Statistical Analysis Plan

Protocol No.: ONO-4538-09

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

Sponsor: Ono Pharmaceutical Co., Ltd.

[redacted]

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History of Revision

Study No [redacted]	ONO-4538-09 [redacted]	**Sponsor** [redacted]	Ono Pharmaceutical Co., Ltd. [redacted]	
Approval Date	**Amended Version**	**Original**	**Amendment**	**Reason**
09 Apr 2015	SAP_ONO-4538-09_version 2.0, 08 Apr 2015	Section 1 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. PD-1 ligand is also expressed in various human cancer tissues other than antigen presentation cells.	Changed to: 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. In Japan, it obtained manufacturing and marketing approval for indications of unresectable malignant melanoma. PD-1 (or CD279), a 55-kilodalton Type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include immunoglobulin super family members CD28, CTLA-4, ICOS, and BTLA. PD-1 is highly expressed on activated T-cells and B-cells. PD-1 expression can also be detected on memory T-cell subsets with variable levels of expression. Two ligands specific for PD-1 have been identified: PD-L1 (also known as B7-H1 or CD274) and PD-L2 (also known as B7-DC or CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems. The product is made with recombinant technology using CHO cells.	Protocol update
		Section 3.2.2 6. Has a history of prior treatment with any of the following systemic anti-cancer products	Changed to: 6. Has a history of prior treatment with any of the following systemic anti-cancer agents	Typo
		Section 3.2.2 12 - AST (GOT) and ALT (GPT) ≤ 3.0 times the upper limit of normal rage of each institute - Total bilirubin ≤ 2.0 times the upper limit of normal rage of	Changed to: - 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	Typo

		each institute	each institute	
		Section 3.2.3 Patients who meet any of the following criteria will be excluded	Changed to: Patients satisfying any of the following criteria will be excluded	Typo
		Section 3.3 Clinical Trial Schedule and Observations This clinical trial consists of the screening period, treatment period, and follow-up period, as is outlined in Figure 3.1. Screening period Treatment period Post-treatment follow-up period Figure 3.1 Schematic of the clinical trial design	Changed to: Study Schedule and Observations The study consists of the screening phase, treatment phase, and follow-up phase, as is outlined in Figure 3.1. Screening phase Treatment phase Follow-up phase Figure 3.1 Summary of study design	Typo
		Section 3.4 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 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 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. The ONO-4538 dose will not be reduced.	Changed to: 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	Protocol update

			infusion solution may be stored under refrigeration condition (2°-8°C, 36°-46°F) for up to 24 hours , and a maximum of 4 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.	
		Section 3.7.2 The threshold response rate (the null hypothesis) was set at 8.8% because the response rate of docetaxel, which was selected as a comparator in non-Korean Phase III studies (CA209017, CA209057), was 8.8% in the phase III trial in patients with NSCLC 7). Under the assumption of the threshold response rate of 8.8% and the expected response rate of 23.1% and 21.4% for patients with squamous and non-squamous NSCLC respecrively,	Changed to: The threshold response rate (the null hypothesis) was set at 8.8% because the response rate of docetaxel, which was selected as a comparator in non-Korean Phase III studies (CA209017, CA209057), was 8.8% in the phase III trial in patients with NSCLC. Under the assumption of the threshold response rate of 8.8% and the expected response rate of 23.1% and 21.4% for patients with squamous and non-squamous NSCLC respectively,	Typo
		Section 4.1 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.	Changed to: This set will be defined as group of subjects who are included in ENR and have received at least one dose of the study drug.	Typo
		Section 4.3 1. Treatment Period Cycle 1 29	Changed to: 1. Treatment Period Cycle 1, Cycles 2 and beyond 29[c)]	Typo
		Section 6.1	Added: With regard to the analysis item (1) in 6.2 Analysis Items and Data Handling, the ENR will be the analysis set.	Add for clarifying the analysis set.
		Section 8.2 “TNM classification (screening), metastasis lesions and stage (screening)” “NSCLC treatment history (surgical history, radiotherapy history, medication history, others)”	Changed to: “TNM classification (baseline), metastasis lesions and stage (baseline)” “NSCLC treatment history (surgical history, radiotherapy history, medication history, others, number of treatment regimens)”	Correct for ensuring consistency with protocol.

		Section 8.3 1) Change of classification : “To be decided by data review” “IIIB, IV, Recurrent, Unknown, Other” “1, 2”	Changed to: “Height : <160.0, 160.0-<170.0, ≥170.0” “Weight: <55.0, 55.0-<65.0, ≥65.0” “BMI: <18.5 ,18.5-<25.0 ,≥25.0” “Time from diagnosis date of primary disease to first dose date of the investigational product: <180, 181-<360, ≥361” “IIIB, IV, Recurrence, Unknown, Other” “Yes, No” Added: “Item : NSCLC treatment History (Number of treatment regimens), Classification: 1, 2, Analysis method: Proportion by category”	Define classifications.
		Section 8.3 2)	Added: “NSCLC treatment history (medication) will be summarized. Agents and medication will be reported using the generic name.”	Add for evaluating the demographic in more detail.
		Section 9.2.4 2) “A Kaplan-Meier curve will be plotted for each analysis variable. The median and its 95% confidence interval will be estimated by Kaplan-Meier method.”	Changed to: “A Kaplan-Meier curve will be plotted for each analysis variable. The median and its 95% confidence interval and overall survival rates at 6 months and its 95% confidence interval will be estimated by Kaplan-Meier method.” Added: “6 months will be calculated assuming 30.4375 days for one month.”	Add for evaluating the efficacy in more detail.
		Section 9.2.4 3) “Two Kaplan-Meier curve will be plotted based on the interpretation by the image central analysis laboratory and that by a investigator at the trial site. The median progression free survival, its 95% confidence interval and progression free survival rates at 3 and 6 months will be estimated by Kaplan-Meier method.”	Changed to: “Two Kaplan-Meier curves will be plotted based on the interpretation by the image central analysis laboratory and that by an investigator at the trial site. The median progression free survival, its 95% confidence interval and progression free survival rates at 3 and 6 months and its 95% confidence interval will be estimated by Kaplan-Meier method. “	Add for evaluating the efficacy in more detail.

			Added: “6 months will be calculated assuming 30.4375 days for one month.”	
		Section 9.2.4 4) “The median and its 95% confidence interval will be estimated by Kaplan-Meier method.”	Changed to: “The median and its 95% confidence interval and duration of response rates at 6 months and its 95% confidence interval will be estimated by Kaplan-Meier method.” Added: “6 months will be calculated assuming 30.4375 days for one month.”	Add for evaluating the efficacy in more detail.
		Section 9.2.4 7)	Added: “In addition, a plot of individual subjects' percent change in tumor diameter of target lesion will be displayed at individual time point.”	Add for evaluating the efficacy in more detail.
		Section 9.2.5 3)	Added: “and totality”	Add for clarification.
		Section 10	Added: “Unless otherwise noted, safety data to be tabulated will be those observed during the period for 28 days after the final dose (or until the start of subsequent anti-cancer therapy for non-small-cell lung cancer after the final dose, whichever comes first).”	Add for evaluating the safety properly.
		Section 10.1.2 2) 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 final dose (or until the start of subsequent anti-cancer therapy for non-small-cell lung cancer, whichever comes first after the final dose).	Added: 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 final dose (or until the start of subsequent anti-cancer therapy for non-small-cell lung cancer after the final dose, whichever comes first after the final dose).	Add for evaluating the safety properly.
		Section 10.1.2 2)	Deleted: “For event counting in such cases, the same adverse events	Typo

