Statistical Analysis Plan

Protocol No.: ONO-4538-13

Multicenter, open-label, uncontrolled,
Phase I in solid tumor

Sponsor: Ono Pharmaceutical Co., Ltd.

[redacted]

Protocol Version: ONO-4538-13-version 1.1, 08-Jan-2015

SAP Version No & Date: SAP_ONO-4538-13_version 1.0, 13-Jan-2015

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History of Revision

Study No [redacted]	ONO-4538-13 [redacted]	**Sponsor** [redacted]	Ono Pharmaceutical Co., Ltd. [redacted]
Approval Date	**Amended Version**		

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ALP	alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (glutamic pyruvic transaminase)
ANA	anti-nuclear antibody
AST (GOT)	Aspartate aminotransferase (glutamate oxaloacetate transaminase)
BMI	body mass index
BUN	blood urea nitrogen
CK (CPK)	creatine kinase (creatine phosphokinase)
Cl	Chloride
CRP	C-reactive protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
G-CSF	granulocyte colony stimulating factor
GH	growth hormone
HBc	hepatitis B virus core protein
HBs	hepatitis B virus surface protein
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus-1
HIV-2	human immunodeficiency virus-2
HLA	human leukocyte antigen
IL	interleukin
IP	interferon-inducible protein
LDH	Lactate dehydrogenase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
NCI	National Cancer Institute, United States
NKT cell	natural killer T cell
NYHA	New York Heart Association

PD-1	Programmed cell death-1
PD-L1	Programmed cell death-ligand 1
PD-L2	Programmed cell death-ligand 2
Performance Status	Performance Status
PT	preferred term
QRS	ventricular activation time
QT	electrocardiogram QT interval (electrical ventricular contraction time)
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RA	rheumatoid factor
RANKL	Receptor activator of NF-κB ligand
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAF	Safety Analysis Set
SOC	System Organ Class
SP-D	pulmonarysurfactant protein D
SpO_2	percutaneous oxygen saturation
TSH	thyroid stimulating hormone
UICC-TNM	Union InternationaleContre Le Cancer TNM
γ-GTP	Gamma-glutamyltranspeptidase

1 INTRODUCTION

ONO-4538 (Bristol-Myers Squibb [BMS] developmental code: BMS-936558, ex-Medarex developmental code: MDX-1106) is a fully human monoclonal antibody to human programmed cell death-1 (PD-1 [also known as CD279]), made by Ono Pharmaceutical Co., Ltd. and Medarex Inc. The product is made with recombinant technology using CHO cells. PD-1 is a receptor of the CD28 family (a molecular group that positively and negatively regulates the activation of T cells in supplementary fashion), which is expressed on activated lymphocytes (T cells, B cells and NKT cells) and myeloid cells. PD-1 binds to PD-1 ligands (PD-L1 [also known as B7-H1 and CD274] and PD-L2 [also known as B7-DC and CD273]), which are expressed on antigen-presenting cells, and transmits regulatory stimuli to lymphocytes to down-modulate the activation of lymphocytes [1)]. PD-1 ligands are expressed on various cancer tissues [2)], in addition to antigen-presenting cells. Based on some non-clinical pharmacological studies, the proliferation and the activation of antigen-specific T cells have been shown as the result of the inhibition to binding of PD-1 on PD-1 ligand by ONO-4538.

Ono is clinically developing the ONO-4538 in Korea and Japan. BMS is clinically developing that in other regions.

We have planned to conduct a clinical trial to investigate the pharmacokinetics of ONO-4538 in patient with solid tumor in Korea. In addition to the pharmacokinetics, the safety and pharmacological action will be evaluated. The data from this study will be included in the documents for the new drug administration of ONO-4538 in Korea.

2 STUDY OBJECTIVES

The objective of the study is to investigate the pharmacokinetics of ONO-4538 administered to Korean patients with advanced or recurrent solid tumors who are refractory or intolerant to standard therapy or for whom no appropriate treatment is available.

3 INVESTIGATIONAL PLAN

3.1 Study Design

Multi-center, open-label, uncontrolled study

3.2 Target

3.2.1 Target

Advanced or recurrent solid tumors who are refractory or intolerant to standard therapy or for whom no appropriate treatment are available.

