug-related neurotoxicity.
5. No drug-related increase by ≥ 2 grades in AST (GOT), ALT (GPT), or total bilirubin from baseline (for instance, an increase from Grade 1 to Grade 3 or from Grade 0 to Grade 2).
6. Subjects are eligible to receive the investigational product at the investigator's discretion.

Subjects who require a delay in administration of the investigational product should be re-evaluated weekly or more frequently if clinically indicated and resume the investigational product when dosing criteria are met. If any adverse event is thought to be related to the investigational product, and only if approved by the Sponsor's Medical Monitor, then the investigational product may be skipped.

7.1.2.2 Dosing Criteria for Chemotherapy

1. Neutrophil count ≥ 1500/mm^3
2. Platelets ≥ 100000/ mm^3
3. No ≥ Grade 3 drug-related adverse event, with the following exceptions for hypertension, lymphopenia, or increases in AST (GOT), ALT (GPT), or total bilirubin:

- Subjects with Grade 3 bevacizumab-related hypertension, which can be controlled by drugs, may be eligible for dosing if discussed with and approved by the Sponsor's Medical Monitor.
- Grade 3 lymphopenia does not require dose delay.
- No drug-related increase by ≥ 2 grades in AST (GOT), ALT (GPT), or total bilirubin from baseline.

4. Subjects are eligible to receive chemotherapy in the opinion of the investigator. For details regarding the dose delay criteria, the investigator should refer to the relevant chemotherapy drug package inserts.

If any non-hematologic adverse event violating the dosing criteria above is thought to be related to the particular drug(s) in the chemotherapy regimen, then only the drug(s) concerned may be skipped in that cycle while the other drugs may be given. If any event that, in the judgment of the investigator, requires skipping a planned dose of any chemotherapy occurs, it can be skipped only if approved by the Sponsor's Medical Monitor. Once the adverse event has improved and the dosing criteria are met, administration of the skipped drug should be resumed with the next scheduled cycle so that the three chemotherapeutic drugs are regularly administered on the same day. Please refer to 7.1.3.2 Dose Reduction Criteria for Chemotherapy to determine if dose reduction of the resumed drug is required. All drugs in the chemotherapy regimen may not be skipped simultaneously; however, once the administration of carboplatin and paclitaxel is completed, it is acceptable that bevacizumab is skipped and the investigational product alone is administered. Subjects who require a delay in administration of chemotherapy should be re-evaluated weekly or more frequently if clinically indicated and resume the chemotherapy when dosing criteria are met.

7.1.3 Dose Reduction Criteria

7.1.3.1 Dose Reduction Criteria for Investigational Product

There are no dose reduction criteria for the investigational product.

7.1.3.2 Dose Reduction Criteria for Chemotherapy

Dose reductions of carboplatin and paclitaxel will be performed according to Table 7.1.3-1 and Table 7.1.3-2 below. Even if subjects do not meet any of the criteria listed in Table 7.1.3-2, dose reductions of carboplatin and paclitaxel may be performed when the investigator deems that subjects need dose reduction. Once carboplatin or paclitaxel is reduced, the subject's safety needs to be carefully monitored by means such as increasing the number of laboratory tests. Chemotherapy will be continued at the same dose or be further reduced in subsequent cycles, and no dose escalation is permitted.

No dose reductions of bevacizumab are allowed.

Table 7.1.3-1: Dose Reductions of Carboplatin and Paclitaxel

Dose Level	Carboplatin	Paclitaxel
Starting dose	AUC 6	200 mg/m^2
First dose reduction	AUC 5	150 mg/m^2
Second dose reduction	AUC 4	100 mg/m^2
Third dose reduction	Discontinue	Discontinue

Table 7.1.3-2: Dose Reduction Criteria for Carboplatin and Paclitaxel

Adverse Event	Carboplatin	Paclitaxel
Febrile neutropenia, Grade ≥ 3	Reduce one dose level	Reduce one dose level
Platelet count decreased, Grade ≥ 3	Reduce one dose level	Reduce one dose level
Diarrhea, Grade ≥ 3	No change	Reduce one dose level
Peripheral neuropathy, Grade ≥ 2	No change	Reduce one dose level

7.1.4 Treatment Discontinuation Criteria

During the treatment period, subjects meeting any of the criteria listed below will discontinue treatment with the investigational product or chemotherapy.

7.1.4.1 Investigational Product Discontinuation Criteria

1. The overall response was PD as assessed by the investigator per RECIST 1.1 criteria.
2. Subjects experienced a worsening of clinical symptoms associated with disease progression.
3. Any Grade ≥ 3 interstitial lung disease (such as interstitial pneumonia, organizing pneumonia, pneumonitis, and pulmonary infiltration), regardless of whether this was related to the investigational product or not.
4. Any Grade ≥ 2 drug-related eye disorder (eye pain or reduced vision) that does not improve to Grade 1 or less by topical therapy.
5. Any Grade ≥ 3 drug-related bronchospasm, diarrhea, colitis, neurotoxicity, hypersensitivity reactions, infusion reactions (including fever, chill, nausea, pain, headache, cough, pruritus, or rash), or uveitis.
6. Any Grade ≥ 3 drug-related thrombocytopenia for > 7 days or associated with bleeding.
7. Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
   - AST (GOT) or ALT (GPT) > 5 to 10 × ULN for > 2 weeks
   - AST (GOT) or ALT (GPT) > 10 × ULN
   - Total bilirubin > 5 × ULN
   - AST (GOT) or ALT (GPT) > 3 × ULN and total bilirubin > 2 × ULN

8. Subjects did not receive any investigational product due to reasons such as adverse events within 6 weeks after the last administration. This does not apply to dosing suspension for > 6 weeks for steroid tapers.
9. Subjects were ineligible for continued investigational product for reasons of efficacy or safety, in the judgment of the investigator.

If the investigator considers that a subject meeting the above criterion 1 or 8 satisfies all the criteria listed below, the investigational product may be continued after consultation with the Sponsor's Medical Monitor. For the above criterion 1, the investigator will confirm the subject's willingness to continue to receive the investigational product before resuming treatment, and obtain written consent through the informed consent form prepared separately.

Treatment with the investigational product must be terminated in subjects with further progression defined as an additional ≥ 20% increase in the sum of diameters of all measurable lesions per RECIST 1.1 criteria from the time of assessment for continued investigational product after initial PD (including all target lesions and new measurable lesions[Note 1]).

1. No rapid disease progression is noted and continued treatment with the investigational product is expected to bring clinical benefit.
2. The investigational product is well tolerated.
3. Stable ECOG Performance Status
4. Continued investigational product will not delay an intervention to prevent serious complications of disease progression (such as brain metastases).

The decision to discontinue the investigational product should be made separately from the decision to discontinue concomitant chemotherapy. If subjects do not meet 7.1.4.2 Chemotherapy Discontinuation Criteria but meet 7.1.4.1 Investigational Product Discontinuation Criteria before the investigational product plus chemotherapy combination therapy cycles have been completed, carboplatin and paclitaxel may be administered for up to 6 cycles and bevacizumab treatment may be continued until RECIST 1.1 defined PD, unacceptable toxicity, or withdrawal of consent.

Note 1): New lesions are considered measurable at the time of initial PD if the longest diameter is at least 10 mm (a short axis of at least 15 mm for pathological lymph nodes). Any new lesion considered non-measurable at the time of initial PD may become measurable if the longest diameter increases to at least 10 mm (a short axis of at least 15 mm for pathological lymph nodes) and therefore be included in the measurement of all measurable lesions.

7.1.4.2 Chemotherapy Discontinuation Criteria

1. The overall response is PD as assessed by the investigator per RECIST 1.1 criteria.
2. Subjects experienced a worsening of clinical symptoms associated with disease progression.
3. Any Grade ≥ 3 peripheral neuropathy; however, bevacizumab may be continued.

4. Any Grade ≥ 3 drug-related thrombocytopenia associated with clinically significant bleeding.
5. Any drug-related liver function test abnormality that meets the following criteria:
   - AST (GOT) or ALT (GPT) > 5 to 10 × ULN for > 2 weeks
   - AST (GOT) or ALT (GPT) > 10 × ULN
   - Total bilirubin > 5 × ULN
   - AST (GOT) or ALT (GPT) > 3 × ULN and total bilirubin > 2 × ULN.
6. Any drug-related adverse event (7.1.3.2 Dose Reduction Criteria for Chemotherapy) that recurs after two prior dose reductions for the same drug-related adverse event requires discontinuation of the chemotherapy, with the exception of bevacizumab.
7. Any Grade ≥ 3 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the chemotherapeutic drug(s) thought to be causing the reaction. The drug(s) not thought to be related to the hypersensitivity reaction or infusion reaction may be continued.
8. Any Grade 4 drug-related adverse event that the investigator deems inappropriate to be managed by dose reduction(s) requires discontinuation of the drug(s) thought to be causing the event. The drug(s) not thought to be related to the event may be continued.
9. Any adverse event that leads to delay in dosing of any chemotherapeutic drug(s) lasting > 6 weeks from the previous dose requires discontinuation of that drug(s) thought to be causing the event. Resuming treatment is allowed in the following cases only if approved by the Sponsor's Medical Monitor prior to re-initiating treatment:
   - Re-initiation following dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons.
   - Re-initiation of a drug(s) unrelated to an adverse event that leads to a dosing delay lasting > 6 weeks.
10. Any adverse event, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued chemotherapy dosing. The investigator should consult the package insert for the chemotherapy drug(s) for additional guidance on dose discontinuation.

The decision to discontinue chemotherapy should be made separately from the decision to discontinue the concomitant investigational product. If subjects meet 7.1.4.2 Chemotherapy Discontinuation Criteria before completing chemotherapy with the investigational product, the investigational product may be continued until RECIST 1.1 defined PD, unacceptable toxicity, or withdrawal of consent. If a subject receiving the investigational product and chemotherapy meets any of the discontinuation criteria and the investigator cannot determine whether the adverse event is related to either the investigational product or chemotherapy, the subject will discontinue receiving all drugs.

7.2 Concomitant Treatments

7.2.1 Treatments Prohibited During the Study

The following treatments are prohibited during the study (from the time of informed consent through completion of the protocol-specified final examination [except outcome survey]); except

when the final examination at the completion of treatment period (the discontinuation) is completed and the treatment is medically unavoidable. For any drugs other than those mentioned below, please refer to the current version of the package inserts for chemotherapy administered concomitantly in the study:

1. Immunosuppressive drugs
2. Adrenocorticosteroids equivalent to prednisone > 10 mg/day[Note 1)]
3. Antineoplastic drugs except chemotherapy assigned in the study (such as chemotherapy, molecular targeted therapy, and immunotherapy[Note 2]])
4. Surgery for malignant tumor
5. Radiotherapy (including chemoradiation)[Note 3)]
6. Radiopharmaceuticals[Note 4)]
7. Bisphosphonates and anti-RANKL antibodies[Note 5)]
8. Transplantation therapy
9. Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment with the investigational product and until 100 days after the last dose of the investigational product
10. Any other unapproved drugs (including investigational treatments, unapproved combination drugs, and drugs with new dosage forms).