			will be considered as different events.”	
		Section 10.1.2 2) 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.	Changed to: 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/incapacitating’) or grade 5 (‘Death related to adverse event’) based on the maximum intensity.	Correct for ensuring consistency with protocol.
		Section 10.1.3 1) (1)	Added: “and totality”	Add for clarification.
		Section 10.1.3 2) (2) “Adverse events will be summarized by SOC, PT and CTCAE grade. The data will be displayed as “subject number (incidence of subjects (%))”.”	Changed to: “Adverse events and adverse drug reactions will be summarized by SOC, PT and CTCAE grade (grade 1, 2, 3, 4, and 5). The data will be displayed as “subject number (incidence of subjects (%))”.”	Add for evaluating the safety in more detail.
		Section 10.1.3 2) (3) “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.”	Changed to: “Incidences of adverse events and adverse drug reactions by SOC and PT will be summarized. In addition, incidences of adverse events and adverse drug reactions will be summarized by SOC, PT and CTCAE grade (any grade, grade 3 or 4, grade 5). And adverse events and adverse drug reactions with an incidence at or above a certain level will be summarized by SOC, PT and CTCAE grade (any grade, grade 3 or 4, grade 5).”	Add for evaluating the safety in more detail.
		Section 10.1.3 2) (5) “Incidences of adverse events and adverse drug reactions leading to discontinuation of the study treatment will be summarized by SOC and PT.”	Changed to: “Incidences of adverse events and adverse drug reactions leading to discontinuation of the study treatment will be summarized by SOC, PT and CTCAE grade (any grade, grade 3 or 4, grade 5).”	Add for evaluating the safety in more detail.
		Section 10.1.3 2) (6) “Incidences of adverse events and adverse drug reactions leading to interruption of the investigational product will be summarized by SOC and PT.”	Changed to: “Incidences of adverse events and adverse drug reactions leading to interruption of the investigational product will be summarized by SOC, PT and CTCAE grade (any grade, grade 3 or 4, grade 5).”	Add for evaluating the safety in more detail.

		Section 10.1.3 2) (7) “Incidences of serious adverse events and adverse drug reactions will be summarized by SOC and PT.”	Changed to: “Incidences of serious adverse events and adverse drug reactions will be summarized by SOC, PT and CTCAE grade (any grade, grade 3 or 4, grade 5).”	Add for evaluating the safety in more detail.
		Section 10.1.3 2) (8) “Incidences of select, Grade 3 or higher, adverse events and adverse drug reactions will be summarized by categories and PT.”	Changed to: “Incidences of select adverse events and adverse drug reactions will be summarized by categories, PT and CTCAE grade (any grade, grade 3 or 4, grade 5).”	Add for evaluating the safety in more detail.
		Section 10.1.3 2)	Added: “(9) Incidences of select adverse events and adverse drug reactions leading to discontinuation will be summarized by categories, PT and CTCAE grade (any grade, grade 3 or 4, grade 5). (10) Incidences of serious select adverse events will be summarized by categories, PT and CTCAE grade (any grade, grade 3 or 4, grade 5).”	Add for evaluating the safety in more detail.
		Section 10.1.4	Added: “and totality”	Add for clarification.
		Section 10.2.3	Added: “and the change from baseline”	Add for evaluating the safety in more detail.
		Section 10.3.3 1)	Added: “and the change from baseline”	Add for evaluating the safety in more detail.
		Section 10.3.3 3)	Added: “and totality”	Add for clarification.
		Section 10.4.3 2) “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.”	Changed to: “Summary statistics (no. of subjects, mean, standard deviation, median, minimum, and maximum) will be provided for each hormonal test parameter value and the change from baseline by the time of measurement.”	Add for evaluating the safety in more detail.
		Section 10.6.2 2)	Added: QTcF will be calculated using the following compensation formula. QTcF (ms) = QT interval / (RR interval)$^{1/3}$.	Add the formula.
		Section 10.6.3 2) For 12-lead ECG parameters (observed values of RR interval,	Added: For 12-lead ECG parameters (observed values of RR interval,	Add for clarification.

		QT interval, Fridericia's corrected QT interval [QTcF], QRS width, and PR interval, and their changes [ΔQTcF, ΔQRS, and ΔPR]), observed value (HR) and change (ΔHR) of heart rate, summary statistics and frequency distr bution for each category will be summarized at each time point.	QT interval, Fridericia's corrected QT interval [QTcF], QRS width, and PR interval, and their changes from baseline [ΔQTcF, ΔQRS, and ΔPR]), observed value (HR) and change from baseline (ΔHR) of heart rate, summary statistics and frequency distribution for each category will be summarized at each time point.	
		Section 10.6.3 “P-R (ms) (observed value)”	Changed to: “PR (ms) (observed value)”	Typo
		Section 10.6.3 “ Δ QTcF (ms) (change)”	Added: “ΔQTcF (ms) (change from baseline)”	Add for clarification.
		Section 11.2 2) (1) [1]	Added: Subjects with at least one baseline neutralizing positive sample for anti-ONO-4538 antibodies including baseline positive ones.	Clarify the definition.
		Section 11.2 2) (2) [2] Persistent positive: Subjects with two or more samples collected at consecutive time points after the first dose of the investigational product and testing positive for anti-ONO-4538 antibodies with a minimum interval of 16 weeks between the first and last positive samples.	Change to: Persistent positive: Subjects with two or more samples collected at consecutive time points after the first dose of the investigational product and testing positive for anti-ONO-4538 antibodies with a minimum interval of 16 weeks (there is a time window for one week) between the first and last positive samples.	Add for evaluating the anti-drug antibody properly.
		Section 11.3	Added: “and totality”	Add for clarification.
		Section 12.3 Background factors and efficacy endpoint	Added: Percent change in tumor diameter of target lesion (%)	Add for clarification.
		Section 12.3 Vital signs	Deleted: Respiratory rate(beats/min)	Typo
		Section 12.3 12-lead ECG QRS complex (ms)	Change to: QRS width (ms)	Typo
		Section 12.4 “Metastatic Lesion” “To be decided by data review” “surgery” “radiotherapy” “Medication” "IIIB, IV, recurrent, unknown or other"	Change to: “Brain metastasis” “Yes, No” “Surgery” “Radiotherapy” “Number of treatment regimens” "IIIB, IV, recurrence, unknown or other" Deleted: “Item: Location of Initial Occurrence”	Modify the subgroup item and its name.

			Added: “Item: Bone metastasis, Classification: Yes, No” “Item: Presence of the anti-ONO-4538 ant body, Classification: Positive (Persistent positive/ Only the last sample positive, Other positive) , Baseline positive, Negative”	
		Section 14.3 1) (1)	Deleted: “Subject Disposition and”	Reflect the result of data review analysis
		Section 14.3 1) (2) Response rate and progression-free survival (centrally assessed)	Change to: Response rate and progression-free survival (investigator-assessed)	Reflect the result of data review analysis
		Section 14.4 3) The response rate (centrally assessed) and its 95% confidence interval (Wilson) will be calculated to examine the appropriateness of the analysis method. In addition, missingness will be evaluated as necessary.	Change to: The response rate (investigator-assessed) and its 95% confidence interval (Wilson) will be calculated to examine the appropriateness of the analysis method. In addition, missingness will be evaluated as necessary.	Reflect the result of data review analysis
		Section 14.4	Added: “4) For progression-free survival (investigator-assessed), a Kaplan-Meier curve will be presented. In addition, using the Kaplan-Meier method, the median and its 95% confidence interval and progression free survival rates at 3 and 6 months and its 95% confidence interval will be estimated for the validation of the analysis methods or handling of data.”	Add progression free survival analysis in data review.
		Section 14	Added: “The above analyses were performed using the data obtained from 96 subjects treated with the study drug as of Feb. 27, 2015.”	Reflect the result of data review analysis
		Section 15 “NA”	Changed to: “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	Add contents of change from protocol.