3.2.2 Subject Inclusion Criteria

Patients satisfying all the following criteria will be included:

1. Male or female (Korean)
2. ≥ 20 years of age (at time of obtaining the Informed Consent)
3. Histologically or cytologically confirmed solid tumor
4. Patients with advanced or recurrent solid tumors who are refractory or intolerant to standard therapy or for whom no appropriate treatment is available
5. ECOG Performance Status (Appendix 2) is 0 to 1
6. Life expectancy is ≥ 90 days at time of patient enrollment
7. Women of childbearing potential (including women who are amenorrheic due to chemical menopause or for another medical reason) [*1] must agree to engage in contraception[*2] from the time of informed consent to at least 400 days after the final dose of the investigational product.
8. Men must agree to use a contraceptive from the start of study treatment until at least 400 days following the last dose of investigational product.
9. Most recently determined laboratory values, within 7 days before patient enrollment on this study, satisfy the criteria listed below. If all the laboratory values were obtained over 7 days before the ONO-4538 initial treatment, the laboratory test has to be performed within 7 days before the ONO-4538 initial treatment and the laboratory values have to meet the all 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

[*1] The term "women of childbearing potential" includes all women who have experienced menarche but have not undergone a sterilization procedure (e.g., hysterectomy, bilateral tubal ligation, bilateral oophorectomy) or experienced menopause. Menopause is constituted by having been amenorrheic for at least 12 months without a notable reason. Women who use an oral contraceptive, an intrauterine device, the barrier method, or other mechanical method of contraception are considered to be of childbearing potential.

[*2] The subject must consent to use any two of the following methods of contraception: vasectomy or condom for patients who are male or their partner and tubal ligation, contraceptive diaphragm, intrauterine device, or oral contraceptive for patients who are female or their partner.

3.2.3 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 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.
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. Original cancer or 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. Cancer pain not stable 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. A serious concomitant disease such as liver failure, renal failure or uncontrollable diabetes.
14. Patients requiring transplantation or with a history of transplantation except autotransplantation
15. 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.
16. Has received an anti-cancer product (e.g., chemotherapy, molecular targeted therapy, and immunotherapy) 28 or fewer days before enrollment.
17. Has undergone surgery for pleural, pericardial, or similar adhesion 28 or fewer days before enrollment.
18. Has undergone surgical treatment accompanying general anesthesia 28 or fewer days before enrollment.
19. Has undergone surgical treatment accompanying local or surface anesthesia 14 or fewer days before enrollment.
20. Has received radiotherapy 28 or fewer days before enrollment or has received radiotherapy for relief of cancer symptoms 14 or fewer days before enrollment.
21. Has received a radiopharmaceutical agent (except when the radiopharmaceutical agent is used for testing or diagnostic purposes) 56 or fewer days before enrollment.

22. Has undergone gamma knife or CyberKnife treatment 14 or fewer days before enrollment.
23. Has a systemic infection that requires treatment.
24. Has tested positive for HIV-1 antibody, HIV-2 antibody, HTLV-1 antibody, HBs antigen, or HCV antibody.
25. 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.
26. Is pregnant, nursing, or possibly pregnant.
27. Has received another investigational product 28 or fewer days before enrollment.
28. 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.
29. Is found incapable of giving consent due to dementia or another such condition.
30. Patients otherwise found by the principal or sub investigator to be ineligible.

3.3 Study Schedule and Observations

The study consists of a screening phase, treatment phase, and follow-up phase (see Figure 3).

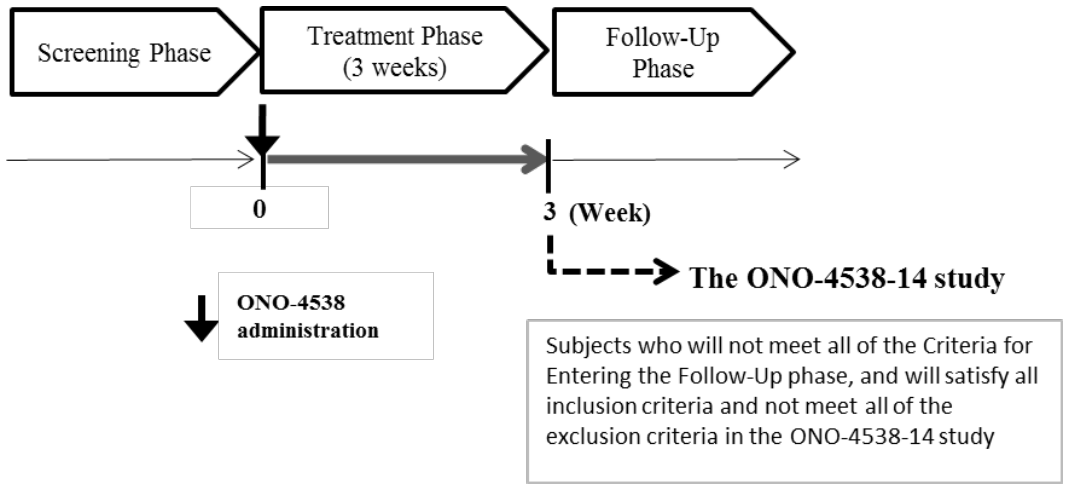

Figure 3 Summary of study design

3.3.1 Screening Phase

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

3.3.2 Treatment Phase

ONO-4538 will be administered once. Subjects who will meet any of the Criteria for Entering the Follow-Up phase will move to the Follow-Up phase. The subjects who complete the treatment phase in this study and not meet all of the Criteria for Entering the Follow-Up phase, and will satisfy all inclusion criteria and not meet all of the exclusion criteria in the ONO-4538-14 study may move to the ONO-4538-14 study, otherwise the subjects will move to the Follow-Up phase.