[Note 1)]: Subjects are permitted the local use of topical, intra-articular, intranasal, ocular, or inhalational adrenocorticosteroids or the temporary use of adrenocorticosteroids for the treatment or prophylaxis of contrast media allergy or adverse events. The Sponsor's Medical Monitor must be consulted for continued treatment with the investigational product or chemotherapy in subjects requiring systemic adrenocorticosteroids for treating drug-related adverse events and if necessary, the investigator will determine whether or not to continue treatment with the investigational product or chemotherapy after consultation with the Sponsor's Medical Monitor.

[Note 2)]: Including local therapy with Picibanil.

[Note 3)]: Radiotherapy to brain or meningeal metastasis in the screening period is permitted unless subjects meet 4.3 Exclusion Criteria 22. As for palliative radiotherapy, only procedures specified in 7.2.2.1 Palliative Radiotherapy are permitted.

[Note 4)]: Use of radiopharmaceuticals for examination and diagnosis is permitted.

[Note 5)]: Use of bisphosphonates and anti-RANKL antibodies is acceptable only when their administration is started before randomization and the same dosage and administration are maintained.

7.2.1.1 Rationale

The information is provided because of potential effects on the efficacy and safety assessments of ONO-4538 in combination with other therapies.

7.2.2 Permitted Therapy

7.2.2.1 Palliative Radiotherapy

Palliative radiotherapy for non-target lesions, except the chest lesion, is permitted only if clinically indicated. Radiographic tumor assessments should be performed wherever possible before starting palliative radiotherapy.

The potential for overlapping toxicities of radiotherapy and ONO-4538 is not currently known. As concurrent radiotherapy and ONO-4538 have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then the investigational product and chemotherapy should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and adverse events related to radiotherapy should resolve to Grade 1 or less prior to resuming administration of the investigational product and chemotherapy.

7.2.2.2 Prophylactic Administration

Prophylactic medications for administration of the investigational product or chemotherapy should follow the procedures specified by the study site. Recommended medications and procedures for administration of the investigational product are described below.

7.2.2.2.1 Prophylactic Medications for Administration of Investigational Product

Prior prophylactic use of acetaminophen or diphenhydramine is recommended for subjects who are at risk of infusion-related reaction after administration of the investigational product.

7.2.2.2.1.1 Rationale

For potential effects on the efficacy and safety assessments of ONO-4538 in combination with other therapies.

7.3 Discontinuation for Supply of Investigational Product

The investigational product may be supplied to subjects by the Sponsor unless subjects meet 7.1.4 Treatment Discontinuation Criteria or 13 Stopping Rules or Discontinuation Criteria for Individual Subjects. The Sponsor will stop the supply of the investigational product if any of the following occurs:

1. The marketing application for this indication is rejected by the relevant regulatory authority;
2. The study is terminated;
3. The subject can obtain ONO-4538 with the same dosage regimen as that used in this study under public or private health insurance; or
4. Therapeutic alternatives become available.

7.4 Post-Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive the investigational product supplied by the Sponsor. The investigational product will be provided via an extension of the study, a rollover study requiring approval by the responsible health authorities and ethics committee, or through another mechanism at the Sponsor's discretion.

8 TIME AND EVENTS SCHEDULE AND OBSERVATIONS

8.1 Time and Events Schedule

The study consists of the screening period, treatment period, and follow-up period. In the protocol synopsis, Figure 2-1 shows an overview of the study design.

8.1.1 Screening Period

Examinations and assessments during the screening period will be performed after obtaining the written consent form from the subject. The investigator will enroll subjects who meet 4.2 Inclusion Criteria and do not meet 4.3 Exclusion Criteria, and are considered eligible for the study. In the protocol synopsis, Table 6-1 shows the assessments and tests in the screening period and the time and events schedule.

8.1.2 Treatment Period

8.1.2.1 Investigational Product

ONO-4538 360 mg or placebo will be administered intravenously over 30 minutes every 3 weeks. Subjects who meet all 7.1.2.1 Dosing Criteria for Investigational Product and do not meet any of 7.1.4.1 Investigational Product Discontinuation Criteria can repeatedly receive ONO-4538 or placebo. In the protocol synopsis, Table 6-1 shows the assessments and tests in the treatment period and the time and events schedule.

8.1.2.2 Chemotherapy

Subjects will receive carboplatin AUC 6, paclitaxel 200 mg/m^2, and bevacizumab 15 mg/kg every 3 weeks. Carboplatin and paclitaxel will be administered for up to 4 cycles and if deemed safe, treatment may continue for up to a maximum of 6 cycles. Even after the completion of treatment with carboplatin and paclitaxel, bevacizumab will be administered intravenously on Day 1 of each cycle until RECIST 1.1 defined PD, unacceptable toxicity, or withdrawal of consent. In the protocol synopsis, Table 6-1 shows the assessments and tests in the treatment period and the time and events schedule.

8.1.3 Follow-up Period

Subjects meeting any of 7.1.4 Treatment Discontinuation Criteria will be evaluated at the completion of the treatment period (at discontinuation) and enter the follow-up period. In the protocol synopsis, Table 6-1 shows the assessments and tests in the follow-up period and the time and events schedule.

8.2 Observations

8.2.1 Demographics

The investigator and study staff will perform examinations and enter the following items on the eCRF during the screening period. Clinical classification and staging will be assessed according to the UICC TNM classification, 7th edition (hereinafter called TNM classification).

- Subject identification code (ID)
- Date of obtaining the informed consent
- Gender
- Date (including the year) of birth
- Race
- Ethnicity
- Height
- Body weight
- Past history (past history collected within 1 year before the randomization and possibly other clinically significant past history)
- Complications
- Smoking history
- ECOG Performance Status
- Date (including the year) of diagnosis of primary disease
- Staging and TNM classification
- Histology of non-squamous non-small cell lung cancer
- Primary site and metastatic site of non-squamous non-small cell lung cancer
- Site of recurrence (recurrent non-squamous non-small cell lung cancer)
- Tumor diameter of target lesion
- Past treatment for cancers (including a history of surgery, radiotherapy, or medical treatment)

8.2.2 Drug Administration and Provision of Concomitant Treatments

8.2.2.1 Administration of Investigational Product and Chemotherapy

The investigator and study staff will enter the details of administration (dosage, date of administration, time of start of administration, and time of completion of administration) of the investigational product and chemotherapy on the eCRF.

8.2.2.2 Administration of Other Drugs and Concomitant Treatments

All drugs and concomitant treatments used from the start date of administration of the investigational product to 100 days after the last administration of the investigational product or chemotherapy, whichever comes later will be reviewed. The name of treatment, duration of administration, route of administration, reason for administration, and dosage regimen will be entered on the eCRF.

Presence or absence of subsequent anticancer therapy for non-squamous non-small cell lung cancer, start date of treatment, and details of therapy in addition to outcome survey will be reviewed as much as possible during the follow-up period.

When drug-related adverse events or adverse events leading to discontinuation are reported at the start of follow-up, concomitant treatments administered for these events should be investigated at appropriate intervals until no further follow-up is required because the events have resolved or are resolving, or the symptoms become stable.

Results of examinations on subsequent anticancer therapy and concomitant treatments for non-squamous non-small cell lung cancer will be entered on the eCRF.

In addition, details of the follow-up are shown in 8.2.10 Follow-up.

8.2.3 Efficacy Endpoints

The investigator and study staff will perform measurements and examinations for the following items at specified time points. For subjects who discontinue the study, measurements and examinations will be performed if possible with sufficiently considering subject safety.

8.2.3.1 Radiographic Tumor Assessments (Measurement of Tumor Diameter and Evaluation of Antitumor Activity)

CT/MRI scans of the chest, abdomen, and pelvis will be obtained. The same imaging method will be used to evaluate the antitumor activity throughout the study. In addition, the presence or absence of brain metastasis will be confirmed by CT/MRI of the head before the start of the study, and the presence or absence of bone metastasis will be confirmed by X-ray, FDG-PET, or bone scintigraphy depending on clinical symptoms. CT/MRI of the head, X-ray, FDG-PET, and bone scintigraphy will be performed depending on clinical symptoms after the start of the study.

The antitumor activity will be evaluated per RECIST 1.1 criteria (refer to APPENDIX 1). In addition, radiographic tumor assessments at the completion of the treatment period (at discontinuation) and 28 days after the completion of the treatment period will be performed as needed if at least 15 days have elapsed since the last examination or if medically indicated; except when the last examination is within the time window for completion of the treatment period (at discontinuation) or 28 days after completion of the treatment period.

Radiographic tumor assessments (measurement of tumor diameter and evaluation of antitumor activity) will be performed at the following time points. The investigator will determine whether

or not treatments can be continued based on radiographic tumor assessments per RECIST 1.1 criteria. Imaging data should be submitted to the IRRC, and at the time of investigator-assessed PD per RECIST 1.1 criteria, the study site must request a radiographic tumor assessment to the IRRC. The radiographic tumor assessment by the IRRC will be conducted by a blinded, independent radiologist, and subjects whose PD is not confirmed by the IRRC will be required to continue radiographic tumor assessments according to the protocol-specified schedule and their subsequent tumor images must be submitted to the IRRC (if clinically feasible). Subjects receiving the investigational product beyond PD must continue radiographic tumor assessments until such treatment has been discontinued. If clinically acceptable, subsequent anticancer therapy should, in principle, begin only after RECIST 1.1 defined PD has been assessed based upon the radiographic tumor assessment by the IRRC. Subjects who start therapy specified in 7.2.2.1 Palliative Radiotherapy without prior assessment of RECIST 1.1 defined PD by the IRRC must undergo radiographic tumor assessments before receiving such therapy wherever possible (if clinically feasible) and their tumor assessment images must be submitted to the IRRC. If thoracentesis, pericardiocentesis, or abdominal paracentesis is considered, for example due to clinical symptoms, a CT scan should be performed wherever possible before these treatments. Radiographic tumor assessments may be discontinued when the investigator and the IRRC both assess the subject to have met RECIST 1.1 criteria for PD or subsequent anticancer therapy is started. Procedures for CT/MRI and data transmission to the central image analysis laboratory will follow the written operating procedures separately specified.

<Time points>

- Screening period
  - The latest results are available if the tumor evaluation is conducted within 28 days prior to the randomization.
- Treatment period
  - The first tumor assessment will be performed 6 weeks after the first day of treatment (+ 7 days). Subsequent tumor assessments will be performed every 6 weeks (± 7 days) for the first 12 months (until Week 48) and after Week 48, assessments will be conducted every 12 weeks (± 7 days) until PD.
  - At the completion of the treatment period (at discontinuation)
- Follow-up period
  - 28 days after the completion of the treatment period[note 1)]
  - Follow-up[note 1)]

Note 1): Subjects who discontinue treatment during the treatment period because of safety concerns or disease progression despite an overall response of CR, PR, or SD should continue radiographic tumor assessments if possible until the start of subsequent anticancer therapy for non-squamous non-small cell lung cancer or where their condition is assessed as PD or recurrence per RECIST 1.1 (refer to APPENDIX 1). Subjects whose PD is not confirmed by the IRRC will be required to continue radiographic tumor assessments according to the protocol-specified schedule and their subsequent tumor images must be submitted to the IRRC (if clinically feasible). If thoracentesis, pericardiocentesis, or abdominal paracentesis is

considered, for example due to clinical symptoms, a CT scan should be performed wherever possible before these treatments.

