# ONO-4538

# Multicenter, open-label, uncontrolled, Phase II study in advanced non-small cell lung cancer

Subtitle: A multicenter, open-label, uncontrolled Phase II study to evaluate safety and efficacy of ONO-4538 in stage IIIB/IV or recurrent non-small cell lung cancer patients who are unsuited to radical radiotherapy and resistant to a platinum-base chemotherapeutic regimen.

# Protocol

## Ono Pharmaceutical Co., Ltd.

Protocol no. ONO-4538-09
English Version 11.0
Release date: November 2, 2020

**Contact Information for Adverse Event Reports**

[redacted]

Confidentiality Statement

This protocol is to be disseminated to the principal investigator, subinvestigators, clinical research coordinators, clinical trial pharmacist, medical laboratory technologist and institutional review boards etc. All information contained in this protocol should be treated as confidential and may not be disclosed to any third party.

Note

ONO-4538 is co-developed by Ono Pharmaceutical Co., Ltd. and Bristol-Myers Squibb (BMS) (BMS code: BMS-936558). ONO-4538 is described in this document as a compound code.

Ethics

This study will be conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki, the study protocol, standards stipulated under ICH Good Clinical Practice Guidelines (GCPs), the applicable local regulatory requirements and revised ordinances and relevant notifications.

This protocol will be amended when revision is needed to ensure the safety conduct of the study.

Protocol Synopsis

## 1. Study Objectives

The objective of the study is to investigate the efficacy and safety of ONO-4538 in stage IIIB/IV or recurrent non-small cell lung cancer unsuited to radical radiotherapy and resistant to a platinum-based chemotherapeutic regimen in a multicenter, open-label, uncontrolled study.

## 2. Study Design

Multicenter, open label, uncontrolled study

## 3. Disease Studied

### 3.1 Disease Studied

Stage IIIB/IV or recurrent non-small cell lung cancer unsuited to radical radiotherapy and resistant to a platinum-based chemotherapeutic regimen

#### 3.1.1 Subject Inclusion Criteria

Patients satisfying all the following criteria will be included:

1. Male or female.
2. ≥ 20 years of age (at time of enrollment).
3. Histologically or cytologically confirmed non-small cell lung cancer.
4. Diagnosis of NSCLC in stage IIIB/IV unsuited to radical radiotherapy according to UICC-TNM classification ($7^{th}$ edition) or recurrent NSCLC.
5. Has at least one measurable lesion, as defined by the RECIST guideline (version 1.1) (Appendix 1), in diagnostic imaging performed 14 or fewer days before enrollment. (Patients who have received radiotherapy for a measurable lesion must have confirmed progress in diagnostic imaging following radiotherapy.)
6. Has a history of prior treatment with any of the following systemic anti-cancer products (e.g., chemotherapy, molecular targeted therapy, immunotherapy):
   1) History of prior platinum-based chemotherapy and up to 1 regimen of prior treatment for patients negative for or with unknown EGFR activity mutation or ALK gene translocation
   2) History of prior platinum-based chemotherapy and an EGFR tyrosine kinase inhibitor, and up to 2 regimens of prior treatment, for patients positive for EGFR activity mutation

3） History of prior platinum-based chemotherapy and an ALK inhibitor, and up to 2 regimens of prior treatment, for patients positive for ALK gene translocation