			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, analysis of the development of tumor diameter and evaluation of baseline characteristics will be performed."	
		Section Addendum 1	Added: Subcategory, Preferred Term	Add for evaluating the safety properly.
29Jul2021	SAP_ONO-4538-09_version 3.0, 29Jul2021	Section 9.2.4 2) A Kaplan-Meier curve will be plotted for each analysis variable. The median and its 95% confidence interval and overall survival rates at 6 months and its 95% confidence interval will be estimated by Kaplan-Meier method. 6 months will be calculated assuming 30.4375 days for one month.	Change to: A Kaplan-Meier curve will be plotted for each analysis variable. The median and its 95% confidence interval and overall survival rates at 6, 12, 18 and 24 months and its 95% confidence interval will be estimated by Kaplan-Meier method. 6, 12, 18 and 24 months will be calculated assuming 30.4375 days for one month.	Add for evaluation of the overall survival rate at 12, 18 and 24 months.
		Section 9.2.4 3) The median progression free survival, its 95% confidence interval and progression free survival rates at 3 and 6 months and its 95% confidence interval will be estimated by Kaplan-Meier method. 3 and 6 months will be calculated assuming 30.4375 days for one month.	Change to: The median progression free survival, its 95% confidence interval and progression free survival rates at 3, 6, 9 and 12 months and its 95% confidence interval will be estimated by Kaplan-Meier method. 3, 6, 9 and 12 months will be calculated assuming 30.4375 days for one month.	Add for evaluation of the progression free survival rates at 9 and 12 months
		Section 9.2.4 4) The median and its 95% confidence interval and duration of response rates at 6 months and its 95% confidence interval will be estimated by Kaplan-Meier method. 6 months will be calculated assuming 30.4375 days for one month.	Change to: The median and its 95% confidence interval and duration of response rates at 6 and 12 months and its 95% confidence interval will be estimated by Kaplan-Meier method. 6 and 12 months will be calculated assuming 30.4375 days for one month.	Add for evaluation of the duration of response rates at 12 months

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADAS	Anti-drug Antibody Analysis Set
ALK	Anaplastic Lymphoma Kinase
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
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
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
FAS	full analysis set
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
NE	not evaluable
NKT cell	natural killer T cell
NYHA	New York Heart Association
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	Performance Status
PR	partial response
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
SD	stable disease
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

Lung cancer is the leading cause of cancer-related deaths globally. An estimated 221,130 new cases of lung cancer will be diagnosed in 2011. The majority of subjects (approximately 78%) are diagnosed with advanced or metastatic disease. Progression after first-line therapy occurred in nearly all of these subjects and the 5 year survival rate is only 3.6% in the refractory setting.

Leading a treatment guidelines (National Comprehensive Cancer Network Guidelines) recommend combination therapy with a platinum agent and a third-generation anticancer agent (e.g., carboplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/pemetrexed) as first-line drug therapy for patients with stage IIIB/IV non-small cell lung cancer (NSCLC) unsuited to radical radiotherapy who are negative for or with unknown EGFR mutation and have an ECOG Performance Status of 0 to 2. For patients with stage IIIB/IV NSCLC unsuited to radical radiotherapy who are positive for EGFR mutation and have an ECOG Performance Status of 0 to 2, these guidelines recommend either combination therapy with a platinum agent and a third-generation anticancer agent or treatment with an EGFR tyrosine kinase inhibitor such as erlotinib as first-line treatment. These first-line therapies of combination therapy with a platinum agent and a third-generation anticancer agent, however, provide a median progression free survival of 4.5 to 6.2 months and median overall survival of 10.3 to 12.3 months. Moreover, docetaxel for patients with NSCLC with disease resistance to the first-line therapies confers a median progression free survival of 2.3 to 3.1 months and median overall survival of 7.2 to 10.0 months. These figures show the efficacy of the existing treatments to be insufficient in patients with stage IIIB/IV NSCLC unsuited to radical radiotherapy. The need for new drug therapies for these patients is great.

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. In Japan, it obtained manufacturing and marketing approval for indications of unresectable malignant melanoma. PD-1 (or CD279), a 55-kilodalton Type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include immunoglobulin super family members CD28, CTLA-4, ICOS, and BTLA. PD-1 is highly expressed on activated T-cells and B-cells. PD-1 expression can also be detected on memory T-cell subsets with variable levels of expression. Two ligands specific for PD-1 have been identified: PD-L1 (also known as B7-H1 or CD274) and PD-L2 (also known as B7-DC or CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems. The product is made with recombinant technology using CHO cells. PD-L1 is expressed at 19.4 to 95.2% and PD-L2 at 50.0% in the cancer tissue of NSCLC. Various

nonclinical pharmacology studies have demonstrated that ONO-4538 inhibits the binding of PD-1 and PD-1 ligands to enhance the growth and activity of antigen-specific T cells. Ono Pharmaceutical within Japan and BMS outside the country are clinically developing ONO-4538. Antitumor activity was assessed according to the RECIST guideline (version 1.1) using data obtained to the March18, 2013 cutoff point in a non-Japanese phase I repeated dose study (Study CA209003). Twenty-two of the 129 study subjects, who had NSCLC resistant to standard treatment, achieved a response. This finding highlights the potential of ONO-4538, which inhibits binding between PD-1 and PD-1 ligand, to become a NSCLC drug therapy with a novel mechanism of action. To investigate this potential, Ono Pharmaceutical planned this phase II study of ONO-4538 in patients with stage IIIB/IV NSCLC unsuited to radical radiotherapy or recurrent NSCLC.

2 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.

The primary efficacy endpoint is response rate (centrally assessed). The secondary efficacy endpoints are 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.

3 INVESTIGATIONAL PLAN

3.1 Study Design

Multi-center, open-label, uncontrolled study

3.2 Target

3.2.1 Target

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

3.2.2 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 (7th edition) or recurrent NSCLC.
5. Has at least one measurable lesion, as defined by the RECIST guideline (version 1.1) 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 agents (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 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 320 days 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 320 days 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

3.2.3 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 safety evaluation of the investigational product.

3. Active autoimmune disease or history of chronic or recurring autoimmune disease.

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.)

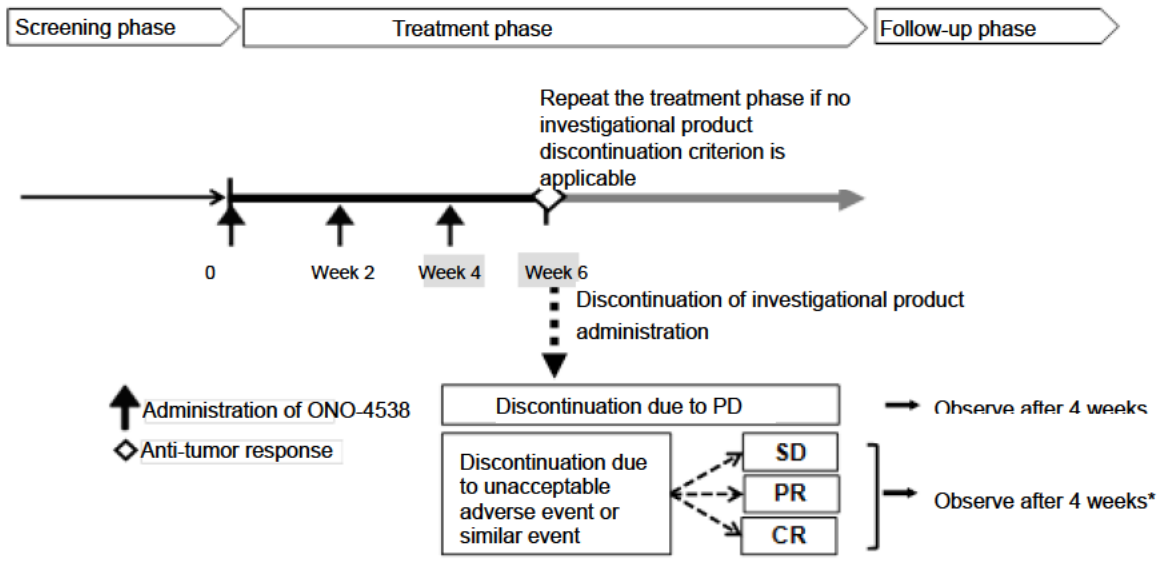
5. Active diverticulitis or symptomatic gastrointestinal ulcerative disease.
6. Multiple primary cancers (except for completely resected basal cell cancer, stage I squamous cell carcinoma, carcinoma in situ, intramucosal carcinoma, or superficial bladder cancer or any other cancer from which the patient 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.