8.2.4 Safety Items

The investigator and study staff will perform measurements and examinations for the items shown in 8.2.4.1 to 8.2.4.7. For subjects who discontinue the study, the investigator and study staff will perform measurements and examinations if possible while taking subject safety into full consideration.

8.2.4.1 Vital Signs, Body Weight, Height, 12-Lead Electrocardiogram

8.2.4.1.1 Vital Signs [Systolic/Diastolic Blood Pressure, Pulse Rate, Percutaneous Oxygen Saturation (SpO_2), and Body Temperature], Body Weight, Height

Vital signs, body weight, and height will be measured at the following time points [body weight will be measured only during the screening period, on Day 1 (predose) and Day 22 of each cycle during the treatment period, at the completion of the treatment period (at discontinuation), and 28 days after the completion of the treatment period; height will be measured only during the screening period]. Systolic/diastolic blood pressure, pulse rate, and SpO_2 will generally be measured at rest in the same position throughout the study.

<Time points>

- Screening period
  - Days −7 to −1 starting from the first day of treatment will be adopted as the time window.
- Treatment period
  - Cycle 1: Predose on Day 1, postdose on Day 1, Day 8, and Day 22
  - Cycle 2 and subsequent cycles: Predose on Day 1 of each cycle[note 1)], Day 22
  - At the completion of the treatment period (at discontinuation)[note 2)]
- Follow-up period
  - 28 days after the completion of the treatment period[note 2)]

Note 1): Data obtained on Day 22 in the previous cycle may be used except when medically indicated. However, an examination must be performed if at least 2 days (vital signs) and 8 days (body weight) have elapsed since the last examination. An examination will be performed as needed if medically indicated.

Note 2): Previous test results may be used except when medically indicated. However, an examination must be performed if at least 2 days (vital signs) and 8 days (body weight) have elapsed since the last examination. An examination will be performed as needed if medically indicated.

8.2.4.1.2 12-Lead Electrocardiogram [Heart Rate (HR), PR Interval, RR Interval, QRS Complex, and QT Interval]

12-lead electrocardiogram (ECG) (HR, PR interval, RR interval, QRS complex, and QT interval) will be recorded at rest using each site's electrocardiograph at the following time points. The investigator will confirm abnormal findings after 12-lead ECG.

<Time points>

- Screening period
  - Days −7 to −1 starting from the first day of treatment is adopted as the time window.
- Treatment period
  - Day 22 of Cycles 2, 6, and 8
  - At the completion of the treatment period (at discontinuation)[note 1)]
- Follow-up period
  - 28 days after the completion of the treatment period[note 1)]

Note 1): Previous test results may be used except when medically indicated. However, an examination must be performed if at least 8 days have elapsed since the last examination. An examination will be performed as needed if medically indicated.

8.2.4.2 Chest X-Ray

Chest X-ray will be taken at the following time points. The investigator will confirm abnormal findings after chest X-ray. In addition, for any symptoms/signs or laboratory data indicative of respiratory disease, chest X-ray may be performed as needed in addition to scheduled examinations during the study (from the time of informed consent through completion of the protocol-specified final examination [except outcome survey]).

<Time points>

- Screening period
  - Days −7 to −1 starting from the first day of treatment is adopted as the time window.
- Treatment period
  - Cycle 2 and subsequent cycles: Day 22 of each Cycle
  - At the completion of the treatment period (at discontinuation)[note 1)]
- Follow-up period
  - 28 days after the completion of the treatment period[note 1)]

Note 1): Previous test results may be used except when medically indicated. However, an examination must be performed if at least 8 days have elapsed since the last examination. An examination will be performed as needed if medically indicated.

8.2.4.3 Laboratory Tests

8.2.4.3.1 Hematology, Serum chemistry, Urinalysis

Hematology, serum chemistry, and urinalysis will be performed at the following time points. Measurement will be generally performed at each study site.

<Time points>

- Screening period
  - Days −7 to −1 starting from the first day of treatment is adopted as the time window.
- Treatment period
  - Cycle 1: Day 8, Day 22
  - Cycle 2 and subsequent cycles: Predose on Day 1 of each cycle[note 1)], Day 22
  - At the completion of the treatment period (at discontinuation)[note 2)]
- Follow-up period
  - 28 days after the completion of the treatment period[note 2)]

Note 1): Data obtained on Day 22 in the previous cycle may be used except when medically indicated. However, an examination must be performed if at least 8 days have elapsed since the last examination. An examination will be performed as needed if medically indicated.

Note 2): Previous test results may be used except when medically indicated. However, an examination must be performed if at least 8 days have elapsed since the last examination. An examination will be performed as needed if medically indicated.

<Test items>

Hematology:	Red blood cell count, MCV, MCH, MCHC, hemoglobin, hematocrit, white blood cell count, differential white blood count (neutrophil, lymphocyte, eosinophil, basophil, monocyte), platelet count
Serum chemistry:	Albumin, ALP, AST (GOT), ALT (GPT), total bilirubin, direct bilirubin, γ-GTP, total protein, creatinine, blood sugar level, LDH, BUN, uric acid, CK (CPK), P, Ca, Na, K, Cl
Urinalysis:	Specific gravity, protein, sugar, occult blood, sediment (white blood cell, red blood cell)

8.2.4.3.2 Immunological/Hormonal Tests

Immunological/hormonal tests will be performed at the following time points. Blood samples will be collected in the morning as much as possible, and the time of blood samples will be recorded on each test day. Measurement will be performed at the designated central laboratory.

<Time points>

- Screening period
  - The latest results are available if the test is conducted within 28 days prior to the randomization.
- Treatment period
  - Cycle 2 and subsequent cycles: Day 22 of even cycles
  - At the completion of the treatment period (at discontinuation)[note 1)]
- Follow-up period
  - 28 days after the completion of the treatment period[note 1)]

Note 1): Previous test results may be used except when medically indicated. However, an examination must be performed if at least 8 days have elapsed since the last examination. An examination will be performed as needed if medically indicated.

<Test items (blood volume per sample collection: 9 mL[note 2]])>

Immunological test:	Rheumatoid factor (RA), C-reactive protein (CRP), antinuclear antibody (ANA), SP-D (optional), KL-6 (optional)
Hormonal test:	Thyroid-stimulating hormone (TSH), free triiodothyronine (free T3), free thyroxine (free T4)

The above items will be measured, and if clinically significant changes in RA, CRP, ANA, TSH, or free T4 are found, the following items will also be measured as soon as possible. SP-D and KL-6 tests are optional. In addition, appropriate items including adrenocorticotropic hormone (ACTH, blood volume per sample collection: 2 mL) will be added as needed.

Note 2): If SP-D and KL-6 are not measured, the blood volume will be 7 mL.

<Added items (blood volume per sample collection: 15 mL)>

Anti-DNA antibody, anti-SSA antibody (Ro), anti-SSB antibody (La), anti-thyroglobulin antibody, anti-LKM antibody, anti-phospholipid antibody, anti-GAD antibody, anti-neutrophil cytoplasmic autoantibody, β1C/β1A globulin (C3), β1E globulin (C4), serum complement level (CH50), thyroid-stimulating hormone stimulating receptor antibody, antithyroid peroxidase antibody

8.2.4.4 Pregnancy Test (Women of Childbearing Potential Only)

Women of childbearing potential[note)] (including those who have no menses for medical reasons, such as chemotherapy-induced menopause) will undergo a serum or urinary pregnancy test at the

following time points. The same approach will be used if possible throughout the study. The test will be generally performed at each study site.

Note): Women of childbearing potential are defined as all premenopausal women who have reached menarche and who have not undergone sterilization (including hysterectomy, bilateral tubal ligation, or bilateral oophorectomy). Menopause is defined as amenorrhea for at least 12 successive months in the absence of significant causes. Women who use oral contraceptives, other hormonal contraceptives (including intravaginal or injectable contraceptives), or mechanical contraception (including intrauterine device or barrier method) are regarded as having childbearing potential.

<Time points>

- Screening period
  - Days −7 to −1 starting from the first day of treatment is adopted as the time window.
- Treatment period
  - Cycle 1: Predose on Day 1
  - Cycle 2 and subsequent cycles: Predose on Day 1 of odd cycles[note 1)]
  - At the completion of the treatment period (at discontinuation) [note 2)]
- Follow-up period
  - 28 days after the completion of the treatment period[note 2)]

Note 1): In Cycle 2 and subsequent cycles, a pregnancy test will be performed within 7 days prior to administration of the investigational product.

Note 2): Previous test results may be used except when medically indicated. However, an examination must be performed if at least 8 days have elapsed since the last examination. An examination will be performed as needed if medically indicated.

8.2.4.5 Viral Test

The following tests will be performed during the screening period. However, if any tests were performed within 1 year before randomization, no new examinations are required except when medically indicated. If subjects test negative for HBs antigen but positive for either the HBs antibody or HBc antibody, an HBV-DNA quantitative test will be performed. These tests will be generally performed at each study site.

<Test items>

HIV-1 antibody, HIV-2 antibody, HTLV-1 antibody, HBs antigen, HBs antibody, HBc antibody, HCV antibody

8.2.4.6 ECOG Performance Status

ECOG Performance Status will be evaluated at the following time points.

<Time points>

- Screening period
  - Days −7 to −1 starting from the first day of treatment is adopted as the time window.
- Treatment period
  - Cycle 1: Day 8, Day 22
  - Cycle 2 and subsequent cycles: Predose on Day 1 of each cycle[note 1)], Day 22
  - At the completion of the treatment period (at discontinuation)[note 2)]
- Follow-up period
  - 28 days after the completion of the treatment period[note 2)]

Note 1): Data obtained on Day 22 in the previous cycle may be used except when medically indicated. However, an examination must be performed if at least 8 days have elapsed since the last examination. An examination will be performed as needed if medically indicated.

Note 2): Previous test results may be used except when medically indicated. However, an examination must be performed if at least 8 days have elapsed since the last examination. An examination will be performed as needed if medically indicated.

8.2.4.7 Adverse Events

All adverse events will be evaluated using NCI-CTCAE Version 4.0. Signs or symptoms that are not included in the CTCAE will be treated as adverse events based on the judgment of the investigator.

For adverse events that occur from the start date of administration of the investigational product to 100 days after the last administration of the investigational product or chemotherapy, the following will be entered on the eCRF: the event name, onset date , grade, judgment on whether the investigational product or chemotherapy is to be continued, action taken, seriousness, causal relationship with the investigational product or chemotherapy, and outcome at the final observation (or resolution date, if the event resolved by the final observation). For subjects who enters the follow-up period, if drug-related adverse events and adverse events leading to discontinuation are found, observations/measurements for clinical symptoms and laboratory tests will be performed and appropriate actions for adverse events will be taken until no further follow-up is required because the events have resolved, are resolving, are considered as permanent events, or are assessed as lost to follow up for any other reason. Serious adverse events will be reported to the Sponsor (or person designated by the Sponsor) according to 9.8 Action taken for Serious Adverse Events.

If the investigator regards an adverse event that is a subjective symptom/objective finding and an abnormal change in laboratory values as a series of the same event, the adverse event will be

generally reported as one event (an adverse event as a subjective symptom/objective finding only). If a subjective symptom/objective finding and an abnormal change in laboratory values cannot be regarded as a series of the same event, the finding and change will be reported as separate adverse events.