3.3.3 Follow-up Phase

Those subjects receiving the investigational product who satisfy any of the Criteria for Entering the Follow-Up phase will proceed to the Follow-Up phase.

Table 3 Study schedule

Category	Screening Phase	Treatment Phase											Follow-Up phase
Study day		1				2	3	4	8	15	22	At discontinuation	28 days after the discontinuation or the Day 22 only if the subjects will not join the ONO-4538-14.
		Before administration	After the start of the administration	After the end of the administration									
			1 hr	2 hr	8 hr								
Allowable range (days)	-7 to -1	-							±2	±3		+3	±7
Written informed consent	○[1]												
Inclusion/exclusion criteria	○												
Virus tests	○[2]												
ONO-4538 administration		○											
Demographics	○												
Pregnancy test[3]	○											○	○
Vital signs/weight /percutaneous oxygen saturation	○	○[4]	○[4]	○[4]	○[4]	○[4]	○[4]	○[4]	○[4]	○[4]	○[4]	○	○
Performance Status	○										○	○	○
Chest X-ray[5]	○										○	○	○
12-lead ECG	○	○	○	○	○		○		○	○	○	○	○
Hematology tests/urinalysis /blood biochemistry tests	○								○		○	○	○
Immunology/hormone tests	○[6]								○		○	○	○
Serum drug concentration[7]		○	○	○	○	○	○	○	○	○	○	○	○
Anti-ONO-4538 antibody		○									○	○	○
[redacted]													
Diagnostic imaging (e.g., CT, MRI)[9]	○[2]												●
Tumor marker[10]	●												
Concomitant drugs/adverse events			←										→

○:essential, ●: optional

1. Begin administering the investigational product within 30 days of informed consent.
2. The data from virus tests performed within 1 year of enrollment, diagnostic imaging (e.g., CT, MRI) performed within 14 days of enrollment will be included.
3. Women of childbearing potential will undergo a serum pregnancy test in the screening phase and subsequently undergo urine pregnancy testing.
4. Other than weight.
5. Also perform at unscheduled visits as necessary if, during the study (from the time of informed consent to the end of the subjects' schedule), signs, subjective and objective symptoms, or test findings suggest respiratory disease.
6. SP-D and KL-6 will be measured in the screening phase and, as necessary, in the treatment phase.
7. Collect blood sample at 24, 48 and 72 hours after the completion of the administration on 2nd, 3rd and 4th day, respectively.
8. [redacted]
9. 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.
10. Perform tumor marker assessment according to the cancer type of patient when required at Investigator's discretion.

3.4 Dose and Administration, and Duration of Treatment

Patients will be assigned any of the following groups in order of increasing dose and ONO-4538 is administered at a dose level of 1, 3 or 10 mg/kg (See Table 5)

Table 5. ONO-4538 Dose

Group	Treatment phase Dose (mg/kg)	Subjects number
A	1	6
B	3	6
C	10	6

ONO-4538 will be administered once in the treatment phase and each subject will be observed for 3 weeks. The appropriate dose of ONO-4538 will be diluted with physiological saline to a total amount of approximately not less than 60 mL before use (so that concentration of diluted solution of ONO-4538 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 or 0.22 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. Regarding the calculation of the dosage amount, the dose will be rounded off to the nearest tenth.

3.5 Prior and Concomitant Therapies

3.5.1 Therapies Prohibited During the Study

The therapies listed below are prohibited during the study (from the time of informed consent to the end of the subjects' schedule).

1. Immunosuppressants and corticosteroids [*1]
2. Anti-cancer products (e.g., chemotherapy, molecular targeted therapy, immunotherapy[*2])
3. Surgical treatment for a malignant tumor
4. Radiotherapy
5. Radiopharmaceuticals[*3] and anti-androgen receptor therapy
6. Bisphosphonate products and anti-RANKL antibodies [*4]
7. Transplant therapy
8. Any other investigational product

[*1] Subjects are permitted to use a local corticosteroid such as topical, intra-articular, intranasal, ocular, inhalational administration, or otherwise temporal systemic corticosteroid for the treatment or prevention of a contrast media allergy or an adverse event.

[*2] This includes local therapies.

[*3] The use of a radiopharmaceutical for a testing or diagnostic purpose is permitted.

[*4] Bisphosphonate products and anti-RANKL antibodies may be used only when the dosage regimen used before study enrollment is maintained.

3.6 Criteria for Entering the Follow-Up phase

Subjects satisfying any of the following criteria in the treatment phase will proceed to the follow-up phase. Only when the subjects do not satisfy all of the following criteria in the treatment phase, the subjects may move to the ONO-4538-14 study.