3.3 Study Schedule and Observations

The study consists of the screening phase, treatment phase, and follow-up phase, as is outlined in Figure 3.1.



*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.

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Figure 3.1 Summary of study design

3.3.1 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.

3.3.2 Treatment Phase

ONO-4538 will be administered every 2 weeks, to 3 times in total, with diagnostic imaging performed at Week 6. This 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 3-1 and Table 3-2.

3.3.3 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 3-3.

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.

3.3.4 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 3-1 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 3-3) 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 3-2 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)					○
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 3-3) 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.

Table 3-3 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 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]		[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]

3.4 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 4 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 4-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.

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 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 other investigational product

3.5.2 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.

3.6 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 productis 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.

3.7 Sample size determination

3.7.1 Planned Number of Subjects

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

3.7.2 Rationale for Number of Subjects

The objective of the study is to investigate the efficacy of ONO-4538 in patients with stage IIIB/IV or recurrent NSCLC unsuited to radical radiotherapy using centrally assessed response rates as the primary endpoint. The sample size for each histology is calculated in order to confirm anti-tumor response of ONO-4538 in Korean population.

From efficacy data of non-Korean phase I multiple-dose study (CA209003) as of March 18, 2013 (Table 3-4), the expected response rate for ONO-4538 in patients with squamous NSCLC was set at 23.1% because responses of 22% (4/18) and 24% (5/21) were achieved in patients with squamous NSCLC in the 3 and 10 mg/kg group, respectively. Similarly, the expected response rate for ONO-4538 in patients with non-squamous NSCLC was set at 21.4% because responses of 26% (5/19) and 19% (7/37) were achieved in patients with non-squamous NSCLC in the 3 and 10 mg/kg group, respectively. The threshold response rate (the null hypothesis) was set at 8.8% because the response rate of docetaxel, which was selected as a comparator in non-Korean Phase III studies (CA209017, CA209057), was 8.8% in the phase III trial in patients with NSCLC. Under the assumption of the threshold response rate of 8.8% and the expected response rate of 23.1% and 21.4% for patients with squamous and non-squamous NSCLC respectively, 41 subjects for squamous and 52 subjects for non-squamous will provide a statistical power of at least 80% in a binomial test (normal approximation) with an one-sided significance level of 2.5% (two-sided significance level of 5.0%). The sample sizes (i.e., 41 subjects with squamous NSCLC and 52 subjects with non-squamous NSCLC) were calculated using the formula as follows.

$$N = \left(\frac{z_{1-\alpha}\sqrt{p_0(1-p_0)} + z_{1-\beta}\sqrt{p_1(1-p_1)}}{p_1 - p_0} \right)^2$$

N: the number of subjects

p_0: threshold response rate

p_1: expected response rate

$z_{1-\alpha}$: $(1 - \alpha)$·100 quantile of the standard normal distribution

$z_{1-\beta}$: $(1 - \beta)$ ·100 quantile of the standard normal distribution

α: one-sided significance level

1 - β: statistical power

Table 3-4 Objective Response Rate per RECIST 1.0 in Non-small Cell Lung Cancer Subjects (CA209003)

Dose (mg/kg)	N	Histology	ORR No. of Subjects (%)	95% CI of ORR
1.0	15	SQ	0	0
	18	NSQ	1 (6)	0.1 - 27
3.0	18	SQ	4 (22)	6 - 48
	19	NSQ	5 (26)	9 - 51
10.0	21	SQ	5 (24)	8 - 47
	37	NSQ	7 (19)	8 - 35

CI: confidence interval, NSQ: non-squamous, ORR: objective response rate; SQ: squamous

4 ANALYSIS SETS

The “Full Analysis Set (FAS)” will be the primary analysis set to be used in the efficacy endpoint evaluation.

The analysis set for the safety endpoint evaluation will be the “Safety Analysis Set (SAF)”.

The analysis set for the evaluation of the production of anti-ONO-4538 antibodies will be the “Anti-drug Antibody Analysis Set (ADAS)”.

4.1 Definitions of Groups

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 are included in ENR and have received at least one dose of the study drug.

3) FAS

This set will be defined as a full group of subjects who are included in SAF.

4) ADAS

This set will be defined as a group of subjects included in SAF and for whom the anti-ONO-4538 antibody level was determined once at baseline and at least once after the start of the study treatment.

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.

2) Subjects with Incomplete Anti-drug Antibody Data

Subjects with incomplete anti-drug antibody data will be defined as those for whom a baseline level of anti-ONO-4538 antibodies was not determined or for whom the levels of anti-ONO-4538 antibodies were never determined after the start of the study treatment.

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, except for those from diagnostic imaging, only when they are measured within the following criteria. To count days of the treatment period, the day of the start of each cycle will be defined as Day 1. 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					
	Cycle 1, Cycles 2 and beyond					
Trial day	1		8[b)]	15[c)]	29[c)]	43
	Before dosing [a)]	After dosing [b)]				
Time window (days)	1		5 - 11	12 - 22	23 - 36	37 - 50

a) In Cycle 1, Performance Status and laboratory test results which have been obtained within seven days before enrollment will be accepted. In Cycle 2 and subsequent cycles, the following data will be accepted: for vital signs, those within 1 day before administration, and for the other examinations, those within seven days before administration.

b) Will only apply to Cycle 1.

c) Data before administration will be accepted, except for serum drug concentrations.

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

Item	End of treatment period	Post-treatment follow-up period	
Trial day		Discontinuation at or within 28 days after the final dose	Follow-up
Time window (days)	-3 - +3	-7 - +7	-

5 DOCUMENTATION OF STATISTICAL METHOD

5.1 Efficacy Endpoints

5.1.1 Primary Endpoint

1. Response rate (centrally assessed)

The response rate is the percentage of subjects given a best overall response assessment of CR or PR by the central imaging analysis facility.

In the overall response order of CR > PR > SD > PD > NE, the following criteria will be used to assess the best overall response from the overall response assessments made to the completion of the study. When the definitions of more than one response category are satisfied, the better of the two will be selected as the best overall response according to the order of CR > PR > SD > PD > NE.

- CR: Assessment of CR at least 2 consecutive times in intervals of 4 weeks (28 days) or longer.
- PR: Assessment of PR or greater (CR or PR) at least 2 consecutive times in intervals of 4 weeks (28 days) or longer.
- SD: The best overall response is neither CR nor PR but no overall response of PD is assessed 6 or more weeks after the start of treatment and at least one overall response of SD or better is assessed.
- PD: The best overall response is not CR, PR, or SD, and the overall response is PD.
- NE: The best overall response, which is not CR, PR, SD, or PD, is not evaluable.
- Without target lesions: there is target lesion in investigator assessment but not in central assessment.