8.2.5 Measurement of Serum Drug Concentration

The serum drug concentration of ONO-4538 will be measured by electrochemi-luminescence assay at Pharmaceutical Product Development, LLC (PPD). Measurement methods are described in detail in the plan prepared by the person responsible for measuring serum drug concentration of ONO-4538. The results will be reported in the ONO-4538 serum concentration measurement report. Retrieval and transportation of specimens will follow the written procedures separately specified.

Blood samples (blood volume per sample collection: 2 mL) for serum drug concentration measurement will be collected at the following time points. Blood samples will also be collected 6 to 12 weeks after the last administration of the investigational product, as much as possible.

In addition, although serum ONO-4538 or anti-ONO-4538 antibodies may be measured using specimens for serum drug concentration measurement in an exploratory manner for the purpose of technical exploration, the results will not be reported.

<Time points>

- Treatment period
  - Cycle 1: Predose of the investigational product on Day 1, immediately before the end of infusion of the investigational product on Day 1, Day 22
  - Cycle 2 and subsequent cycles: Immediately before the end of infusion of the investigational product on Day 1 of Cycle 7, Day 22 of Cycles 2, 6, 8, 12, and 16
    Not required for the subject who discontinued the investigational product but remained in the treatment period.
- Follow-up period
  - 28 days after the completion of the treatment period (only if the subject enters the follow-up period following the discontinuation of the investigational product by Cycle 16)
  - 6 to 12 weeks after the last administration of the investigational product (if possible). For the subject who discontinued only the investigational product, the measurement may be performed during the treatment period.

8.2.6 Measurement of Anti-ONO-4538 Antibodies

Anti-ONO-4538 antibodies will be measured by electrochemi-luminescence assay at Pharmaceutical Product Development, LLC (PPD). Neutralizing activity will be evaluated at BMS as needed. Measurement methods are described in detail in the plan prepared by the person responsible for measuring anti-ONO-4538 antibodies. The results will be reported in the serum

anti-ONO-4538 antibody measurement report. Retrieval and transportation of specimens will follow the written procedures separately specified.

Blood samples (blood volume per sample collection: 4 mL) for measurement of anti-ONO-4538 antibodies will be collected at the following time points. Blood samples will also be collected 6 to 12 weeks after the last administration of the investigational product, as much as possible.

If there is an insufficient volume of specimens for measurement of anti-ONO-4538 antibodies, specimens for measurement of serum drug concentration that were collected at the same time point may be used. In addition, although serum ONO-4538 or anti-ONO-4538 antibodies may be measured using specimens for measurement of serum anti-ONO-4538 antibodies in an exploratory manner for the purpose of technical exploration, the results will not be reported.

<Time points>

- Treatment period
  - Cycle 1: Predose of the investigational product on Day 1, Day 22
  - Cycle 2 and subsequent cycles: Day 22 of Cycles 2, 6, 8, 12, and 16
    Not required for the subject who discontinued the investigational product but remained in the treatment period.
- Follow-up period
  - 28 days after the completion of the treatment period (only if the subject enters the follow-up period following the discontinuation of the investigational product by Cycle 16)
  - 6 to 12 weeks after the last administration of the investigational product (if possible). For the subject who discontinued only the investigational product, the measurement may be performed during the treatment period.

8.2.7 Exploration of Biomarkers

[redacted]

[redacted]

8.2.7.3 Tumor Markers (As Needed)

Wherever possible, tumor markers will be continuously measured in subjects who have tumor markers exceeding the upper limit of normal. Tumor markers should be measured as needed. Measurement will be generally performed at each study site.

[redacted]

[redacted]

8.2.7.5 Tumor Tissues

Formalin-fixed, paraffin-embedded (FFPE) tumor tissues collected within 6 months prior to enrollment must be submitted to the central laboratory for determination of PD-L1 status using the analytically validated IHC assay. Either a tissue block or a minimum of 10 unstained tumor tissue sections are required. Submission of fewer than 10 unstained slides may be acceptable in some circumstances following discussion with the Sponsor's Medical Monitor. PD-L1-stained tissue specimens will be evaluated by a pathologist at the central laboratory designated by the Sponsor. If at least 1% of the cancer cells among 100 or more evaluable cancer cells have stained cell membranes, the specimen is considered to be PD-L1+, and if less than 1%, it is considered to be PD-L1−. Specimens must contain at least 100 evaluable cancer cells. Specimens with an insufficient number of cancer cells are considered as unevaluable and the subject is not randomized. Even where specimens meet the criteria for evaluation, if it is difficult to assess the staining of the cell membrane region due to the biological characteristics of the tumor tissue specimen rather than the inappropriate preparation and handling of specimens, such specimens will be considered indeterminate.

[redacted]

Tumor tissues will be stored frozen at the specified central laboratory for up to 10 years after the study concludes. Handling, storage, assessment , and disposal of samples and disclosure of genetic information will follow the written operating procedures separately specified.

8.2.8 Patient Reported Outcome

Health-related QoL evaluation is gaining more importance from the viewpoint of clinical efficacy. Obtained QoL data elucidate the effects of treatments from the patient's perspective and experience in a way that cannot be obtained from a physician's report.

Systemic health status will be measured using EQ-5D. EQ-5D is a standardized evaluation instrument used to measure self-reported health status. EQ-5D consists of 5 dimensions (degree of movement, management of selfcare, daily activities, pain/discomfort, and anxiety/depression) and a visual analogue scale (VAS). Disease-related symptoms will be measured using LCSS. LCSS is a standardized evaluation instrument used to measure self-reported disease-related symptoms. LCSS consists of 6 symptoms: cough, dyspnea, fatigue, pain, hemoptysis, and decreased appetite. It is recommended that efficacy data obtained from EQ-5D and LCSS be used for analysis of cost effectiveness analysis; and the data are commonly used.

To minimize bias, QoL evaluation will be generally performed before study procedures at each visit.

<Time points>

- Screening period
  - Days −7 to −1 starting from the first day of treatment is adopted as the time window.
- Treatment period
  - Every 6 weeks from the start date of Cycle 1
  - At the completion of the treatment period (at discontinuation)[note 1)]
- Follow-up period
  - Follow-up[note 2)]

Note 1): Previous test results may be used except when medically indicated. However, an examination must be performed if at least 8 days have elapsed since the last examination.

Note 2): EQ-5D will be collected every 3 months in the first year of follow-up and every 6 months thereafter.

8.2.9 Other Examinations

8.2.9.1 Healthcare Resource Utilization

Information regarding hospitalization associated with administration of the investigational product or diseases and non-protocol specified visits and the like will be collected for all randomized subjects. Healthcare resource utilization will be evaluated at the following time points.

<Time points>

- Screening period
  - Days −7 to −1 starting from the first day of treatment is adopted as the time window.
- Treatment period
  - Every 6 weeks from the start date of Cycle 1
  - At the completion of the treatment period (at discontinuation)

8.2.10 Follow-up

Subjects who discontinue the treatment period because of safety issues or disease progression despite an overall response of CR, PR, or SD per RECIST 1.1 criteria (refer to APPENDIX 1) should continue radiographic tumor assessments if possible until the start of subsequent anticancer therapy for non-squamous non-small cell lung cancer or where their condition is assessed as PD or recurrence. The antitumor activity will be assessed according to the RECIST 1.1 criteria (refer to APPENDIX 1) based on obtained images, and results will be entered on the eCRF.

All adverse events and concomitant treatments will be examined from the start date of administration of the investigational product to 100 days after the last administration of the investigational product or chemotherapy, whichever comes later. When drug-related adverse events or adverse events leading to discontinuation are reported at the start of follow-up, concomitant treatments administered for these events should be investigated at appropriate intervals until no further follow-up is required because the events have resolved or are resolving, or the symptoms become stable. The results of follow-up should be entered on the eCRF.

An outcome survey (if the subject dies, confirm the date of death and cause of death) for subjects who were randomized into the study will be performed as a part of follow-up. The outcome survey can be conducted by telephone or letter, which will be performed approximately every 3 months or as needed depending on the incidence of events. Any new information on survival status should be entered on the eCRF accordingly. In addition, the presence or absence of subsequent anticancer therapy for non-squamous non-small cell lung cancer, the date of starting such therapy, and details of the therapy should also be investigated wherever possible.

8.2.11 Lost to Follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject to provide information on the follow-up. Lost to follow-up is defined as the inability to reach the subject after a minimum of 3 documented phone calls, faxes, or emails as well as lack of response by subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If an investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the

study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

9 ADVERSE EVENTS AND ITEMS TO ENSURE SUBJECT SAFETY

9.1 Definition of Adverse Events

An adverse event is any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational product or chemotherapy whether or not considered related to the investigational product or chemotherapy. In addition, the primary disease, associated symptoms of the primary disease, and worsening of complications that are medically considered to exceed the range of the natural course are regarded as adverse events. Tumor expansion and onset of a new lesion after the start of the study (except development of malignant tumor histologically different from the primary focus) that are medically considered to exceed the range of the natural course are also regarded as adverse events.

9.2 Definition of Serious Adverse Events

Events that correspond to any of the following among those meeting the definition for an adverse event are considered to be serious adverse events.

1. Results in death
2. Is life-threatening
3. Requires inpatient hospitalization or prolongation of existing hospitalization[note 1)]
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect
6. Is other medically important event or reaction[note 2)]

Note 1): Serious adverse events do not include hospitalization for conduct of the study or those listed below.

- Hospitalization or prolongation of existing hospitalization for therapeutic reasons planned before the start of the study (including surgery or examinations planned before the start of the study)
- Hospitalization or prolongation of existing hospitalization for examinations and education (including hospitalization for routine examinations or for education)
- Hospitalization or prolongation of existing hospitalization for surgery as a result of a change in the therapeutic policy for handling complications and associated symptoms rather than due to exacerbation of complications and associated symptoms
- Hospitalization or prolongation of existing hospitalization for follow-up despite the disease having resolved or in the process of resolving
- Hospitalization/residence at hospice, nursing home, or rehabilitation facility

- Hospitalization or prolongation of existing hospitalization for new treatments for the primary disease, including subsequent anticancer therapy after administration of the investigational product has ended
- Hospitalization or prolongation of existing hospitalization for social reasons (including caregiver's respite, absence of family members)

Note 2): For other important medical events, medical and scientific judgment should be exercised in deciding if an emergency report is required when such events might not be immediately life-threatening or resulting in death or hospitalization but might jeopardize the subject or might require intervention to prevent such results as described in 1 to 5 above, and such events should be, in general, also considered serious. Examples of such events are intensive treatment in an emergency room, etc. for bronchospasm, blood dyscrasias or convulsions (even if the event does not result in hospitalization), development of drug dependency or drug abuse, onset of malignant tumors histologically different from the primary focus. If transmission of an infectious drug (with or without virulence) via the investigational product is suspected, it should be reported as "other medically important event."

9.3 Grading

Adverse events are graded into 5 levels (1 to 5) depending on their severity. If an observed adverse event meets the definitions for several grades as listed in CTCAE, it is graded according to the nearest match among Grades 1 to 5 based on comprehensive consideration. In addition, in subjects who died, if any adverse event within a CTCAE category has been reported as Grade 5, the grade of other observed adverse events at the time of death will be determined based on the clinical evaluation of the investigator. It is not necessary to follow the CTCAE's rule (Grade 5 is applicable to only 1 adverse event). The grade of adverse events not listed in CTCAE will be determined based on the following criteria.