1. The development of PD is identified by the principal or sub investigator according to the RECIST guideline (version 1.1) only in case in which the unplanned tumor assessment with diagnostic imaging is performed in the treatment phase.
2. It is determined that continuing the treatment is not appropriate because the 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, and rash) or uveitis occurs whose causal relationship with the investigational product cannot be ruled out.
6. The investigator or sub-investigator otherwise determines that continuing to administer the investigational product is inappropriate.

3.7 Sample size determination

3.7.1 Planned Number of Subjects

Total 18 subjects (6 subjects in each group)

Rationale

ONO-4538 is a fully human IgG4 monoclonal antibody and it is reported that there is no great distinction between Japanese and non-Japanese regarding the pharmacokinetics of monoclonal antibody. Therefore the sample size which the pharmacokinetics can be evaluated is set at 6 subjects in each group in this study.

4 ANALYSIS SETS

The “Safety Analysis Set (SAF)” will be used in the safety endpoint evaluation.

4.1 Definitions of Groups

These sets will be defined as a group of subjects who have provided informed consent. Definitions of the individual groups are shown below.

1) Enrolled Set (ENR)

This set will be defined as group of subjects who have been enrolled.

2) SAF

This set will be defined as group of subjects who included in ENR and have received at least one dose of the study drug.

4.2 Criteria for Subject Handling

Details of subject handling are shown below.

1) Subject without Administration

Subject without Administration will be defined as those who have never administered the investigational product.

How to handle subjects with other unexpected problems in the analyses will be decided by the sponsor before data lock through discussions about the details with the medical expert.

4.3 Criteria for Handling Evaluation Time Points

If the actual date of examination is not the protocol-specified date of examination, the examination data will be accepted, only when they are measured within the following criteria. If multiple data are present within the time window of a given time point, data which are obtained at a time point nearest the specified timing of examination will be preferred. If multiple safety data are obtained before and after the specified date and the lengths of time from the specified date and time are identical, those obtained after the specified date and time will be preferred.

1. Treatment Period

Item	Treatment period							
Trial day	1				2,3,4	8	15	22
	Before administration[a)]	After the start of the administration	After the end of the administration					
		1 hr	2 hr	8 hr				
Time window (days)	1	±10 min	±15 min	±30 min	1	-2 - +2	-3 - +3	-3 - +3

a) Performance Status and laboratory test results which have been obtained within seven days before enrollment will be accepted.

2. Post-treatment Follow-up Period (subjects who have terminated the treatment period)

Item / Trial day	At Discontinuation	Follow-up during 28 days after the discontinuation or 22 days only if the subjects will not join ONO-4538-14
Time window (days)	+3	-7 - +7

5 DOCUMENTATION OF STATISTICAL METHOD

5.1 Safety Endpoints

1. Adverse events
2. Laboratory tests:

   Hematology: RBC, MCV, MCH, MCHC, hemoglobin, hematocrit, WBC, differential WBC (neutrophils, lymphocytes, eosinophils, basophils, and monocytes) and platelet count

   Blood biochemistry: Albumin, ALP, AST (GOT), ALT (GPT), total bilirubin, direct bilirubin, γ-GTP, total protein, creatinine, blood glucose, LDH, BUN, uric acid, CK (CPK), P, Ca, Na, K, and Cl

   Qualitative urinalysis: Specific gravity, protein, glucose, occult blood, and sediment (WBC and RBC)

   Immunology: Rheumatoid factor (RA), C-reactive protein (CRP), antinuclear antibody (ANA), SP-D, KL-6

   Hormone tests: Thyroid-stimulating hormone (TSH), free triiodothyronine (free T3), and free thyroxine (free T4)
3. Vital signs (systolic blood pressure/diastolic blood pressure, pulse rate, body temperature), body weight, percutaneous oxygen saturation (SpO_2)
4. 12-lead ECG
5. Chest X-ray
6. Performance Status (ECOG)

6 DISPOSITION AND PROTOCOL DEVIATIONS

6.1 Assessment of Reliability of Clinical Trial

6.1.1 Analysis Set

Analysis will be performed in SAF. With regard to the analysis item (1) in 6.1.2 Analysis Items and Data Handling, the ENR will be the analysis set.

6.1.2 Analysis Items and Data Handling

1) Analysis Items

(1) Reason for exclusion from the analysis set

(2) Reason for termination of the treatment period

(3) Participants in the clinical trial per institution

2) Data Handling

There will be no special handling.

6.1.3 Analysis Methods

The analysis results will be summarized by dose level groups separately and totality.

1) Classification of subjects will be indicated according to 4.1 Definitions of Groups.

2) Frequency of subjects who have terminated the treatment period and frequency by reason for termination will be summarized.

3) Frequency of participants in the clinical trial per institution will be summarized.

7 Study Drug Exposure and Compliance

7.1.1 Analysis Set

Analysis will be performed in SAF.

7.1.2 Analysis Items and Data Handling

1) Analysis Items

(1) Actual dose (mg/kg)

2) Data Handling

(1) The actual dose (mg/kg) will be calculated using the following formula.