7. ECOG Performance Status (Appendix 2) is 0 to 1.
8. Life expectancy is ≥ 90 days.
9. Women of childbearing potential (including women who are amenorrheic due to chemical menopause or for another medical reason) must agree to engage in contraception from the time of informed consent to at least 5 months after the final dose of the investigational product. Women must not be breastfeeding from the time of informed consent to at least 5 months after the final dose of the investigational product.
10. Men must agree to use a contraceptive from the start of study treatment until at least 7 months following the last dose of investigational product.
11. Percutaneous oxygen saturation by pulse oximetry performed 7 or fewer days before enrollment is ≥ 94% in the absence of oxygen supplementation.
12. Most recently determined laboratory values, determined 7 or fewer days before enrollment, satisfy the criteria listed below. Laboratory testing must be performed with no granulocyte colony stimulating factor (G-CSF) treatment or blood transfusion having taken place 14 or fewer days before testing.
    - WBC count ≥ 2,000/$mm^3$ and neutrophil count ≥ 1,500/$mm^3$
    - Platelet count ≥ 100,000/$mm^3$
    - Hemoglobin ≥ 9.0 g/dL
    - AST (GOT) and ALT (GPT) ≤ 3.0 times the upper limit of normal range of each institute
    - Total bilirubin ≤ 2.0 times the upper limit of normal range of each institute
    - Creatinine ≤ 1.5 mg/dL or creatinine clearance (raw or estimated using Cockcroft/Gault formula) > 45 mL/min

### 3.1.2 Subject Exclusion Criteria

Patients satisfying any of the following criteria will be excluded:

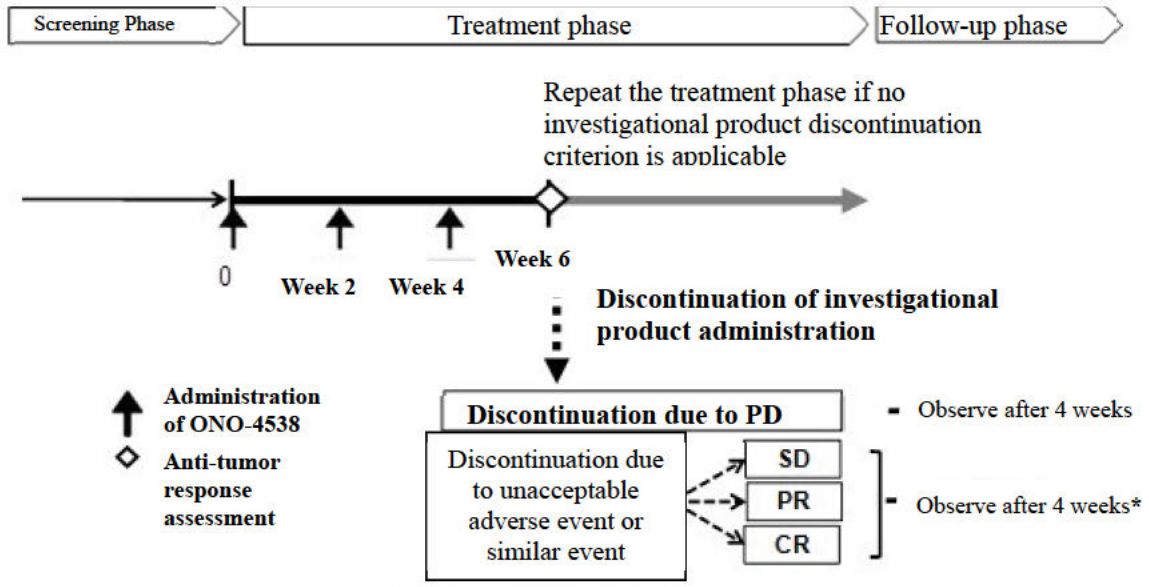
1. Current or prior severe hypersensitivity to another antibody product.
2. Adverse drug reactions due to prior treatments or remaining effects of surgical therapy that, in the principal or sub investigator’s opinion, may interfere with the safety evaluation of the investigational product.
3. Active autoimmune disease or history of chronic or recurring autoimmune disease (Appendix 3).