Grade 1 Mild; no symptoms or mild symptoms; clinical or diagnostic observations only; intervention not required

Grade 2 Moderate; minimal/local/non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADLs)[note 1)]

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting selfcare ADLs[note 2)]

Grade 4 Life-threatening; urgent intervention indicated

Grade 5 Death related to adverse events

Semicolon (;) indicates "or" within the explanation on grade.

Note 1): Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Note 2): Selfcare ADLs refer to bathing, dressing/undressing, feeding self, using the toilet, taking medications and not bedridden.

9.4 Causal Relationship with Investigational Product or Chemotherapy

A causal relationship with the investigational product or chemotherapy falls under either of the following two categories based on the subject's condition, past history, concomitant drugs, and temporal relationship of onset. In addition, if the investigator determined that the adverse event was related to either the investigational product or chemotherapy, the reasons for this determination will be entered in the comment field of the eCRF.

1. Related: There is a reasonable causal relationship between study drug administration and the adverse event.
2. Unrelated: There is not a reasonable causal relationship between study drug administration and adverse event.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

9.5 Outcome

The outcome of an adverse event (symptom or abnormal laboratory finding) will be assessed according to the following criteria. If the event resolves, the resolution date will be determined, and, otherwise, the outcome at the final observation will be determined.

Outcome	Criteria (for information)
Resolved	The symptom resolved, or the test value normalized or returned to the pre-therapy level.
Resolving	The event decreased in intensity, or the symptom showed an improving tendency.
Not resolved	The symptom or the test value has not improved.
Resolved with sequelae	The event resolved or was resolving, but with remaining symptoms of disability or other sequela.
Fatal	The subject died.
Unknown (Lost to follow-up)	The subject was lost to follow-up.

9.6 Continuation of Investigational Product or Chemotherapy

The investigator's or subinvestigator's decision to continue administration of the investigational product or chemotherapy for each adverse event will be classified into the following 7 levels and recorded. Note that the subject's decision is not included in this classification.

Decision	Criteria
1 Dose not changed	As a result of the adverse event, the investigator or subinvestigator has judged that administration of the investigational product or chemotherapy may be continued.
2 Drug interrupted	As a result of the adverse event, the investigator or subinvestigator has judged that administration of the investigational product or chemotherapy needs to be interrupted. The investigational product or chemotherapy has been resumed after interruption or is expected to be resumed after early interruption.
3 Drug delayed	As a result of the adverse event, the investigator or subinvestigator has judged that administration of the investigational product or chemotherapy needs to be delayed (or skipped).
4 Dose reduced	As a result of the adverse event, the investigator or subinvestigator has judged that the dose of the investigational product or chemotherapy needs to be reduced.
5 Drug withdrawn	As a result of the adverse event, the investigator or subinvestigator has judged that administration of the investigational product or chemotherapy needs to be discontinued.
6 Not applicable	The adverse event developed after the end of administration of the investigational product or chemotherapy.
7 Other	None of the above applies, but as a result of the adverse event the investigator or subinvestigator has changed the mode of administration of the investigational product or chemotherapy.

9.7 Treatment

Treatments for the adverse event will be recorded.

9.8 Action taken for Serious Adverse Events (SAE)

All SAEs, whether related or not related to the investigational product or chemotherapy, including those thought to be associated with protocol-specified procedures, must be collected that occur between first dose and 100 days after the last dose of the investigational product or chemotherapy. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, biopsy during the follow-up period).

The investigator should report any SAEs that occurs after these time periods and that is believed to be related to the investigational product or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to the investigational product or chemotherapy, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs (including overdose), whether related or not related to the investigational product or chemotherapy, and pregnancies must be reported to the Sponsor (or person designated by the Sponsor) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The report will be sent to the following by e-mail or confirmed fax transmission, and an original of the report will be retained at each study site (as for Japan, refer to the country specific amendment for all sites in Japan).

SAE Email Address: [redacted]

SAE Facsimile Number: Refer to Table 9.8-1.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Table 9.8-1.

Table 9.8-1: Facsimile Number and Telephone Contact by Country

Country	Facsimile Number	Telephone Contact
South Korea	[redacted]	[redacted]
Taiwan	[redacted]	[redacted]

As necessary, the Sponsor will conduct assessment of the details, together with medical experts or the Coordinating Committee or Independent Data Monitoring Committee (IDMC), and if medical experts, the Coordinating Committee, or the IDMC requests the submission of data such as scan images for safety evaluation, the Sponsor will submit these data, with personal information masked according to the regulations in the relevant countries.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to the investigational product or chemotherapy, or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the Sponsor (or person designated by the Sponsor) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution, resolving, or stabilization.

9.9 Action taken for Pregnancy

Between the start of administration of the investigational product and 28 days after the completion of the treatment period (discontinuation of administration of the investigational product and chemotherapy), if it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product or chemotherapy exposure, the investigational product and chemotherapy will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify the Sponsor (or person designated by the Sponsor) of this event and complete and forward a Pregnancy Surveillance Form to the Sponsor (or person designated by the Sponsor) within 24 hours and in accordance with SAE reporting procedures described in Section 9.8.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Sponsor (or person designated by the Sponsor). Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.10 Action taken for Overdose

Overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose of the investigational product must be reported as an SAE (refer to Section 9.8 for reporting details).

9.11 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, chest X-ray, and any other potential safety assessment, whether or not required by the protocol, should also be recorded as a non-serious or serious adverse event, as appropriate, and reported accordingly.

9.12 Provision of New Information

If new information is obtained that might adversely affect the safety of the subject, impact the conduct of the study, or require a change in the approval of the institutional review board regarding study continuation, or information on serious and unexpected adverse drug reactions is obtained, the Sponsor will promptly report it in writing to all investigators and study staff and the heads of the study sites involved in the study. If the investigator agrees that there is a need to revise the written informed consent forms, such documents should be revised promptly. In addition, the Sponsor will revise the protocol/Investigator’s Brochure if and when required.

10 STATISTICAL ANALYSIS

Statistical analysis will be performed by ONO PHARMACEUTICAL CO., LTD. Although the analysis procedure is described below, a more detailed version of the analytical method will be included in the interim analysis plan and statistical analysis plan prepared by the person responsible for statistical analysis and the person in charge of statistical analysis.

Version 1.0 of the interim analysis plan and statistical analysis plan will be fixed by cutoff data lock for interim analysis. After fixation of version 1.0, revision will be carried out as needed.

If analysis other than that described in the statistical analysis plan is performed, it will be reported in the clinical study report.

10.1 Explanation of Statistical Methods including Timing of Planned Interim Analysis

One interim analysis for PFS per IRRC will be performed in the ITT population to determine whether to stop the study early for superiority based on the stratified log-rank test with allocation factors (PD-L1 expression level, ECOG PS, and gender) as stratification factors when approximately 82.4% (n = 280) of the target number of PFS events over the entire study (n = 340) have occurred. To control the overall type I error rate at no more than 5% (two-sided), the significance levels used in the interim and final analyses will be calculated by the Lan-DeMets α spending function (O'Brien-Fleming type) based on the actual number of events. When the planned interim analysis is performed when exactly 280 PFS events have been reported, the nominal two-sided significance levels for the interim and final analyses are calculated as shown in Table 10.1-1.

Whether the study is to be stopped for superiority based on the interim analysis will be decided by the IDMC. The details of the interim analysis are separately specified in the IDMC procedural manual and the interim analysis plan.

Table 10.1-1: Criteria for Success at Interim and Final Analyses

Analysis	Timing	Nominal two-sided significance level
Interim analysis	280 events	2.70%
Final analysis	340 events	4.22%[a)]

[a)]: In the final analysis using the ITT and the PD-L1 1% Positive Set, Hochberg's method will also be used to adjust multiplicity.

10.2 Independent Data Monitoring Committee (IDMC)

The IDMC will be established to independently monitor safety, efficacy, and the conduct of the study. It will evaluate data regularly to ensure that the safety of subjects is carefully monitored. In addition, the IDMC will hold extraordinary meetings as needed. After each meeting, the IDMC will recommend continuation, change, or discontinuation of the study depending on the

observed toxicity. In addition, the IDMC will review the results of the interim analysis to decide whether or not it meets the discontinuation criteria on superiority at the time of interim analysis. For details of the committee's activities, refer to the written operating procedures separately prepared.

10.3 Significance Level Used

10.3.1 Efficacy

To control the overall type I error rate at ≤ 5% (two-sided), a significance level for interim and final analyses will be calculated using the Lan-DeMets α spending function (O'Brien-Fleming) based on the actual number of events. In addition, multiplicity of the test for final analysis will be adjusted using the Hochberg's method. The significance level of the analysis for secondary endpoints is to be 5% (two-sided). In addition, interaction will be examined using a two-sided significance level of 15%.

10.3.2 Safety

Not established because the test will not be performed.

10.4 Selection of Subjects to Be Included in Analyses

10.4.1 Definition of Analysis Sets

The analysis sets for efficacy endpoints are the ITT and the PD-L1+ (≥ 1%) set (PD-L1 1% Positive Set: PDL1-PS).

The analysis set for safety endpoints is the Safety Set (SAF).

The analysis set for Immunogenicity endpoints is the Anti-Drug Antibody Set.

Definition of each analysis set is as follows.

10.4.1.1 Enrolled Set (ENR)

The Enrolled Set (ENR) will consist of all subjects enrolled (enrollment) in this study via IWRS.

10.4.1.2 ITT/Randomized Set (RND)

The ITT and Randomized Set (RND) will consist of all randomized (randomization) subjects.

10.4.1.3 SAF

The SAF will consist of all subjects who received the investigational product or chemotherapy at least once.

10.4.1.4 PDL1-PS

The PDL1-PS will consist of all subjects included in the ITT and who are PD-L1+ (≥ 1%).

10.4.1.5 Anti-Drug Antibody Set

The ADA will consist of all subjects who meet the following item in the SAF population.

1. Subjects have had their anti-ONO-4538 antibodies (samples with potential positive measurement result at screening assay without obtaining result by confirmatory assay are not included) measured at at least 1 time point after administration of ONO-4538 and before administration of ONO-4538.

10.4.2 Criteria for Handling of Subjects

Details of handling of subjects are shown below.

10.4.2.1 Non-randomized Subjects

Subjects who were not randomized through the IWRS after enrollment are defined as non-randomized subjects.

10.4.2.2 Untreated Subjects

Subjects who have not received any of the investigational products or chemotherapy are defined as untreated subjects.

10.4.2.3 Incomplete Anti-Drug Antibody Subjects

Subjects with missing anti-ONO-4538 antibody measurements before administration of ONO-4538 or missing all anti-ONO-4538 antibody measurements after administration of ONO-4538 are defined as incomplete anti-drug antibody subjects.

For unexpected, problematic cases other than above, the Sponsor will examine such cases and decide how cases will be handled in the analysis by the data lock point.

10.4.3 Criteria for Handling of Time Points

When analysis by time point is performed, if the test day specified in the protocol is different from the actual test day, only data measured within the time window described in Table 6-1 should be adopted.