- Actual dose (mg/kg) = (actual dose [mg]) / (body weight immediately before dosing [kg])

7.1.3 Analysis Methods

The analysis results will be summarized by dose level groups separately and totality.

1) Summary statistics of the actual dose will be calculated.

8 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

8.1 Analysis Set

Analysis will be performed in SAF.

8.2 Analysis Items and Data Handling

1) Background Factors

(1) Demographic Variables:

Sex, age, height, weight, and body mass index (BMI).

(2) Patient Characteristics:

Time from diagnosis date of primary cancer to first dose date of the investigational product, Performance Status (ECOG), the type of primary cancer, stage classification and TNM classification (baseline) if applicable, medical history, concurrent diseases, cancer treatment history (surgical history, radiotherapy history, medication history, others, number of treatment regimens), drinking history, smoking history

2) Data Handling

Data will be analyzed as observed without imputing missing data.

Time from diagnosis date of primary cancer to first dose date of the investigational product will be calculated using the following formula.

- Time from diagnosis date of primary cancer to first dose date of the investigational product (days) = (the first dose date of investigational product) – (diagnosis date of primary disease) + 1

8.3 Analysis Methods and Classification

For the background factors shown in 1) under Section 8.2 Analysis Items and Data Handling, the summary statistics and frequency distribution of each category will be calculated.

The ordinal scale classification and continuous quantity classification will be decided by clinical significance or dividing the sample size into three, four, or five nearly equal parts etc.

The level of measurement will be as shown below.

Item	Classification	Analysis method

Sex	Male or female	Proportion by category
Age	<65, 65 - <75, ≥75	Summary statistics and proportion by category
Height	-	Summary statistics
Weight	-	Summary statistics
BMI	-	Summary statistics
Time from diagnosis date of primary cancer to first dose date of the investigational product	-	Summary statistics
Primary cancer	< According as collected data >	Proportion by category
Performance Status (ECOG)	0, 1	Proportion by category
Smoking history	Non-Smoker, Smoker or Ex-Smoker	Proportion by category
Drinking history	Non-Drinker, Drinker or Ex-Drinker	Proportion by category
TNM classification (T)	TX, T0, Tis, T1, T1a, T1b, T2, T2a, T2b, T3, T3a, T3b, T4, T4a, T4b	Proportion by category
TNM classification (N)	NX, N0, N1, N1a, N1b, N2, N2a, N2b, N2c, N3	Proportion by category
TNM classification (M)	MX, M0, M1, M1a, M1b, M1c	Proportion by category
Stage	0, I, IIa, IIb, II, IIIa, IIIb, IIIc, III, IVa, IVb, IV, Unknown or Other	Proportion by category
Past Medical History	Yes, No	Proportion by category
Concurrent diseases	Yes, No	Proportion by category
Cancer treatment History (Surgery)	Yes, No	Proportion by category
Cancer treatment History (Radiotherapy)	Yes, No	Proportion by category
Cancer treatment History (Medication)	Yes, No	Proportion by category
Cancer treatment History (Others)	Yes, No	Proportion by category
Cancer treatment History (Number of treatment regimens)	1, 2, 3, 4, 5, 6	Proportion by category

Proportion by category: The frequency by category and the proportion will be calculated.

Summary statistics: Summary statistics will be calculated.

The analysis results will be summarized by dose level groups separately and totality.

9 SAFETY EVALUATION

9.1 Adverse Events

9.1.1 Analysis Set

Analysis will be performed in SAF.

9.1.2 Analysis Items and Data Handling

1) Analysis Items

(1) Overall adverse events, adverse drug reactions and number of deaths.

(2) Classification of adverse events

2) Data Handling

An adverse event is any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease during a clinical trial, whether or not related to the investigational product. Of note, tabulation will include adverse events whose symptoms have occurred/worsened during the period from the first dose of the study drug until 28 days after the discontinuation or Day 22 only if subjects will not join the ONO-4538-14 study (or until the start of subsequent anti-cancer therapy, whichever comes first). In addition, all adverse events that occur during the treatment period or the post-treatment follow-up period will be listed and reported.

All adverse events reported in this clinical study will be coded by SOC (System Organ Class) and PT (Preferred Term) using MedDRA (Current version). Treatment-emergent adverse events are those events that occur or worsen on or after the first dose of study treatment up until end of study treatment.

For the analysis of adverse events, only treatment-emergent adverse events (TEAEs) will be included in the summary tables.

In case the same adverse events in terms of SOC and PT occurs to one subject more than once, it will be considered as a single event, and the highest severity and relationship status among all events will be taken into account.

Severity of adverse events will be classified using NCI-CTCAE, and where NCI-CTCAE is inapplicable, it will be classified as grade 1 (‘Mild’), grade 2 (‘Moderate’), grade 3 (‘Severe’), grade 4 (‘Life-threatening or disabling’) or grade 5 (‘Death’) based on the maximum intensity. With respect to the relationship to study drug, ‘Related’ will be regarded as related, and ‘Not related’ will be regarded as unrelated.