4. Current or prior interstitial lung disease or pulmonary fibrosis diagnosed based on diagnostic imaging or clinical findings. (Radiation pneumonitis allows to be enrolled as long as not acute phase with fibrosis or without symptoms.)
5. Active diverticulitis or symptomatic gastrointestinal ulcerative disease.
6. Multiple primary cancers (except for completely resected basal cell cancer, stage I squamous cell carcinoma, carcinoma in situ, intramucosal carcinoma, or superficial bladder cancer or any other cancer from which the patient has been recurrence-free for at least 5 years).
7. Metastases to the brain or meninges (unless such lesions are asymptomatic and do not require treatment).
8. Pericardial effusion, pleural effusion, or ascites requiring treatment.
9. Pain associated with bone metastases and others not controllable with a fixed regimen of an analgesic.
10. History of transient ischemic attack, cerebrovascular accident, thrombosis, or thromboembolism (pulmonary arterial embolism or deep vein thrombosis) within 180 days of enrollment.
11. Any of the following cardiovascular diseases that are uncontrollable or severe:
    - Myocardial infarction within 180 days of enrollment
    - Uncontrollable angina pectoris within 180 days of enrollment
    - New York Heart Association (NYHA) Grade III or IV congestive cardiac failure
    - Hypertension (systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 90 mmHg persisting for ≥ 24 hours) despite appropriate treatment
    - Arrhythmia requiring treatment
12. On anticoagulant therapy (other than antiplatelet therapy with low-dose aspirin) or having a disease requiring anticoagulant therapy.
13. Uncontrollable diabetes.
14. Has received a systemic corticosteroid (unless temporarily for testing, prophylaxis, or a similar purpose unrelated to an autoimmune disease) or an immune suppressant 28 or fewer days before enrollment.
15. Has received an anti-cancer product (e.g., chemotherapy, molecular targeted therapy, and immunotherapy) 28 or fewer days before enrollment.
16. Has undergone surgery for pleural, pericardial, or similar adhesion 28 or fewer days before enrollment.
17. Has undergone surgical treatment accompanying general anesthesia 28 or fewer days before enrollment.

18. Has undergone surgical treatment accompanying local or surface anesthesia 14 or fewer days before enrollment.
19. Has received radiotherapy 28 or fewer days before enrollment or thoracic radiotherapy or a radiopharmaceutical agent (except when the radiopharmaceutical agent is used for testing or diagnostic purposes) 56 or fewer days before enrollment.
20. Has undergone gamma knife or CyberKnife treatment 14 or fewer days before enrollment.
21. Has a systemic infection that requires treatment.
22. Has tested positive for HIV-1 antibody, HIV-2 antibody, HTLV-1 antibody, HBs antigen, or HCV antibody.
23. Has tested positive for HBs antibody or HBc antibody and has a result of at least detectable in HBV-DNA assay despite testing negative for HBs antigen.
24. Is pregnant, nursing, or possibly pregnant.
25. Has received another investigational product 28 or fewer days before enrollment.
26. Has previously received ONO-4538 (MDX-1106 or BMS-936558), an anti-CTLA-4 antibody, or other antibody therapy or drug therapy intended to control T-cells.
27. Is found incapable of giving consent due to dementia or another such condition.
28. Patients otherwise found by the principal or sub investigator to be ineligible.
29. Patients who have received a live/attenuated vaccine 28 or fewer days before enrollment.

## 4. Study Schedule and Observations

The study consists of a screening phase, treatment phase, and follow-up phase (see Figure 4-1).




*Perform diagnostic imaging (e.g., CT, MRI) where possible until a subsequent treatment for NSCLC is initiated or the development of PD or disease recurrence is identified.

**Figure 4-1 Summary of study design**

### 4.1 Screening Phase

Patients who satisfy all of the subject inclusion criteria and none of the exclusion criteria and who are found eligible by the principal or sub investigator can be enrolled and then moved to the treatment phase.

### 4.2 Treatment Phase

ONO-4538 will be administered every 2 weeks, to 3 times in total, which constitutes one cycle. Subjects who satisfy all initiation criteria for the subsequent investigational product course and none of the investigational product discontinuation criteria may repeat this cycle. The study schedule for the treatment phase is shown in Table 4-1 and Table 4-2.