10.5 Analytical Methods

10.5.1 Examinations on Reliability of Study

10.5.1.1 Presence of Subjects Who Are Excluded

Frequency of subjects who are included or excluded in each analysis set and frequency by reason for exclusion will be summarized by treatment group.

10.5.1.2 Discontinuations from Study

Discontinuations from the study will be summarized by treatment group.

10.5.2 Administration of Investigational Product and Chemotherapy

Administration of the investigational product and chemotherapy will be summarized by treatment group.

10.5.3 Distribution of Background Factors

Frequency distribution and summary statistics will be calculated by treatment group for the following items to ascertain comparability between treatment groups.

10.5.3.1 Demographic Variables

Categorical data including gender, age, race, and ethnicity will be summarized using frequency distribution by treatment group. In addition, continuous variables including height, body weight, and BMI will be summarized using summary statistics (mean, standard deviation, median, minimum, and maximum) by treatment group.

10.5.3.2 Patient Characteristics

Past history, complications, smoking history, ECOG Performance Status, period from the date of diagnosis of primary disease through randomization, staging (Stage) and TNM classification, histology of non-squamous non-small cell lung cancer, primary site and metastatic site of non-squamous non-small cell lung cancer, site of recurrence (for recurrent non-squamous non-small

cell lung cancer), and previous treatment for cancers (including history of surgery, radiotherapy, or medical treatment) will be summarized by treatment group.

10.5.3.3 Baseline Values during Observation Period

The sum of tumor diameters of target lesions will be summarized using summary statistics (mean, standard deviation, median, minimum, and maximum) by treatment group.

10.5.4 Efficacy Endpoints

10.5.4.1 Objectives

To verify the superiority, with PFS (as assessed by the IRRC) as the primary endpoint, of ONO-4538 in combination with chemotherapy over placebo in combination with chemotherapy in chemotherapy-naïve subjects with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer unsuitable for radical radiation.

10.5.4.2 Hypothesis

Efficacy in the ONO-4538 group is superior to that in the placebo group in terms of PFS (as assessed by the IRRC).

10.5.4.3 Analysis Item and Handling of Data

1. Analysis item

   PFS (as assessed by the IRRC)

2. Handling of data

   PFS (as assessed by the IRRC) will be calculated using the following formula:

   PFS (days) = “date when overall response is assessed as PD or date of death (for any reason), whichever comes first” – “date of randomization” + 1

   If the overall response is not assessed as PD and the subject is alive, the date on which the final evaluable radiographic tumor assessment is performed will be defined as the date of censoring. If no evaluable radiographic tumor assessments have been performed and the subject is alive, the date of randomization will be the date of censoring. If the subject received subsequent anticancer therapy for non-squamous non-small cell lung cancer before the overall response is assessed as PD or the subject dies, the day on which the final evaluable radiographic tumor assessment is performed before subsequent anticancer therapy for non-squamous non-small cell lung cancer will be the date of censoring.

   Details on the assessment of events or censoring will be provided in the statistical analysis plan.

10.5.4.4 Analytical Methods

10.5.4.4.1 Analytical Methods (Interim Analysis)

1) Analysis for primary endpoint

PFS (as assessed by the IRRC) will be analyzed as follows using the ITT as the analysis set. A significance level α for analysis will be adjusted using the Lan-DeMets α spending function (O'Brien-Fleming) based on the actual number of events.

(1) Primary analysis

Comparison between treatment groups will be performed via the log-rank test stratified by randomization factors (PD-L1 expression level, ECOG Performance Status, and gender).

(2) Secondary analysis

The hazard ratio of the ONO-4538 group to the placebo group and its two-sided 100* (1-α)% confidence interval will be calculated using the Cox proportional hazard model stratified by randomization factors used for the primary analysis.

The Kaplan-Meier curves by treatment group will be displayed. In addition, the medians and their two-sided 100* (1-α)% confidence intervals by treatment group will be calculated using the Kaplan-Meier method. To determine the confidence interval using the Kaplan-Meier method, the Brookmeyer and Crowley method utilizing double log transformation will be used.

10.5.4.4.2 Analytical Methods (When Study Is Continued Based on Results of Interim Analysis)

1) Analysis for primary endpoint

PFS (as assessed by the IRRC) will be analyzed as follows using the ITT and PDL1-PS as the analysis sets. A significance level α for analysis will be adjusted using the Lan-DeMets α spending function (O'Brien-Fleming) and Hochberg's method based on the actual number of events.

(1) Primary analysis

Analysis will be performed by adjusting multiplicity using the Hochberg's method according to the following procedures 1 to 4.

1. For PFS (as assessed by the IRRC), comparison between treatment groups will be performed in the ITT via the log-rank test stratified by randomization factors (PD-L1 expression level, EOCG Performance Status, and gender).

2. For PFS (as assessed by the IRRC), comparison between treatment groups will be performed in the PDL1-PS via the log-rank test stratified by randomization factors (PD-L1 expression level, EOCG Performance Status, and gender).
3. The p value in the ITT and PDL1-PS obtained from the stratified log-rank test in 1. and 2. above refer to $p_{(1)}$ and $p_{(2)}$ in ascending order, then its corresponding null hypotheses refer to $H_{0(1)}$ and $H_{0(2)}$, respectively.

Example: If the p value in the PDL1-PS < the p value in the ITT:
$H_{0(1)}$: In the PDL1-PS, the survival function for the ONO-4538 group is equal to that for the placebo group.
$H_{0(2)}$: In the ITT, the survival function for the ONO-4538 group is equal to that for the placebo group.

4. Superiority of the ONO-4538 group to the placebo group will be verified using $p_{(1)}$ and $p_{(2)}$.
   a. If $p_{(2)} < \alpha$, both null hypotheses $H_{0(1)}$ and $H_{0(2)}$ will be rejected.
   b. If $p_{(2)} \geq \alpha$ and $p_{(1)} < \alpha/2$, only null hypothesis $H_{0(1)}$ will be rejected.

(2) Secondary analysis

As a result of primary analysis of the primary endpoint, if the superiority of the ONO-4538 group over the placebo group is verified in the ITT, the ITT will be used as the analysis set. On the other hand, if the superiority of the ONO-4538 group over the placebo group is not verified in the ITT, the ITT and PDL1-PS will be used as the analysis sets.

An analysis same as 10.5.4.4.11)(2) Secondary analysis will be performed.

10.5.5 Efficacy Secondary Endpoints

10.5.5.1 Objective

To evaluate the efficacy of ONO-4538 in combination with other therapies for non-squamous non-small cell lung cancer from a range of viewpoints

10.5.5.2 Analysis Items and Handling of Data

10.5.5.2.1 Analysis Items

1. OS
2. PFS (as assessed by the study site's investigator)
3. Objective response rate (ORR [as assessed by the IRRC and study site's investigator])
4. Disease control rate (DCR [as assessed by the IRRC and study site's investigator])
5. Duration of response (DOR [as assessed by the IRRC])
6. Time to response (TTR [as assessed by the IRRC])

7. Best overall response (BOR [as assessed by the IRRC and study site's investigator])
8. Maximum percentage of change in the sum of diameters of target lesions (as assessed by the IRRC)

10.5.5.2.2 Handling of Data

The overall response and the best overall response will be determined based on radiographic tumor assessments per RECIST 1.1 criteria, and clinical deterioration will not be included in the results of radiographic tumor assessments. Evaluable diagnostic images should be those with the assessment of overall response other than NE.

Handling of each endpoint is shown below.

1. OS will be calculated using the following formula:

   OS (days) = "date of death (for any reason)" – "date of randomization" + 1

   If the subject cannot be followed up or the subject is alive at the date of data cutoff, the date on which survival was last confirmed will be the date of censoring.
2. PFS will be calculated according to 10.5.4.3 Analysis Item and Handling of Data.
3. ORR represents the proportion of subjects whose best overall response was assessed as CR or PR.
4. DCR represents the proportion of subjects whose best overall response was assessed as CR, PR, or SD.
5. DOR will be calculated using the following formula:

   DOR (days) = "date on which overall response was first assessed as PD or date of death (for any reason) after confirmed response, whichever comes first" – "date on which response was first assessed as confirmed CR or PR" + 1

   Subjects whose response was assessed as confirmed CR or PR throughout the study will be evaluated.
6. TTR will be calculated using the following formula:

   TTR (days) = "date on which response was first assessed as confirmed CR or PR" – "date of randomization" + 1

   TTR data in subjects without response will be censored at the maximum time to response + 1 day of subjects with response in each treatment group.
7. Maximum percentage of change in the sum of diameters of target lesions

   Maximum percentage of change in the sum of diameters of target lesions assessed according to the RECIST 1.1 criteria will be calculated in subjects with target lesions using the following formula. However, the sum of tumor diameters of target lesions, after overall response was assessed as PD, after subsequent anticancer therapy was performed for non-squamous non-small cell lung cancer, or after investigations on subsequent anticancer therapy were completed, will not be used for calculation of the maximum percentage of change.

$$\text{Maximum percentage of change in the sum of tumor diameters of target lesions (\%)} = \left(\frac{\text{“Minimum sum of tumor diameters of target lesions after administration”}}{\text{“Sum of tumor diameters of target lesions before administration of the investigational product”}} - 1\right) \times 100$$

For PFS and DOR, details of the assessment of events or censoring will be provided in the statistical analysis plan.

10.5.5.3 Analytical Methods

In the case of early efficacy stop based on the results of the interim analysis, the ITT will be used as the analysis set. In addition, if the study is continued based on the results of the interim analysis and the superiority of the ONO-4538 group over the placebo group is verified in the ITT at the final analysis, the ITT will be used as the analysis set. On the other hand, if the superiority of the ONO-4538 group over the placebo group is not verified in the ITT, the ITT and PDL1-PS will be used as the analysis sets.

1. For analysis items 1 and 2, comparison between treatment groups will be performed via the log-rank test stratified by randomization factors. In addition, the hazard ratio of the ONO-4538 group to the placebo group and its two-sided 95% confidence interval will be calculated using the Cox proportional hazard model stratified by randomization factors.
2. For analysis items 1, 2, 5, and 6, the Kaplan-Meier curves by treatment group will be displayed. In addition, the medians and the two-sided 95% confidence intervals by treatment group will be calculated using the Kaplan-Meier method. To determine the confidence interval using the Kaplan-Meier method, the Brookmeyer and Crowley method utilizing double log transformation will be used.
3. For analysis items 3 and 4, comparison between treatment groups will be performed via the Cochran-Mantel-Haenszel test stratified by randomization factors. In addition, the Cochran-Mantel-Haenszel method will be used to calculate the odds ratio of the ONO-4538 group to the placebo group adjusted by the same stratification factors and its two-sided 95% confidence interval as well as differences in the proportion and its two-sided 95% confidence interval.
4. For analysis items 3 and 4, the proportion by treatment group and its two-sided 95% confidence interval (Clopper-Pearson method) will be calculated.
5. For an analysis item 7, the proportions of CR, PR, SD, PD, and NE by treatment group will be calculated, and their two-sided 95% confidence intervals (Clopper-Pearson method) for the proportions of CR, PR, and SD will be calculated.
6. For an analysis item 8, a waterfall plots by treatment group will be created.