(1) Number of deaths

The number of deaths will be defined as the total number of subjects who have died during the period from the first dose of the study drug until 28 days after the discontinuation or 22 days only if subjects will not join the 4538-14 study (or until the start of subsequent anti-cancer therapy, whichever comes first).

Select adverse events will be defined as adverse events to be coded as PTs in any of the categories specified in Addendum 1 List of Select Adverse Events (i.e., Endocrine Adverse Events, Hypersensitivity/Infusion Reactions, Gastrointestinal Adverse Events, Hepatic Adverse Events, Pulmonary Adverse Events, Renal Adverse Events and Skin Adverse Events).

9.1.3 Analysis Methods

The analysis results will be summarized by dose level groups separately and totality.

1) Overall Adverse Events, Adverse Drug Reactions and Number of Deaths

(1) The number of subjects (incidence rate) will be provided for all adverse events and adverse drug reactions). The data will be displayed as “subject number (incidence of subjects (%))”.

(2) The numbers of deaths, subjects with Grade 3 or higher adverse events and adverse drug reactions, and serious adverse events and adverse drug reactions, and discontinuations due to adverse events and adverse drug reactions, and adverse events and adverse drug reactions led to death will be summarized.

2) Classification of Adverse Events

(1) Adverse events will be summarized by SOC and PT. The data will be displayed as “subject number (incidence of subjects (%))”.

(2) Incidences of adverse events and adverse drug reactions by SOC and PT will be summarized according to Grade. In addition, incidences of Grade 3 or higher adverse events and adverse drug reactions will be summarized by SOC and PT.

(3) Incidences of adverse events and adverse drug reactions led to death will be summarized by SOC and PT.

(4) Incidences of adverse events and adverse drug reactions leading to discontinuation of the study treatment will be summarized by SOC and PT.

(5) Incidences of serious adverse events and adverse drug reactions will be summarized by SOC and PT.

(6) Incidences of select adverse events and adverse drug reactions will be summarized by categories and PT. In addition, incidences of select, Grade 3 or higher adverse events and adverse drug reactions will be summarized by categories and PT.

9.2 Clinical Laboratory Evaluation

9.2.1 Analysis Set

Analysis will be performed in SAF.

9.2.2 Analysis Items and Data Handling

1) Analysis Items

(1) Hematology

Red blood cell count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), hemoglobin, hematocrit, white blood cell count, differential white blood cell count (neutrophils, lymphocytes, eosinophils, basophils, and monocytes), and platelet count.

(2) Blood biochemistry

Albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST) (glutamic oxaloacetic transaminase [GOT]), alanine aminotransferase (ALT) (glutamic pyruvic transaminase [GPT]), total bilirubin, direct bilirubin, gamma-glutamyl transpeptidase (γ-GTP), total protein, creatinine, blood glucose, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), uric acid, creatine kinase (CK) (creatine phosphokinase [CPK]), phosphorus (P), calcium (Ca), sodium (Na), potassium (K), and chloride (Cl).

(3) Urinalysis (qualitative)

Specific gravity, protein, glucose, occult blood, and sediment (white blood cells and red blood cells).

2) Data Handling

Data will be analyzed as observed without imputing missing data.

Any laboratory values that fall below the detection or quantification limit will be imputed to be the detection or quantification limit.

9.2.3 Analysis Methods

The analysis results will be summarized by dose level groups separately and totality.

1) For laboratory values as continuous quantities, summary statistics (no. of subjects, mean, standard deviation, median, minimum, and maximum) will be provided for each laboratory parameter by the time of measurement, and frequency distribution will be created for laboratory values on ordinal scale parameters.

9.3 Immunologic Test

9.3.1 Analysis Set

Analysis will be performed in SAF.

9.3.2 Analysis Items and Data Handling

1) Analysis Items

Rheumatoid factor (RA), C-reactive protein (CRP), antinuclear antibody (ANA), SP-D, and KL-6.

2) Data Handling

Data will be analyzed as observed without imputing missing data.

Any immunologic test values that fall below the detection or quantification limit will be imputed to be the detection or quantification limit.

9.3.3 Analysis Methods

The analysis results will be summarized by dose level groups separately and totality.

1) Summary statistics (no. of subjects, mean, standard deviation, median, minimum, and maximum) will be provided for immunologic test values as continuous quantities, while frequency distribution will be created for those on an ordinal scale.

9.4 Hormonal Test

9.4.1 Analysis Set

Analysis will be performed in SAF.

9.4.2 Analysis Items and Data Handling

1) Analysis Items

Thyroid-stimulating hormone (TSH), free triiodothyronine (free T3), and free thyroxine (free T4).

2) Data Handling

Data will be analyzed as observed without imputing missing data.

Any hormonal test values that fall below the detection or quantification limit will be imputed to be the detection or quantification limit.