### 4.3 Follow-up Phase

Those subjects receiving the investigational product who satisfy any of the investigational product discontinuation criteria will proceed to the follow-up phase. The study schedule for the follow-up phase is shown in Table 4-3.

Subjects discontinuing the treatment phase for a safety-related reason despite having achieved CR, PR, or SD according to the RECIST guideline (version 1.1) will undergo diagnostic imaging (e.g., CT,

MRI) whenever possible until beginning subsequent treatment for non-small cell lung cancer or until developing PD or recurrence.

Even after the conclusion of the tests performed on discontinuation, all treatment-related adverse events will be followed every 2 weeks whenever possible until resolution or improvement or when no further follow-up is necessary due to symptom stability. Laboratory tests or diagnostic imaging will be repeated and other measures taken as necessary to adequately ensure subject safety.

### 4.4 Determination of Outcome

Follow-up to determine survival status (and, if the subject has died, the date and cause of death) will be performed every 6 months or so beginning 6 months after the first day of treatment of the last subject enrolled in the study. Outcome information may be obtained by phone, letter, or another means. The use, start dates, and types of any subsequent treatments for NSCLC will also be investigated whenever possible.

**Table 4-1 Study schedule (Cycle 1)**

| Category | Screening phase | Treatment phase (Cycle 1) | | | | | |
|---|---|---|---|---|---|---|---|
| Study day | | 1 | | 8 | 15 | 29 | 43[6] |
| | | Before administration | After administration | | | | |
| Allowable range (days) | -7 to -1 | 1 | | ±3 | -3 to +7 | -6 to +7 | -6 to + 7 |
| Visit | V 1-0 | V 1-1 | | V 1-2 | V 1-3 | V 1-4 | V 1-5 |
| Written informed consent | ○[7] | | | | | | |
| Demographics and inclusion/exclusion criteria | ○ | | | | | | |
| Investigational product administration [1] | | ○ | | | ○ | ○ | |
| Virus tests | ○[8] | | | | | | |
| Pregnancy test[2] | ○[8] | ○ | | | | | |
| Performance Status | ○[8] | | | ○ | ○[9] | ○[9] | ○ |
| Vital signs/weight/percutaneous oxygen saturation | ○[8] | ○[10] | ○[10] | ○[10] | ○[9, 10] | ○[9, 10] | ○ |
| Chest X-ray[3] | ○[8] | | | | | | ○ |
| 12-lead ECG | ○[8] | ○ | ○[11] | | | | ○ |
| Hematology tests, blood biochemistry tests, urinalysis | ○[8] | | | ○ | ○[9] | | ○ |
| Immunology/hormone tests | ○[8, 12] | | | | | | ○ |
| Serum drug concentration | | ○ | ○[13] | | ○[9] | ○[9] | |
| Anti-ONO-4538 antibody | | ○ | | | ○[9] | ○[9] | |
| [redacted] | | | | | | | |
| Diagnostic imaging (e.g., CT, MRI) | ○[8, 14] | | | | | | ○ |
| Concomitant drugs/adverse events | | ← | | | | | → |

1. Administer the investigational product after at least 10 days have passed since the most recent dose.
2. Women of childbearing potential will undergo a serum pregnancy test in the screening phase and subsequently undergo urine pregnancy testing.
3. Also perform at unscheduled visits as necessary if, during the study (from the time of informed consent to the completion of the final tests (other than the survey for 'determination of outcome') specified in the protocol), signs, subjective and objective symptoms, or test findings suggest respiratory disease.