10.5.6 Examination of Interactions

Interactions between treatment groups and background factors will be examined using the Cox proportional hazard model stratified by randomization factors for the primary endpoint. The

background factors used for examining the interactions will be presented in the statistical analysis plan.

10.5.7 Adjusted Analysis

If it is found that some of the background factors show imbalance between the treatment groups or some of the background factors are affecting the assessment, using such factors as adjusted factors, the Cox proportional hazard model stratified by randomization factors will be used to adjust the analysis for the primary endpoint. Adjusted factors used for the adjusted analysis will be described in the statistical analysis plan.

10.5.8 Safety Analysis

10.5.8.1 Objective

To evaluate the safety of ONO-4538 in combination with other therapies from a range of viewpoints

10.5.8.2 Analysis Items

1. Adverse events
2. Laboratory tests
3. Vital signs
4. Chest X-ray
5. 12-lead ECG
6. ECOG Performance Status

10.5.8.3 Analytical Methods

1. The number of subjects with adverse events and adverse drug reactions will be summarized by treatment group.
2. Adverse events and drug-related adverse events in each treatment group will be summarized by SOC, PT, and grade.
3. A shift table of the worst grade after administration compared to the baseline grade will be created for test parameters the grades of which are defined in the CTCAE, version 4.0 by treatment group.
4. The number of subjects with abnormal hepatic function or abnormal thyroid function will be summarized by treatment group.

10.5.9 Blinded Review

After data collection, distribution of background factors will be preliminarily examined using blinded data before data lock to confirm appropriateness of the planned analytical methods.

10.5.10 Other Items

1. Sub-group analysis will be performed for efficacy and safety endpoints.
2. Patient reported outcome will be analyzed.
3. Anti-ONO-4538 antibody will be analyzed.

In addition, other items associated with efficacy, safety, and biomarkers will be analyzed in an exploratory manner as needed. Pharmacokinetic (PK) analysis and pharmacokinetic/pharmacodynamic (PK/PD) analysis may be performed as needed. If performed, a report will be separately prepared.

11 ETHICAL CONSIDERATIONS RELATING TO THE STUDY

11.1 Good Clinical Practice

This study will be conducted in accordance with ethical principles underlying Good Clinical Practice (GCP), as defined by International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

The study will be conducted in compliance with the protocol. The protocol and any amendments as well as the subject informed consent form will receive the approval/favorable opinion of the Institutional Review Board/Independent Ethics Committee (IRB/IEC) prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety, or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel at a study site involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

11.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

Before study initiation, the investigator must have the documented and dated approval/favorable opinion from the IRB/IEC for the protocol, informed consent form, subject recruitment materials and methods (eg, advertisements), and any other written information to be provided to subjects. The investigator or Sponsor should also provide the IRB/IEC with a copy of the Investigator's Brochure or product labeling information to be provided to subjects and any updates.

The investigator or Sponsor (or person designated by the Sponsor) should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to the regulatory requirements or study site's procedures.

11.3 Protection of Subject's Privacy

Protection of subject's privacy should be fully considered. Subject Identification Codes will be used in place of subjects' names to distinguish individuals on the eCRFs and in other data. In addition, the prepared eCRF will be used only for study purposes. Moreover, information obtained by the Sponsor should never be leaked to a third party.

12 SUBJECT INFORMED CONSENT

12.1 Informed Consent

The investigator must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which subjects volunteer to participate.

In situations where consent cannot be given by the subjects themselves, their legally acceptable representatives (according to local guidelines) should be clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

The Sponsor (or person designated by the Sponsor) will provide the investigator with an appropriate (ie, global or local) sample of the informed consent form, which will include all elements required by ICH-GCP and applicable regulatory requirements. The sample informed consent form will comply with the ethical principles that have their origin in the Declaration of Helsinki.

The investigator must:

1. Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easy to understand.
2. Allow time necessary for the subject or subject's legally acceptable representative to inquire about the details of the study.
3. Obtain an informed consent form signed and personally dated by the subject or subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4. Obtain the IRB/IEC's documented approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5. If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6. Revise the informed consent form whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the

investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements and the subjects' signed informed consent form.

The informed consent form must also include a statement that the Sponsor and regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over the interests of science and society.

12.2 Withdrawal of Consent

Subjects who request to discontinue the investigational product will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator of their decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator as to whether the withdrawal is from further study treatments only or from the follow-up after completion of study procedures and/or treatments, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information will be used to determine vital status only as appropriately directed in accordance with the local law.

13 STOPPING RULES OR DISCONTINUATION CRITERIA FOR INDIVIDUAL SUBJECTS

If any of the following applies, the subject will be immediately discontinued from the treatment period or follow-up period, the investigator will provide the subject with the appropriate treatment and also observe/measure clinical symptoms and laboratory tests at discontinuation if possible. The date of discontinuation, reason for discontinuation, and treatment and clinical course after discontinuation will be entered on the eCRF and the Sponsor (or person designated by the Sponsor) will be promptly contacted. If subjects did not visit on the scheduled day and cannot receive the investigational product and/or chemotherapy, the investigator will follow up the reason and the course by telephone or letter, confirm the subject's status, and enter the details on the eCRF.

1. The subject requests that the study be discontinued.
2. It is revealed that inclusion criteria are not met.

3. It is revealed that exclusion criteria are met.
4. The investigator considers that it is difficult to continue the study because of adverse events, regardless of whether a causal relationship with the investigational product and chemotherapy exists.
5. The investigator considers that it is not appropriate to continue the study because of disease progression.
6. The subject did not visit on the scheduled day and cannot continue the study.
7. The investigator considers that it is not appropriate to continue the study for any other reason.

14 STUDY MANAGEMENT

14.1 Compliance with the Protocol and Protocol Revisions

The study will be conducted as described in this approved protocol. The investigator should not deviate from or change the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of any amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Sponsor
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB/IEC must be sent to the Sponsor.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the informed consent form must be revised and submitted to the IRB/IEC for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if subjects are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, the investigator and study staff must inform their IRB/IEC.

15 ENTRY OF DATA ON ELECTRONIC CASE REPORT FORM (ECRF)

15.1 eCRF

The investigator and study staff will promptly enter data on the eCRF after completion of each observation of the subject according to the provisions of the protocol for all subjects who have provided written informed consent to participate in the study. The study staff are permitted only to transcribe data from the source document. In addition, data that are derived from source documents and reported on the eCRF must be consistent with the source documents or the discrepancies must be explained by the investigator. The investigator will confirm that all entries on the eCRF (including audit trail and responses to queries) are accurate and complete and verify the entries by electronically signing the eCRF. An electronic signature has the same legal binding force as a hand-written signature, and electronically signed content cannot be repudiated later. Entry/change or amendment of the eCRF and procedures for electronic signature will follow the written operating procedures separately specified.

In addition, the investigator and study staff must meet the Sponsor's training requirements and access to the Sponsor's EDC system using the unique user account provided by the Sponsor. User accounts are not to be shared or reassigned to other individuals.

16 MONITORING

Representatives of the Sponsor must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site, representatives of the Sponsor will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by the Sponsor's internal auditors and regulatory inspectors who must be allowed access to eCRFs, source documents, other study files, and study facilities. The Sponsor's audit reports should be kept confidential.

The investigator must notify the Sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to the Sponsor.

17 PROCEDURES FOR CONFIRMING COMPLIANCE WITH ADMINISTRATION TO SUBJECTS AND OTHER AGREEMENTS

The investigator will confirm compliance with administration of the investigational product and appropriate on-site collection of blood.

18 ARCHIVING OF ESSENTIAL DOCUMENTS

18.1 Archiving of Records

Essential documents to be archived should be retained until 2 years have elapsed from the date of approval of a marketing application in ICH regions and clearance of marketing application status or planned marketing application status in ICH regions or after 2 years have elapsed from the date on which it was decided to terminate development of the investigational product. In addition, the expiration date of essential documents is the day defined by the local regulatory authority or the day agreed to by the Sponsor, whichever comes later. These essential documents should not be discarded or moved to another storage place without prior notification in writing to the Sponsor. If storage of these essential documents is not required, this should be notified to the investigator or the study site.

19 PUBLICATION OF RESULTS

Results of the study conducted in accordance with this protocol are the property of the Sponsor. Any publications of the study results require prior approval by the Sponsor. Issues related to publication will be resolved by discussions between the Sponsor and coordinating investigator.

20 REFERENCES

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APPENDIX 1 Criteria for Antitumor Activity Used in the Study

In this study, tumor response will be evaluated by CT, etc. according to the RECIST 1.1 criteria[note 1)].

Note 1): Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

A. Imaging Evaluation according to the RECIST 1.1 Criteria

A-1 Examinations Used for Response Assessment

- Chest, abdominal, and pelvic CT (slice thickness of 5 mm is recommended) (or MRI as needed)
- Tumor marker

A-2 Baseline Evaluations

At baseline assessment, tumor lesions and lymph nodes will be categorized as measurable or non-measurable according to the criteria in A-3 and A-4.

Tumor diameter will be measured using images in the axial plane on CT scan rather than 3-dimensional images in the sagittal or coronal plane.

Baseline evaluation will be performed using current images taken within 28 days prior to randomization into the study. After randomization, if imaging is repeated before the start of administration of the investigational product, the newest images should be used.

A-3 Definition of Measurable Lesions

Non-lymph node lesions (tumor lesions)

Measurable lesions are defined as those where a maximal diameter (longest diameter) in the plane of measurement is double or more the slice thickness and 10 mm or more by CT or MRI.

Malignant lymph nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis (CT scan slice thickness recommended to be no greater than 5 mm).

A-4 Definition of Non-measurable Lesions

All lesions other than measurable lesions. However, the following lesions, irrespective of the tests and size, will be considered non-measurable:

- Bone lesions (Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above [blastic bone lesions are non-measurable])
- Cystic lesions ("Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions if the lesions meet the definition of measurability. However, if non-cystic lesions are present in the same subject, these are preferentially selected as target lesions.)
- Lesions previously treated with local therapies including radiotherapy (except lesions that have become larger confirmed by radiographic tumor assessments after radiotherapy)
- Leptomeningeal disease
- Ascites, pleural or pericardial effusion
- Inflammatory breast disease
- Lymphangitic involvement of skin or lung
- Abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques

A-5 Target Lesions

Measurable lesions up to a maximum of five lesions in total (and a maximum of two lesions per organ) in descending order of diameter (longest diameter for non-lymph node lesions and short axis for lymph node lesions) should be identified as target lesions. Target lesions should be representative of all involved organs. In addition, the lesions should be those that lend themselves to reproducible repeated measurements (lesions with a longest diameter but are difficult to measure should be avoided).

The sum of diameters is defined as the sum of diameters of all target lesions (longest diameter for non-lymph node lesions and short axis for lymph node lesions).

A-6 Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions. It is possible to record multiple non-target lesions involving the same organ as a single item (eg, multiple enlarged pelvic lymph nodes or multiple liver metastases).

A-7 Response Criteria

Evaluation of Target Lesions

CR: Complete Response

Disappearance of all (non-lymph node) target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in the short axis to < 10 mm.

PR: Partial Response

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

PD: Progressive Disease

At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

SD: Stable Disease

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters on study.