The following overall responses will not be used to assess the best overall response:

- Overall response following the start or the end of follow-up of a subsequent NSCLC therapy
- Overall responses after an assessment of PD is made

5.1.2 Secondary Endpoint

1 Response rate (investigator-assessed)

2 Overall survival

3 Progression free survival (centrally assessed and investigator-assessed)

4 Time to progression (centrally assessed)

5 Duration of response (centrally assessed)

6 Time to response (centrally assessed)

7 Best overall response (centrally assessed and investigator-assessed)

8 Percent change in tumor diameter of target lesion (investigator-assessed)

5.2 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)

5.3 Other Endpoints

5.3.1 Anti-drug Antibody Endpoint

1 Anti-ONO-4538 antibody

6 DISPOSITION AND PROTOCOL DEVIATIONS

6.1 Analysis Set

Analysis will be performed in SAF. With regard to the analysis item (1) in 6.2 Analysis Items and Data Handling, the ENR will be the analysis set.

6.2 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) Reason for discontinuation or dropout of the clinical trial

(4) Participants in the clinical trial per institution

2) Data Handling

There will be no special handling.

6.3 Analysis Methods

1) The analysis results will be summarized by squamous NSCLC and non-squamous NSCLC separately and totality.

2) Classification of subjects will be indicated according to subject criteria.

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

4) Frequency of subjects who have discontinued and dropped out of the clinical trial and frequency by reason for discontinuation and drop out will be summarized.

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

7 STUDY DRUG EXPOSURE AND COMPLIANCE

7.1 Analysis Set

Analysis will be performed in SAF.

7.2 Analysis Items and Data Handling

1) Analysis Items

(1) Number of doses

(2) Number of cycles

(3) Duration of treatment (days)

(4) Total dose (mg/kg)

(5) Relative dose intensity (%)

2) Data Handling

(1) The number of doses will be the count of doses at all time points.

(2) The number of cycles will refer to all cycles started, including those discontinued or temporarily suspended.

(3) The duration of treatment will be calculated using the following formula.

- Duration of treatment (days) = (the final dose date of investigational product) – (the first dose date of investigational product) + 1

(4) The total dose (mg/kg) will be the sum of doses at all time points. The dose at each time point will be calculated using the following formula.

- Dose at each time point (mg/kg) = (actual dose [mg]) / (body weight immediately before dosing [kg])

(5) The relative dose intensity will be calculated using the following formula.

- Relative dose intensity (%) = total dose (mg/kg) / {(the final dose date of investigational product – the first dose date of investigational product + 14[days]) × 3 (mg/kg)/14 (days)} × 100

7.3 Analysis Methods

1) The analysis results will be summarized by squamous NSCLC and non-squamous NSCLC separately and totality.

2) Frequency distribution and summary statistics of the number of doses will be calculated.

3) Frequency distribution and summary statistics of the number of cycles will be calculated.

4) Frequency distribution and summary statistics of the duration of treatment will be calculated.

5) Summary statistics of the total dose will be calculated.

6) Frequency distribution and summary statistics of the relative dose intensity 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 disease to first dose date of the investigational product, histologic type, location of initial occurrence, TNM classification (baseline), metastasis lesions and stage (baseline), past medical history, concurrent diseases, NSCLC treatment history (surgical history, radiotherapy history, medication history, others, number of treatment regimens), drinking history, smoking history, performance status (ECOG).

2) Data Handling

Data will be analyzed as observed without imputing missing data. The cancer treatment history will refer to non-small-cell lung cancer.

The time from diagnosis date of primary disease to first dose date of the investigational product will be calculated using the following formula.

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

8.3 Analysis Methods and Classification

1) For the background factors shown in 1) under Section 8.2Analysis 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	<160.0, 160.0-<170.0, ≥170.0	Summary statistics and proportion by category
Weight	<55.0, 55.0-<65.0, ≥65.0	Summary statistics and proportion by category
BMI	<18.5 ,18.5-<25.0, ≥25.0	Summary statistics and proportion by category
Time from diagnosis date of primary disease to first dose date of the investigational product	<180, 181-<360, ≥361	Summary statistics and 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
Histologic type	Squamous cell carcinoma, Adenocarcinoma, Large cell carcinoma or Other	Proportion by category
Location of Initial Occurrence	LUL, LLL, RUL, RML, RLL, Unknown, Other	Proportion by category
TNM classification (T)	X, 0, is, 1a, 1b, 2a, 2b, 3, 4, Other	Proportion by category
TNM classification (N)	X, 0, 1, 2, 3, Other	Proportion by category
TNM classification (M)	X, 0, 1a, 1b, Other	Proportion by category
Metastatic Lesion	Lung(LUL, LLL, RUL, RML, RLL, Unknown, Other), Lymph Node, Liver, Bone, Brain or Other, No	Proportion by category
Stage	IIIB, IV, Recurrence, Unknown, Other	Proportion by category
Past Medical History	Yes, No	Proportion by category
Concurrent diseases	Yes, No	Proportion by category
NSCLC treatment History (Surgery)	Yes, No	Proportion by category
NSCLC treatment History (Radiotherapy)	Yes, No	Proportion by category
NSCLC treatment History (Medication)	Yes, No	Proportion by category
NSCLC treatment History (Others)	Yes, No	Proportion by category
NSCLC treatment History (Number of treatment regimens)	1, 2	Proportion by category

The analysis results will be summarized by squamous NSCLC and non-squamous NSCLC separately and totality.

2) NSCLC treatment history (medication) will be summarized. Agents and medication will be reported using the generic name.

9 EFFICACY EVALUATION

9.1 Primary Efficacy Analysis

9.1.1 Objective

To confirm the efficacy of ONO-4538 in stage IIIB/IV or recurrent NSCLC unsuited to radical radiotherapy and resistant to a platinum-based chemotherapeutic regimen using the response rate assessed by the central imaging analysis facility (centrally assessed) as the primary efficacy endpoint.

9.1.2 Analysis Set

Analysis will be performed in FAS.

9.1.3 Analysis Items and Data Handling

1) Analysis Items

Response rate (centrally assessed).

2) Data Handling

The response rate (centrally assessed) is defined as the number of subjects whose confirmed best overall response determined by the central imaging analysis facility (RECIST guideline version 1.1) is a CR or PR divided by the number of FAS. The subject whose confirmed best overall response is missed will be defined as the non-responder.

9.1.4 Analysis Methods

Response rate (centrally assessed) and its 95% confidence interval (Wilson) will be calculated. The analysis results will be summarized by squamous NSCLC and non-squamous NSCLC separately and totality.

9.2 Secondary Efficacy Analysis

9.2.1 Objective

To perform the exploratory analyses in the endpoints other than the primary endpoint and evaluate the efficacy of investigational product from various viewpoints

9.2.2 Analysis Set

Analysis will be performed in FAS.

9.2.3 Analysis Items and Data Handling

1) Analysis Items

(1) Response rate (investigator-assessed)

(2) Overall survival

(3) Progression-free survival (centrally assessed and investigator-assessed)

(4) Time to progression (centrally assessed)

(5) Duration of response (centrally assessed)

(6) Time to response (centrally assessed)

(7) Best overall response (centrally assessed and investigator-assessed)

(8) Percent change in tumor diameter of target lesion (investigator-assessed)

2) Data Handling

Overall response and best overall response will be defined as diagnostic imaging results evaluated in compliance with RECIST guideline version 1.1 and will not include clinical deterioration. Evaluable diagnostic imaging will be defined as diagnostic imaging which provides assessment other than NE.

(1) The response rate (investigator-assessed) is defined as the number of subjects whose confirmed best overall response determined by the study site investigator is a CR or PR divided by the number of FAS. The subject whose objective response is missed will be defined as the non-responder.

(2) Overall survival will be calculated using the following formula.