[redacted]

6. For subjects again proceeding to the treatment phase, administer the investigational product on Day 1 of the next cycle within the Day 43 allowable range (i.e., Days 37 to 50). Proceed to the follow-up phase (Table 4-3) on completing the treatment phase.
7. Begin administering the investigational product within 30 days of informed consent.
8. The data from virus tests performed within 1 year of enrollment, diagnostic imaging (e.g., CT, MRI) performed within 14 days of enrollment, and other tests performed within 7 days of enrollment will be included.
9. Perform before administering the investigational product.
10. Other than weight.
11. Perform immediately before collecting the sample for serum drug concentration analysis.
12. SP-D and KL-6 will be measured in the screening phase and, as necessary, in the treatment phase.
13. Collect sample immediately before the completion of investigational product administration.
14. Check for brain metastases with head CT/MRI. Check for bone metastases with X-ray imaging, FDG-PET, or bone scintigraphy as required by the clinical symptoms.

**Table 4-2 Study schedule (Cycles 2 and beyond)**

| Category | Treatment phase (Cycles 2 and beyond) | | | | |
|---|---|---|---|---|---|
| Study day | 1[5] | 15 | | 29 | 43[5] |
| | | Before administration | After administration | | |
| Allowable range (days) | 1 | -3 to +7 | | -6 to +7 | -6 to +7 |
| Visit | V n-1 | V n-2 | | V n-3 | V n-4 |
| Investigational product administration [1] | ○ | ○ | | ○ | |
| Performance Status | ○[6, 7] | | | | ○ |
| Vital signs/weight/percutaneous oxygen saturation | ○[6, 7] | ○[8] | | ○[7, 8] | ○ |
| Chest X-ray[2] | | | | | ○ |
| 12-lead ECG | ○[6, 7, 9] | | | | ○[9] |
| Hematology tests, blood biochemistry tests, urinalysis | ○[6, 7] | | | | ○ |
| Immunology/hormone tests | | | | | ○ |
| Serum drug concentration [3] | ○[7, 10] | ○[11] | ○[11, 12] | | |
| Anti-ONO-4538 antibody [3] | ○[7, 10] | ○[11] | | | |
| Tumor markers [4] | ○ | | | | |
| Diagnostic imaging (e.g., CT, MRI) | | | | | ○[13] |
| Concomitant drugs/adverse events | ← | | | | → |

1. Administer the investigational product after at least 10 days have passed since the most recent dose.
2. Also perform at unscheduled times as necessary if, during the study (from the time of informed consent to the completion of the final tests (other than the determination of outcome) specified in the protocol), signs, subjective and objective symptoms, or test findings suggest respiratory disease.
3. To be collected until the end of the 1-year period after the start of investigational drug administration (i.e., Cycle 9).
4. Analyze tumor markers whenever possible in each subject with a tumor marker at a level exceeding the normal range. Perform tumor marker analysis when required.
5. For subjects again proceeding to the treatment phase, administer the investigational product on Day 1 of the next cycle within the Day 43 allowable range (i.e., Days 37 to 50). Proceed to the follow-up phase (Table 4-3) on completing the treatment phase.
6. Unless medically necessary, vital signs will be measured no sooner than 2 days, and other tests will be performed no sooner than 8 days after the previous measurement.
7. Perform before administering the investigational product.
8. Other than weight.
9. Perform only in Cycle 4.
10. Perform only in Cycles 2, 4, 5, 7, and 9.
11. Perform only in Cycle 3.
12. Collect sample immediately before the completion of investigational product administration.
13. Perform every cycle (every 6 weeks) between Cycle 2 and 29 and every 2 cycles (every 12 weeks) after Cycle 30.