NE: Not Evaluable

When no imaging/measurement is done at all at a particular time point for any reason or the lesion cannot be considered as either CR, PR, PD, or SD.

$$\text{Percentage reduction in the sum of diameters} = \frac{\text{Baseline sum diameter} - \text{Sum diameter at evaluation}}{\text{Baseline sum diameter}} \times 100\%$$

$$\text{Percentage increase in the sum of diameters} = \frac{\text{Sum diameters at evaluation} - \text{Smallest sum diameter}}{\text{Smallest sum diameter}} \times 100\%$$

* All lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, <5 mm). However, when target lesions are "too small to measure," and if the lesion has likely disappeared, the measurement should be recorded as 0 mm, irrespective of CT slice thickness. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.
* If the shrinkage rate qualifies for PR and the increase rate qualifies for PD at the same time, PD should be recorded.
* When lesions fragment, the individual lesion diameters should be added together to calculate the target lesion sum.
* When lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

Evaluation of Non-target Lesions

CR: Complete Response

Disappearance of all (non-lymph node) non-target lesions and normalization of tumor marker level (ie, ≤ upper normal limit of the study site). All lymph nodes must be non-pathological in size (< 10mm short axis).

Non-CR/Non-PD

Persistence of one or more (non-lymph node) non-target lesion(s) and/or presence of one or more (lymph node) non-target lesion(s) with the short axis of ≥ 10 mm and/or maintenance of tumor marker level above the normal limits of the study site.

PD: Progressive Disease

"Unequivocal progression" of existing non-target lesions (including recurrence)

To achieve "unequivocal progression", there must be an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit discontinuation of study treatment. In presence of SD or PR in target lesions, "unequivocal progression" will be selected if there is substantial worsening in non-target lesions beyond the extent of reduction in target lesion burden. If not, "Non-CR/Non-PD" should be selected.

When the patient has no target lesions, "unequivocal progression" will be selected if, as a rough guide, the increase in overall non-target lesion burden is apparently greater than a 20% increase in diameter or a 73% increase in volume.

NE: Not Evaluable

When no imaging/measurement is done at all at a particular time point for any reason or assessment is impossible as either CR, Non-CR/Non-PD, or PD.

New Lesions

A lesion, which did not exist at baseline, found after start of administration of the investigational product denotes the appearance of a "new lesion."

However, a "new lesion" should not be the result of differences in the scanning technique from that used at baseline, or changes on the image due to a change in imaging modality or findings thought to represent something other than a tumor. A lesion newly identified in an anatomical location that was not considered essential to scan at baseline qualifies as a new lesion.

If a lesion disappears and reappears at a subsequent time point, it should continue to be measured. However, the subject's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. If the subject's tumor had reached CR status and the lesion reappeared, then the subject would be considered PD at the time of reappearance. In contrast, if the tumor status was PR or SD and one lesion that had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response; in other words, the reappearance of an apparently "disappeared" single lesion amongst many that remain is not in itself enough to qualify for assignation of PD: that requires the sum of all lesions to meet the PD criteria. This is based upon the realization that most lesions do not actually

"disappear" but are not visualized because the lesions are beyond the resolving power of the imaging modality employed.

If a lesion could be new but cannot be confirmed, it is not regarded as a new lesion, and imaging is repeated after a clinically appropriate interval. If repeated imaging confirms that it is a new lesion, the new lesion is considered to have appeared on the date when imaging confirmed it as a new lesion.

A-8 Overall Response

Overall response is assessed by a combination of effect on target lesions, effect on non-target lesions, and appearance of new lesions according to the following Table A. Overall response when no non-target lesions exist at baseline is assessed by target lesion assessment and appearance of new lesions, and that when no target lesions exist at baseline is assessed by non-target lesion evaluation and appearance of new lesions according to Table B.

Table A: Criteria for overall response (with target lesions)

Assessment of target lesions	Assessment of non-target lesions	Appearance of new lesion	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table B: Criteria for overall response (without target lesions)

Assessment of non-target lesions	Appearance of new lesion	Overall response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
NE	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

A-9 Best Overall Response

The best overall response is determined based on the overall response determined until the end of the study. However, CR and PR should be confirmed and determined according to the criteria in Table C. In addition, overall response after the start of subsequent anticancer therapy for non-squamous non-small cell lung cancer or after the end of the follow-up investigation and overall response after determination of PD will not be used to evaluate the best overall response. In order for the best overall response to be assessed as SD in this study, the overall response as assessed on or after Day 43 including at least one SD or better rather than PD should be obtained. Also, to determine the best overall response to be CR, the assessment including at least 2 successive determinations of CR at no less than 4-week (28 days) intervals should be obtained, and to classify best overall response as PR, the assessment including at least 2 successive determinations of PR or better (CRs or PRs) at no less than 4-week (28 days) intervals should be obtained. In addition, if a subject is considered as having no target lesion as a result of imaging assessment before the start of administration, assessment of the best overall response is “NE.”

Table C: Criteria for best overall response

Overall response First time point	**Overall response Subsequent time point**	**Best overall response**
CR	CR	CR
CR	PR	SD, PD or PR[#]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

#: If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

APPENDIX 2 Performance Status Scale/Scores ECOG

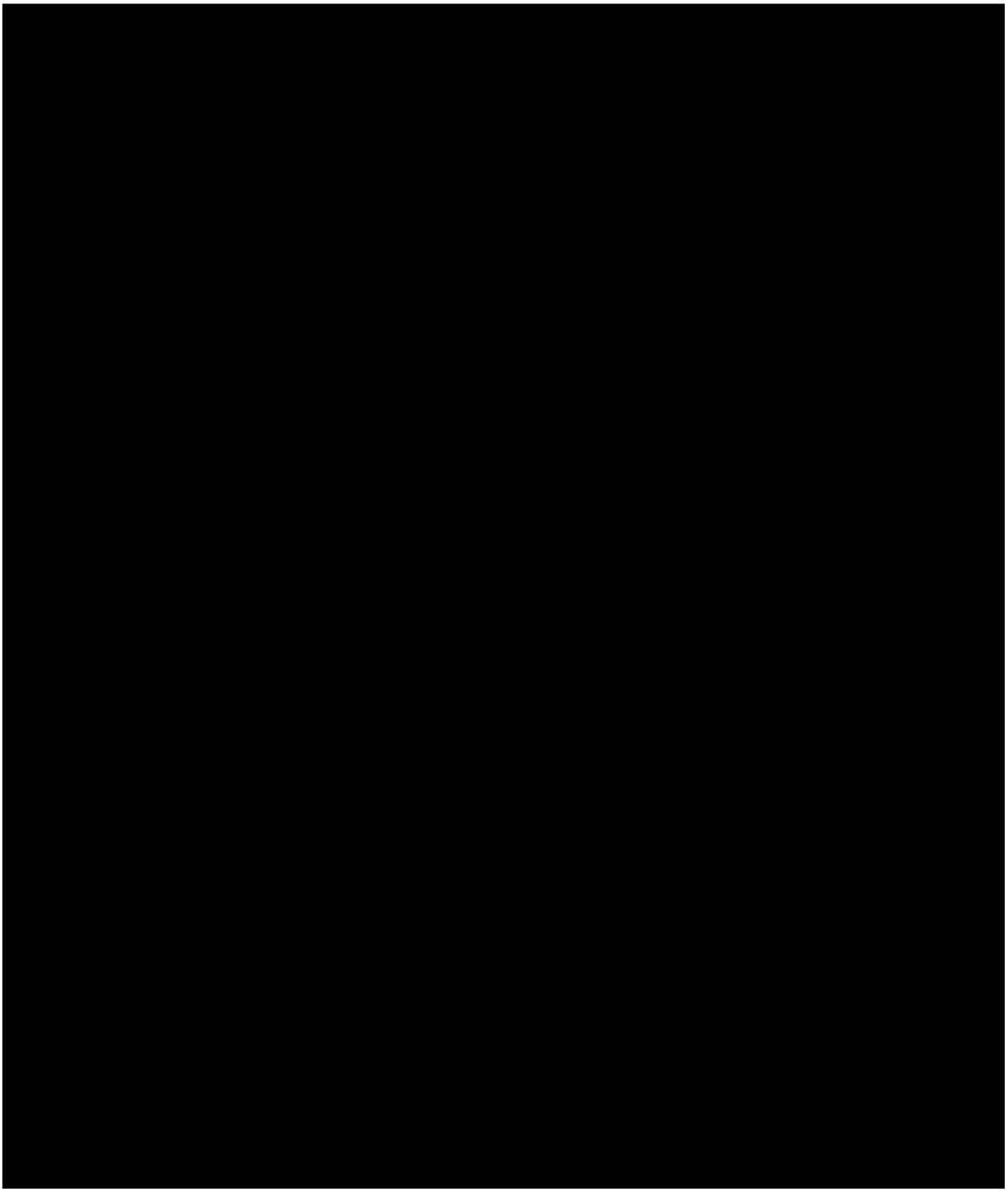
Score	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

APPENDIX 3 List of Autoimmune Diseases (reference)

Subjects who have complications of any of the following autoimmune diseases or previously had any chronic or recurrent autoimmune disease should not be enrolled in this study, as a rule. For a subject with any other autoimmune disease, the investigator should carefully consider the eligibility of the patient and, if there are safety concerns, should not enroll the subject in this study.

· Acute disseminated encephalomyelitis	· IgA nephropathy	· Addison's disease
· Inflammatory bowel disease	· Alopecia universalis	· Interstitial cystitis
· Ankylosing spondylitis	· Lambert–Eaton myasthenic syndrome	· Antiphospholipid syndrome
· Lupus erythematosus	· Aplastic anemia	· Lyme disease (chronic)
· Asthma	· Meniere's syndrome	· Autoimmune hemolytic anemia
· Mooren ulcer	· Autoimmune hepatitis	· Morphea
· Autoimmune hypophysitis	· Multiple sclerosis	· Autoimmune hypoparathyroidism
· Myasthenia gravis	· Autoimmune myocarditis	· Neuromyotonia
· Autoimmune oophoritis	· Opsoclonus myoclonus syndrome	· Autoimmune orchitis
· Optic neuritis	· Autoimmune thrombocytopenic purpura	· Ord's thyroiditis
· Behcet's disease	· Pemphigus	· Bullous pemphigoid
· Pernicious anemia	· Celiac disease	· Polyarteritis nodosa
· Chronic fatigue syndrome	· Polyarthritis	· Chronic inflammatory demyelinating polyradiculopathy
· Autoimmune polyglandular syndrome	· Churg–Strauss syndrome	· Primary biliary cirrhosis
· Crohn's disease (gastrointestinal ulceration)	· Psoriasis	· Dermatomyositis
· Reiter's syndrome	· Type 1 diabetes mellitus	· Rheumatoid arthritis
· Dysautonomia	· Sarcoidosis	· Eczema
· Scleroderma	· Sjögren's syndrome	· Acquired epidermolysis bullosa
· Stiff-man syndrome	· Pemphigoid gestationis	· Takayasu's arteritis
· Giant cell arteritis	· Ulcerative colitis	· Goodpasture's syndrome
· Graves' disease	· Vogt–Koyanagi–Harada syndrome	· Guillain–Barre syndrome
· Vulvodynia	· Hashimoto's disease	· Wegener's granulomatosis
· Kawasaki's disease		

Signature of the Clinical Protocol



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