- Overall survival (days) = (the date of death due to any cause) - (the first dose date of investigational product) + 1

A subject who has not died will be censored at last known date alive.

(3) Progression-free survival (centrally assessed and investigator-assessed) will be calculated using the following formula.

- Progression free survival (days) = (the earlier date of the first documented PD or death due to any cause) - (the first dose date of investigational product) + 1

Clinical deterioration will not be included as an event in progression-free survival when progression-free survival is evaluated based on diagnostic imaging results interpreted by the image central analysis laboratory; it will be included, however, when progression-free survival is evaluated based on diagnostic imaging results interpreted by a physician at the trial site.

In addition, event/censoring assessment will be performed according to Table 9-1.

Table 9-1 Criteria for event/censoring assessment in progression-free survival (centrally assessed and investigator-assessed)

Status	Event or censoring date	Result
Subjects for whom diagnostic imaging was missed at baseline.	Date of starting the study treatment	Censoring
Subjects for whom evaluable diagnostic imaging has not been performed and who are alive	Date of starting the study treatment	Censoring
Subjects who received subsequent anti-cancer therapy for non-small-cell lung cancer before he/she died or were assessed as having PD	Date when the last evaluable diagnostic imaging was performed before starting subsequent anti-cancer therapy for non-small-cell lung cancer	Censoring
Subjects for whom the outcome follow-up for non-small-cell lung cancer was ended before death or assessment as PD	Date when the last evaluable diagnostic imaging was performed before the end of the outcome follow-up for non-small-cell lung cancer	Censoring
Subjects who are alive and have not been assessed as having PD	Date when the last evaluable diagnostic imaging was performed	Censoring
Subjects who died or have been assessed as having PD	Date of death or date when the first diagnostic imaging to provide assessment as PD was performed, whichever comes first	Event
Subjects who died before initial evaluable diagnostic imaging	Date of death	Event

(4) Time to progression (centrally assessed) will be calculated based on assessment by the central imaging analysis facility with the following formula:

- Time to progression (days) = (the date of the first documented PD) - (the first dose date of investigational product) + 1

In addition, event/censoring assessment will be performed according to Table 9-2.

Table 9-2 Criteria for aggravation/censoring assessment in time to progression (centrally assessed and investigator-assessed)

Status	Event or censoring date	Result
Subjects for whom diagnostic imaging was missed at baseline.	Date of start of the study treatment	Censoring
Subjects for whom evaluable diagnostic imaging has not been performed	Date of start of the study treatment	Censoring
Subjects who received subsequent anti-cancer therapy for non-small-cell lung cancer before assessment as PD	Date when the last evaluable diagnostic imaging was performed before starting subsequent anti-cancer therapy for non-small-cell lung cancer	Censoring

Status	Event or censoring date	Result
Subjects for whom the outcome follow-up for non-small-cell lung cancer was ended before death or assessment as PD	Date when the last evaluable diagnostic imaging was performed before the end of the outcome follow-up for non-small-cell lung cancer	Censoring
Subjects who have not been assessed as having PD	Date when the last evaluable diagnostic imaging was performed	Censoring
Subjects who have been assessed as having PD	Date when the first diagnostic imaging to provide assessment as PD was performed	Event

(5) Duration of response (centrally assessed) will be calculated based on assessment by the central imaging analysis facility with the following formula:

- Duration of response (days) = (the date of the first documented PD or death due to any cause after response is confirmed) - (the date of the first confirmed CR or PR) + 1

Subjects without documented PD and who did not die will be censored at the last evaluable tumor assessment. Subjects who are not evaluated a confirmed CR or PR at any time during the study will be excluded from this analysis.

(6) Time to response (centrally assessed) will be calculated based on assessment by the central imaging analysis facility with the following formula:

- Time to response (days) = (the date of the first confirmed CR or PR) - (the first dose date of investigational product) + 1

Subjects who are not evaluated confirmed CR or PR at any time during the study will be excluded from this analysis.

(7) Percent change in tumor diameter of target lesion (investigator-assessed)

With regard to the tumor diameter (sum of the longest diameters of target lesions) evaluated by a investigator at the trial site according to RECIST guideline version 1.1, the best percent change and percent change at each time point will be calculated using the following formulas.

The calculation of the best percent change will not include the longest diameters of target lesions measured after the overall response is assessed as PD; any subsequent anti-cancer therapy is performed for non-small-cell lung cancer; or subsequent anti-cancer therapy follow-up is ended. The percent change at each time point will be calculated also after the overall response is assessed as PD but will not after any subsequent anti-cancer therapy for non-small-cell lung cancer or the outcome follow-up is ended.

- Best percent change = $\frac{\text{Smallest tumor diameter after first dose} - \text{Baseline tumor diameter}}{\text{Baseline tumor diameter}} \times 100$

- Percent change = $\frac{\text{Tumor diameter at evaluation point} - \text{Baseline tumor diameter}}{\text{Baseline tumor diameter}} \times 100$

Subjects without measurable lesion or without any tumor assessment after first dose will be excluded from this analysis.

9.2.4 Analysis Methods

With regard to the analysis items shown in 1) under Section 9.1.3 Analysis Items and Data Handling, the following analyses will be performed. The analysis results will be summarized by squamous NSCLC and non-squamous NSCLC separately and totality.

1) Response rate (investigator-assessed) and its 95% confidence interval (Wilson) will be calculated.
2) The following analyses will be performed for overall survival and time to progression.

   A Kaplan-Meier curve will be plotted for each analysis variable. The median and its 95% confidence interval and overall survival rates at 6, 12, 18 and 24 months and its 95% confidence interval will be estimated by Kaplan-Meier method. 6, 12, 18 and 24 months will be calculated assuming 30.4375 days for one month.
3) The following analyses will be performed for progression free survival.

   Two Kaplan-Meier curves will be plotted based on the interpretation by the image central analysis laboratory and that by an investigator at the trial site. The median progression free survival, its 95% confidence interval and progression free survival rates at 3, 6, 9 and 12 months and its 95% confidence interval will be estimated by Kaplan-Meier method. 3, 6, 9 and 12 months will be calculated assuming 30.4375 days for one month.
4) Summary statistics will be calculated for duration of response. The median and its 95% confidence interval and duration of response rates at 6 and 12 months and its 95% confidence interval will be estimated by Kaplan-Meier method. 6 and 12 months will be calculated assuming 30.4375 days for one month.
5) Summary statistics will be calculated for time to response. The median and its 95% confidence interval will be estimated by Kaplan-Meier method.
6) For best overall response, the percentages of CR, PR, SD, PD, and NE will be calculated based on the interpretation by the image central analysis laboratory and that by an investigator at the trial site. In addition, the 95% confidence intervals (Wilson) will be calculated in CR, PR and SD.
7) Waterfall plot will be displayed for best percent change in tumor diameter of target lesion. In addition, a plot of individual subjects' percent change in tumor diameter of target lesion will be displayed at individual time point.

9.2.5 Subgroup Analysis of Efficacy Endpoint

The response rate (centrally assessed) as the primary endpoint will be analyzed in subgroups defined by risk factors.

1) Analysis Item

Response rate (centrally assessed)

2) Data Handling

Background factors shown in Section 12.4 Subgroup Definitions will be used as risk factors. Classification according to risk factors will be based on clinical significance or dividing the sample size into two or three nearly equal parts etc.

3) Analysis Methods

The response rate (centrally assessed) and its 95% confidence intervals (Wilson) will be calculated for each subgroup. The analysis results will be summarized by squamous NSCLC and non-squamous NSCLC separately and totality.

10 SAFETY EVALUATION

Unless otherwise noted, safety data to be tabulated will be those observed during the period for 28 days after the final dose (or until the start of subsequent anti-cancer therapy for non-small-cell lung cancer after the final dose, whichever comes first).