**Table 4-3 Study schedule (for subjects completing the treatment phase)**

| Category | At end of treatment phase [6] | Follow-up phase | |
|---|---|---|---|
| Study day | | 28 days after final dose or on discontinuation<br>28 or fewer days after final dose [6] | Follow-up[7] |
| Allowable range (days) | -3 to +3 | -7 to +7 | - |
| Visit | V f-0 | V f-1 | V f-n |
| Pregnancy test[1] | ○[8] | ○ | |
| Performance Status | ○ | ○ | |
| Vital signs/weight/percutaneous oxygen saturation | ○ | ○ | |
| Chest X-ray | ○ | ○ | |
| 12-lead ECG | ○[8] | ○ | |
| Hematology tests, blood biochemistry tests, urinalysis | ○ | ○ | |
| Immunology/hormone tests | ○ | ○ | |
| Serum drug concentration [2] | ○[8] | ○ | |
| Anti-ONO-4538 antibody [2] | ○[8] | ○ | |
| Diagnostic imaging (e.g., CT, MRI) | ○ | ○ | ○ |
| [redacted] | [redacted] | [redacted] | |
| | [redacted] | [redacted] | |
| | [redacted] | [redacted] | |
| Concomitant drugs/adverse events [5] | ← | → | |

1. Women of childbearing potential will undergo urine pregnancy testing.
2. Perform only if the subject proceeds to the follow-up phase within 1 year after the start of investigational product administration (by Cycle 9). Collect sample if possible 6 to12 weeks after the final investigational product dose.

[redacted]

5. Investigate all adverse events and concomitant treatments to the completion of the final tests (other than the survey for 'determination of outcome') specified in the protocol. Beyond the completion of the final tests (other than the survey for 'determination of outcome') specified in the protocol, follow any persisting adverse event for which a causal relationship with the investigational product cannot be ruled out, adverse events that resulted in discontinuation, and the concomitant treatments associated with those events until the events resolve, improve,or are determined to be permanent or no further follow-up is necessary. And all treatment-related adverse events will be followed every 2 weeks if possible.
6. Information from a prior measurement may be included if the day of that measurement falls within the acceptable range at the end of the treatment phase or discontinuation. Unless medically necessary, vital signs will be measured no sooner than 2 days, diagnostic imaging (e.g., CT, MRI) performed no sooner than 15 days, and other tests no sooner than 8 days after the previous measurement.
7. Those subjects who are CR, PR, or SD at the time of discontinuation of the investigational product will undergo follow-up whenever possible with diagnostic imaging and to determine the use and types of any subsequent treatments for non-small cell lung cancer until a subsequent therapy for non-small cell lung cancer is begun or the subject experiences PD or recurrence.
8. Perform only when the test after 28 days of the final investigational product dosage or on discontinuation within 28 days after the final investigational product dosage is not performed due to withdrawal or other reasons. Perform 12-lead ECG also at the discontinuation of treatment phase if the treatment phase is discontinue in Cycle 1 or 4.

[redacted]

## 5. Dose and Administration, and Duration of Treatment

ONO-4538 is administered at a 3 mg/kg dose with a 2-week dosing interval. One cycle consists of 6 weeks. ONO-4538 administration will continue until the development of PD as identified by the investigator or sub investigator according to the RECIST guideline (version 1.1). The appropriate dose of ONO-4538 will be diluted with physiological saline or dextrose 5% in water to a total amount of approximately not less than 60 mL before use (so that the solution drug concentration is no less than 0.35 mg/mL). The entire dose of ONO-4538 will be administered as an intravenous infusion over approximately 60 minutes through a 0.20 ~ 1.20 μm in-line filter. The lower limit of the infusion time is 54 minutes. The target upper limit is 90 minutes. At the end of the infusion, the line will be flushed with a sufficient quantity of physiological saline or dextrose 5% in water. The ONO-4538 dose will not be reduced. The administration of ONO-4538 infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration condition (2°-8°C, 36°-46°F) for up to 24 hours , and a maximum of 8 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

The dose will be changed if the body weight of the subject changes by at least 10% relative to the weight at enrollment. Each subsequent 10% or greater change in body weight is to be handled in a similar manner.

## 6. Prior and Concomitant Therapies

### 6.1 Therapies Prohibited During the Study

The therapies listed below are prohibited during the study (from the time of informed consent to the completion of the final tests (other than the determination of outcome) specified in the protocol).