9.4.3 Analysis Methods

The analysis results will be summarized by dose level groups separately and totality.

1) Summary statistics (no. of subjects, mean, standard deviation, median, minimum, and maximum) will be provided for each Hormonal test parameter by the time of measurement.

9.5 Vital Signs

9.5.1 Analysis Set

Analysis will be performed in SAF.

9.5.2 Analysis Items and Data Handling

1) Analysis Items

Systolic blood pressure/diastolic blood pressure, pulse rate, temperature, weight, and percutaneous oxygen saturation as measured using pulse oximetry (SpO_2).

2) Data Handling

Data will be analyzed as observed without imputing missing data.

Any vital sign parameter values that fall below the detection or quantification limit will be imputed to be the detection or quantification limit.

9.5.3 Analysis Methods

The analysis results will be summarized by dose level groups separately and totality.

Summary statistics (no. of subjects, mean, standard deviation, median, minimum, and maximum) will be provided for each vital sign parameter by the time of measurement.

9.6 12-lead ECG

9.6.1 Analysis Set

Analysis will be performed in SAF.

9.6.2 Analysis Items and Data Handling

1) Analysis Items

Heart rate, RR interval, QT interval, QTcF, PR interval, QRS complex.

2) Data Handling

12-lead ECG data will be analyzed as observed without imputing missing data.

Any 12-lead ECG parameter values that fall below the detection or quantification limit will be imputed to be the detection or quantification limit.

QTcF will be calculated using the following compensation formula.

QTcF (ms) = QT interval / $(\text{RR interval})^{1/3}$.

9.6.3 Analysis Methods

The analysis results will be summarized by dose level groups separately and totality.

1) For 12-lead ECG parameters (observed values of RR interval, QT interval, Fridericia's corrected QT interval [QTcF], QRS complex, and PR interval, and their changes [ΔQTcF, ΔQRS, and ΔPR]), observed value (HR) and change (ΔHR) of heart rate, summary statistics and frequency distribution for each category will be summarized at each time point.
2) For maximum QTcF, maximum ΔQTcF, maximum QRS, maximum PR, and maximum heart rate of subjects, frequency distribution for each category will be calculated.

Item	Classification
RR (ms) (observed value)	≤600, >600–1200, >1200
P-R (ms) (observed value)	≤120, >120–200, >200
QRS (ms) (observed value)	≤60, >60–109, >109
Heart rate (observed value)	≤50, >50–100, >100
QT interval, ΔQTcF (ms) (observed value)	≤450, >450–480 >480–500, >500
ΔQTcF (ms) (change)	≤30, >30–60, >60

10 GENERAL PRESENTATION OF SUMMARIES AND ANALYSES

10.1 Summary Statistics

As summary statistics, mean, standard deviation, median, maximum, and minimum will be calculated unless otherwise noted.

10.2 Significance Level to Be Used

No significance level is defined because no tests will be performed.

10.3 Decimals

When displaying the individual data, the number of significant figures will be as shown below. For the mean, standard deviation, and median, the number of significant figures will be the number of significant figures for the individual data + 1. For example, if the number of significant decimal places for individual items of data is 1, that for the mean, standard deviation, and median will be 2.

· Background factors and efficacy endpoint

Integer value (No decimal places)	One decimal place
Time from diagnosis date of primary cancer to first dose date of the investigational product (days) Age (years)	Height (cm) Weight (kg) BMI (kg/m^2)

· Laboratory values

Integer value (Figures after the decimal point will not be displayed.)	One decimal place
White blood cell count (/mm^3) Red blood cell count (10^4/mm^3) MCV (fL) AST (GOT) (U/L) ALT (GPT) (U/L) ALP (U/L) γ-GTP (U/L) LDH (U/L) CK (CPK) (U/L) Blood glucose (mg/dL) BUN (mg/dL) Na (mEq/L) Cl (mEq/L) Neutrophil (/mm^3) Lymphocyte (/mm^3) Eosinophil (/mm^3) Basophil (/mm^3) Monocyte (/mm^3) RA (IU/mL) KL-6 (U/mL)	MCH (pg) MCHC (%) Hemoglobin (g/dL) Hematocrit (%) Platelet count (10^4/mm^3) Albumin (g/dL) Total protein (g/dL) Total bilirubin (mg/dL) Direct bilirubin (mg/dL) Uric acid (mg/dL) K (mEq/L) Ca (mEq/L) P (mEq/L) CRP (mg/dL) SP-D (ng/mL)
Two decimal places	Three decimal places
Creatinine (mg/dL) Free triiodothyronine (pg/mL) Free thyroxine (ng/dL)	Urine specific gravity Thyroid-stimulating hormone (μIU/mL)

· Vital signs

Integer value (No decimal places)	One decimal place
Systolic blood pressure (mmHg) Diastolic blood pressure (mmHg) Pulse rate (bpm) Respiratory rate (beats/min)	Temperature (ºC) SpO_2 (%)

· 12-lead ECG

Integer value (No decimal places)
Heart rate (beats/min)
RR interval (ms)
QT interval (ms)
QTcF (ms)
PR interval (ms)
QRS complex (ms)

10.4 Site Pooling Method

NA

10.5 Software for Statistical Analysis

To display analysis, tabulation, and part of figures and tables, SAS Ver. 9.3 or higher, SAS institute, Cary, NC, USA will be used.