10.1 Adverse Events

10.1.1 Analysis Set

Analysis will be performed in SAF.

10.1.2 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 final dose (or until the start of subsequent anti-cancer therapy for non-small-cell lung cancer after the final dose, whichever comes first after the final dose). In addition, all adverse events that occur during the treatment period or the subsequent anti-cancer therapy 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/incapacitating’) or grade 5 (‘Death related to adverse event’) 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. If the relationship is unclear due to a missing, the relationship to study drug is considered as 'Related'.

(1) Time to a Grade 3 or higher adverse event will be calculated using the following formula.

- Time to a Grade 3 or higher adverse event (days) = (date of the onset of the Grade 3 or higher adverse event, or the date of worsening to Grade 3 or higher, whichever comes first) - (the first dose date of investigational product) + 1

Data will be censored if the subject has no Grade 3 or higher adverse event at 28 days after the final dose (or at the start of subsequent anti-cancer therapy for non-small-cell lung cancer after the final dose, whichever comes first).

(2) Time to a Grade 3 or higher adverse drug reaction will be also calculated in the same manner.

(3) 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).

Time to a select adverse event will be calculated by category using the following formula.

- Time to select adverse event (days) = (date of the onset of the earliest select adverse event in the category) – (the first dose date of investigational product) + 1

Data will be censored if the subject has no select adverse event in any of the categories at 28 days after the final dose (or at the start of subsequent anti-cancer therapy for non-small-cell lung cancer after the final dose, whichever comes first).

(4) Time to select adverse drug reaction will be also calculated in the same manner.

(5) 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 final dose (or until the start of subsequent anti-cancer therapy for non-small-cell lung cancer after the final dose, whichever comes first).

10.1.3 Analysis Methods

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

(1) The analysis results will be summarized by squamous NSCLC and non-squamous NSCLC separately and totality.

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

(3) 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) The analysis results will be summarized by squamous NSCLC and non-squamous NSCLC separately and totality.

(2) Adverse events and adverse drug reactions will be summarized by SOC, PT and CTCAE grade (grade 1, 2, 3, 4, and 5). The data will be displayed as “subject number (incidence of subjects (%))”.

(3) Incidences of adverse events and adverse drug reactions by SOC and PT will be summarized. In addition, incidences of adverse events and adverse drug reactions will be summarized by SOC, PT and CTCAE grade (any grade, grade 3 or 4, grade 5). And adverse events and adverse drug reactions with an incidence at or above a certain level will be summarized by SOC, PT and CTCAE grade (any grade, grade 3 or 4, grade 5).

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

(5) Incidences of adverse events and adverse drug reactions leading to discontinuation of the study treatment will be summarized by SOC, PT and CTCAE grade (any grade, grade 3 or 4, grade 5).

(6) Incidences of adverse events and adverse drug reactions leading to interruption of the investigational product will be summarized by SOC, PT and CTCAE grade (any grade, grade 3 or 4, grade 5).

(7) Incidences of serious adverse events and adverse drug reactions will be summarized by SOC, PT and CTCAE grade (any grade, grade 3 or 4, grade 5).

(8) Incidences of select adverse events and adverse drug reactions will be summarized by categories, PT and CTCAE grade (any grade, grade 3 or 4, grade 5).

(9) Incidences of select adverse events and adverse drug reactions leading to discontinuation will be summarized by categories, PT and CTCAE grade (any grade, grade 3 or 4, grade 5).

(10) Incidences of serious select adverse events will be summarized by categories, PT and CTCAE grade (any grade, grade 3 or 4, grade 5).

(11) Kaplan-Meier curves will be presented for time to onset of select adverse events and adverse drug reactions. Kaplan-Meier curves will also be displayed for time to onset of Grade 3 or higher adverse events and adverse drug reactions.

10.1.4 Subgroup Analysis of Safety Endpoints

Incidences of select adverse events and adverse drug reactions will be analyzed in subgroups. Risk factors and classification methods using these factors will be based on items established in Section 9.2.5 Subgroup Analysis of Efficacy Endpoint. The analysis results will be summarized by squamous NSCLC and non-squamous NSCLC separately and totality.

10.2 Clinical Laboratory Evaluation

10.2.1 Analysis Set

Analysis will be performed in SAF.

10.2.2 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. The analysis period of clinical laboratory evaluation is treated as well as adverse events.

Any laboratory values that fall below the detection or quantification limit will be imputed to be the detection or quantification limit. The laboratory values will be summarized by Grade, if necessary, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

10.2.3 Analysis Methods

1) The analysis results will be summarized by squamous NSCLC and non-squamous NSCLC separately and totality.
2) For laboratory values and the change from baseline 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, while frequency distribution will be created for laboratory values on an ordinal scale.
3) Frequency distribution of abnormal laboratory values will be calculated at each time point.
4) A Grade shift table will be prepared for changes in hemoglobin, platelet count, white blood cell count, neutrophil count, lymphocyte count, ALT (GPT), AST (GOT), ALP, total bilirubin and creatinine from baseline to the worst value observed during the period from the first dose of the study drug until 28 days after the final dose (or until the start of subsequent anti-cancer therapy for non-small-cell lung cancer after the final dose, whichever comes first).
5) Frequency distribution will be calculated for subjects whose liver function test values meet any of the following criteria.
   (1) ALT or AST > 3 times ULN (Upper Limit of Normal), 5 times ULN, 10 times ULN, 20 times ULN
   (2) Total bilirubin > 2 times ULN
   (3) ALT or AST > 3 times ULN and total bilirubin within 1 day > 2 times ULN
   (4) ALT or AST > 3 times ULN and total bilirubin within 30 days > 2 times ULN
   (5) ALT or AST > 3 times ULN, total bilirubin within 1 day ≥ 2 times ULN, and ALP < 2 times ULN

10.3 Immunologic Test

10.3.1 Analysis Set

Analysis will be performed in SAF.

10.3.2 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. The analysis period of immunologic test is treated as well as adverse events.

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

10.3.3 Analysis Methods

1) Summary statistics (no. of subjects, mean, standard deviation, median, minimum, and maximum) will be provided for immunologic test values and the change from baseline as continuous quantities, while frequency distribution will be created for those on an ordinal scale.
2) Frequency distribution of abnormal immunologic test values will be calculated at each time point.
3) The analysis results will be summarized by squamous NSCLC and non-squamous NSCLC separately and totality.

10.4 Hormonal Test

10.4.1 Analysis Set

Analysis will be performed in SAF.

10.4.2 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. The analysis period of hormonal test is treated as well as adverse events.

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

10.4.3 Analysis Methods

1) The analysis results will be summarized by squamous NSCLC and non-squamous NSCLC separately and totality.
2) Summary statistics (no. of subjects, mean, standard deviation, median, minimum, and maximum) will be provided for each hormonal test parameter value and the change from baseline by the time of measurement.

3) Frequency distribution of abnormal hormonal test values will be calculated at each time point.

4) Frequency distribution will be calculated for subjects whose thyroid function test values meet any of the following criteria.

(1) TSH > ULN

(2) TSH > ULN with TSH ≤ ULB at Baseline

(3) TSH > ULN with at least one FT3/FT4 test values < LLN (Lower Limit of Normal)

(4) TSH > ULN with all other FT3/FT4 test values ≥ LLN

(5) TSH > ULN with FT3/FT4 test missing

(6) TSH < LLN

(7) TSH < LLN with TSH ≥ LLN at Baseline

(8) TSH < LLN with at least one FT3/FT4 test values > ULN

(9) TSH < LLN with all other FT3/FT4 test values ≤ ULN

(10) TSH < LLN with FT3/FT4 test missing

10.5 Vital Signs

10.5.1 Analysis Set

Analysis will be performed in SAF.