1. Immunosuppressants and corticosteroids
2. Anti-cancer agents (e.g., chemotherapy, molecular targeted therapy, immunotherapy)
3. Surgical treatment for a malignant tumor
4. Radiotherapy
5. Radiopharmaceuticals
6. Bisphosphonate products and anti-RANKL antibodies
7. Transplant therapy
8. Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR])
9. Any other investigational product

### 6.2 Prophylactic Drug Use

Prophylactic pretreatment with acetaminophen and diphenhydramine before ONO-4538 administration is recommended for subjects who develop an infusion related reaction to a previous dose of ONO-4538.

## 7. Investigational Product Discontinuation Criteria

Subjects satisfying any of the following criteria in the treatment phase will be discontinued the investigational product and proceed to the follow-up phase.

1. The development of PD is identified by the principal or sub investigator according to the RECIST guideline (version 1.1).
2. A worsening of clinical symptoms attributed to disease progression occurs.
3. The subject develops Grade 2 or higher interstitial lung disease, regardless of the causal relationship to the investigational product.
4. Grade 2 or greater eye pain, or visual acuity reduced occurs whose causal relationship with the investigational product cannot be ruled out and does not improve to Grade 1 severity with local treatment.
5. Grade 3 or greater bronchospasm, hypersensitivity reaction, infusion reaction (e.g., pyrexia, chills, nausea, pain, headache, cough, pruritus, rash) or uveitis occurs whose causal relationship with the investigational product cannot be ruled out.
6. An adverse event or other events delay the administration of the investigational product by more than 6 weeks.
7. The investigator or sub-investigator otherwise determines that continuing to administer the investigational product is inappropriate due to an efficacy- or safety-related reason.

Even when Criterion 1 is applicable, investigational product treatment may be continued if it is determined through consultation with the sponsor that no worsening of clinical symptoms attributable to disease progression occurs, continued treatment is expected to provide a clinical benefit, and the investigational product can continue to be safely administered. If the investigational product is to be continued, the subject should first be consulted about his or her willingness to continue receiving treatment, and this process should be documented in the medical records. Laboratory tests will be frequently repeated and other measures taken to adequately ensure subject safety. Any subject who is

found to have again developed PD according to the RECIST guideline (version 1.1)based on a point where a decision is made to continue investigational product treatment must cease using the investigational product regardless of whether clinical symptoms have worsened or not.

## 8. Endpoints

### 8.1 Efficacy

1. Primary endpoint: Response rate (centrally assessed)
2. Secondary endpoints: Response rate (study site assessment by investigator), overall survival, progression free survival, time to progression, duration of response, time to response, best overall response, and percent change in tumor diameter

### 8.2 Safety

1. Adverse events
2. Laboratory tests (hematology, blood biochemistry, qualitative urinalysis, immunology tests, hormone tests)
3. Vital signs (systolic blood pressure/diastolic blood pressure, pulse, body temperature), body weight, percutaneous oxygen saturation ($SpO_2$)
4. 12-lead ECG
5. Chest X-ray
6. Performance Status (ECOG)

### 8.3 Pharmacokinetics

1. Serum ONO-4538 concentrations

### 8.4 Anti-drug Antibodies

1. Anti-ONO-4538 antibody

[redacted]

[redacted]

## 9. Planned Number of Subjects

Total of 93 subjects (41 subjects with squamous NSCLC and 52 subjects with non-squamous NSCLC)

## 10 Investigational Product Supply Restrictions

Each subject to whom the investigational product discontinuation criteria and individual subject discontinuation criteria are not applicable is eligible to receive the investigational product from the sponsor. The sponsor will stop supplying the investigational product if:

1. Ministry of Food and Drug Safety rejects the application for approval for the present indication.
2. The study is cancelled due to safety concerns.
3. The subject is able to receive the drugs through public or private health insurance.
4. An alternative therapy becomes available.

## 11. Planned Study Period

January 2014 to December 2021

The data cut-off may be performed based on progress of the clinical studies.