For lists, figures, and tables, Microsoft Word will be used.

11 INTERIM ANALYSIS

No interim analysis will be performed

12 DATA REVIEW

12.1 Objectives

After data collection, a preliminary inspection will be performed using unlocked data to examine whether to accept data and subjects, possible variable transformation, definitions of outliers, classification by stratification factors, and others and thereby to decide an appropriate analysis method compatible with data.

12.2 Analysis Set

Analysis will be performed in subjects receiving the study drug.

12.3 Analysis Items and Data Handling

1) Analysis Items

(1) Background Demographic factors

(2) Summary of TEAE and Incidence of TEAEs by SOC and PT

2) Data Handling

All items will be handled as defined previously in the analysis policy.

12.4 Analysis Methods

The analysis results will be summarized by dose level groups separately and totality.

1) Summary statistics and frequency distribution of background factors will be calculated, and classification will be decided.

2) Incidences of adverse events will be calculated. In addition, incidences of adverse events by SOC and PT will be summarized according to Grade.

The above analyses included a total of 18 subjects for whom data entry was completed as of Dec 17, 2014.

13 CHANGE FROM PROTOCOL

1) 4.1 Definitions of Groups 1) Enrolled Set (ENR)

(1) Content of change

The Enrolled Set (ENR) was added.

(2) Reason for change

The Enrolled Set (ENR) will be evaluated for subject without administration as an analysis population.

2) 8.2 Analysis Items and Data Handling 1) Background Factors

(1) Content of change

Tumor diameter of target lesion was deleted.

(2) Reason for change

As part of the efficacy analysis in the ONO-4538-14, analysis of the development of tumor diameter and evaluation of baseline characteristics will be performed using data of ONO-4538-14 study incorporated with data of this study.

14 SAS PROCEDURE FOR ANALYSIS

NA

15 REFERENCES

NA

Addendum 1 List of Select Adverse Events

Category	Preferred Term
Endocrine Adverse Events	Adrenal insufficiency
	Adrenal suppression
	Blood corticotrophin decreased
	Blood corticotrophin increased
	Hypothalamic pituitary adrenal axis suppression
	Secondary adrenocortical insufficiency
	Diabetes mellitus
	Latent autoimmune diabetes in adults
	Hypophysitis
	Autoimmune thyroiditis
	Blood thyroid stimulating hormone decreased
	Blood thyroid stimulating hormone increased
	Hyperthyroidism
	Hypothyroidism
	Thyroid function test abnormal
	Thyroiditis
	Thyroiditis acute
	Thyroxine decreased
	Thyroxine free decreased
	Thyroxine free increased
	Thyroxine increased
	Tri-iodothyronine uptake increased
Hypersensitivity/Infusion Reactions	Anaphylactic reaction
	Anaphylactic shock
	Bronchospasm
	Hypersensitivity
	Infusion related reaction
Gastrointestinal Adverse Events	Colitis
	Colitis ulcerative
	Diarrhoea
	Enteritis
	Enterocolitis
	Frequent bowel movements
	Gastrointestinal perforation

Hepatic Adverse Events	Acute hepatic failure Alanine aminotransferase increased Aspartate aminotransferase increased Bilirubin conjugated increased Blood bilirubin increased Drug-induced liver injury Gamma-glutamyltransferase increased Hepatic enzyme increased Hepatic failure Hepatitis Hepatitis acute Hyperbilirubinaemia Liver disorder Liver function test abnormal Liver injury Transaminases increased
Pulmonary Adverse Events	Acute respiratory distress syndrome Acute respiratory failure Interstitial lung disease Lung infiltration Pneumonitis
Renal Adverse Events	Blood creatinine increased Blood urea increased Creatinine renal clearance decreased Hypercreatininaemia Nephritis Nephritis allergic Nephritis autoimmune Renal failure Renal failure acute Renal tubular necrosis Tubulointerstitial nephritis Urine output decreased
Skin Adverse Events	Blister Dermatitis Dermatitis exfoliative Drug eruption

	Eczema Erythema Erythema multiforme Exfoliative rash Palmar-plantar erythrodysaesthesia syndrome Photosensitivity reaction Pruritus Pruritus allergic Pruritus generalised Psoriasis Rash Rash erythematous Rash generalised Rash macular Rash maculo-papular Rash papular Rash pruritic Skin exfoliation Skin hypopigmentation Skin irritation Stevens-Johnson syndrome Toxic epidermal necrolysis Urticaria Vitiligo

MedDRA version 17.1