10.5.2 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.

10.5.3 Analysis Methods

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. The analysis results will be summarized by squamous NSCLC and non-squamous NSCLC separately and totality.

10.6 12-lead ECG

10.6.1 Analysis Set

Analysis will be performed in SAF.

10.6.2 Analysis Items and Data Handling

1) Analysis Items

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

2) Data Handling

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

QTcF will be calculated using the following compensation formula.

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

10.6.3 Analysis Methods

1) The analysis results will be summarized by squamous NSCLC and non-squamous NSCLC separately and totality.

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

3) 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
PR (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, QTcF (ms) (observed value)	≤450, >450–480 >480–500, >500
ΔQTcF (ms) (change from baseline)	≤30, >30–60, >60

11 Anti-drug Antibody Analysis

11.1 Analysis Set

Analysis will be performed in the Anti-drug Antibody Analysis Set.

11.2 Analysis Items and Data Handling

1) Analysis Items

Presence of the anti-ONO-4538 antibody

2) Data Handling

(1) Handling per sample

Samples will be handled as follows.

[1] Baseline positive samples

Samples testing positive for anti-ONO-4538 antibodies at baseline. Subjects with at least one baseline neutralizing positive sample for anti-ONO-4538 antibodies including baseline positive ones.

[2] Anti-ONO-4538 antibody-positive samples

Samples were obtained within 100 days of final dose meeting either of the following criteria:

1. Samples after the first dose of the investigational product (collected from subjects who tested negative for anti-ONO-4538 antibodies at baseline) testing positive for anti-ONO-4538 antibodies.
2. Samples after the first dose of the investigational product (collected from subjects who tested positive for anti-ONO-4538 antibodies at baseline) testing positive for anti-ONO-4538 antibodies and with titers at least 4-hold higher than those at baseline.

[3] Anti-ONO-4538 antibody-negative sample

Samples after the first dose of the investigational product testing negative for anti-ONO-4538 antibodies (excluding missing ones), including baseline negative samples (excluding missing ones).

(2) Handling per subject

[1] Baseline positive subjects

Subjects with baseline positive samples as defined in (1) but subjects without any positive samples for anti-ONO-4538 antibodies after the first dose of the investigational product. And “baseline neutralizing positive” subjects with at least one positive sample for anti-ONO-4538 antibodies after the first dose of the investigational product including neutralizing ones within “baseline positive” subject.

[2] Anti-ONO-4538 antibody-positive subjects

Subjects with at least one positive sample for anti-ONO-4538 antibodies after the first dose of the investigational product. They will be classified as follows.

1. Persistent positive: Subjects with two or more samples collected at consecutive time points after the first dose of the investigational product and testing positive for anti-ONO-4538 antibodies with a minimum interval of 16 weeks (there is a time window for one week) between the first and last positive samples.
2. Only the last sample positive: Subjects for whom only the last sample is positive for anti-ONO-4538 antibodies.
3. Other positive: Other subjects (not meeting 1 or 2) with samples positive for anti-ONO-4538 antibodies.
4. Neutralizing positive: Subjects with at least one positive sample for anti-ONO-4538 antibodies including neutralizing ones.

[3] Anti-ONO-4538 antibody-negative subjects

Subjects without any positive sample for anti-ONO-4538 antibodies after the first dose of the investigational product.

11.3 Analysis Methods

The following will be calculated: the proportions of baseline positive subjects, anti-ONO-4538 antibody-positive subjects and anti-ONO-4538 antibody-negative subjects in the Anti-drug Antibody Analysis Set; the proportions of “persistent positive” subjects, “only the last sample positive” subjects and "other positive" subjects among anti-ONO-4538 antibody-positive subjects; and if necessary, the proportion of “baseline neutralizing positive” subjects and “neutralizing positive” subjects among anti-ONO-4538 antibody-positive subjects. The analysis results will be summarized by squamous NSCLC and non-squamous NSCLC separately and totality.

12 GENERAL PRESENTATION OF SUMMARIES AND ANALYSES

12.1 Summary Statistics

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

12.2 Significance Level to Be Used

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

12.3 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	Two decimal places
Time from diagnosis date of primary disease to first dose date of the investigational product (days) Age (years)	Height (cm) Weight (kg) BMI (kg/m^2)	Percent change in tumor diameter of target lesion (%)

· Laboratory values

Integer value (No decimal places)	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)	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 width (ms)

12.4 Subgroup Definitions

Item	Classification
Age (years)	<65, 65 - <75, ≥75
Sex	Male or female
Performance Status (ECOG)	0, 1
Brain metastasis	Yes, No
Bone metastasis	Yes, No
Stage	IIIB, IV, recurrence, unknown or other
NSCLC treatment history (Surgery)	Yes, No
NSCLC treatment history (Radiotherapy)	Yes, No
NSCLC treatment history (Number of treatment regimens)	1, 2
Presence of the anti-ONO-4538 antibody	Positive(Persistent positive/ Only the last sample positive, Other positive), Baseline positive, Negative

12.5 Site Pooling Method

NA

12.6 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.

13 INTERIM ANALYSIS

No interim analysis will be performed

14 DATA REVIEW

14.1 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.

14.2 Analysis Set

Analysis will be performed in subjects receiving the study drug.

14.3 Analysis Items and Data Handling

1) Analysis Items

(1) Background factors

Demography

(2) Efficacy endpoints

Response rate and progression-free survival (investigator-assessed)

(3) Safety endpoints

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.

14.4 Analysis Methods

1) The analysis results will be summarized by squamous NSCLC and non-squamous NSCLC separately and totality.
2) Summary statistics and frequency distribution of background factors will be calculated, and classification will be decided.
3) The response rate (investigator-assessed) and its 95% confidence interval (Wilson) will be calculated to examine the appropriateness of the analysis method. In addition, missingness will be evaluated as necessary.
4) For progression-free survival (investigator-assessed), a Kaplan-Meier curve will be presented. In addition, using the Kaplan-Meier method, the median and its 95% confidence interval and

progression free survival rates at 3 and 6 months and its 95% confidence interval will be estimated for the validation of the analysis methods or handling of data.

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

The above analyses were performed using the data obtained from 96 subjects treated with the study drug as of Feb. 27, 2015.

15 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, analysis of the development of tumor diameter and evaluation of baseline characteristics will be performed.

16 SAS PROCEDURE FOR ANALYSIS

16.1 95% confidence interval (Wilson)

```
PROC FREQ DATA=[Analysis data set];
        TABLES [Binary data] / BINOMIAL(WILSON) alpha=0.05;
        BY [Histologic type];
RUN;
```

16.2 Kaplan-Meier curve

```
PROC LIFETEST DATA= [Analysis data set] METHOD=KM CONFTYPE=LOGLOG;
 TIME [Time to onset of initial event or censoring] * [Censoring variable]([Censoring value]);
 STRATA [Histologic type];
RUN;
```

17 REFERENCES

NA

Addendum 1 List of Select Adverse Events

Category	Subcategory	Preferred Term
Endocrine Adverse Events	Adrenal disorder	Adrenal insufficiency
		Adrenal suppression
		Blood corticotrophin decreased
		Blood corticotrophin increased
		Hypothalamic pituitary adrenal axis suppression
		Secondary adrenocortical insufficiency
	Diabetes	Diabetes mellitus
		Diabetic ketoacidosis
		Latent autoimmune diabetes in adults
	Pituitary disorder	Hypophysitis
	Thyroid disorder	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 Autoimmune hepatitis Bilirubin conjugated increased Blood bilirubin increased Drug-induced liver injury Gamma-glutamyltransferase increased Hepatic enzyme increased Hepatic failure Hepatitis Hepatitis acute Hepatotoxicity 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

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