ONO-4538 PHASE III STUDY

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND TRIAL IN SUBJECTS WITH NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

STATISTICAL ANALYSIS PLAN

ONO PHARMACEUTICAL CO., LTD.

Protocol No.: ONO-4538-52

Version No.: 2.0

Date of preparation: MAY 7, 2020

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	25OCT2018	[redacted]	Not Applicable – First Version
2.0	07MAY2020	[redacted]	Descriptions for efficacy endpoint were modified and updated. Minor update for overall descriptions.

TABLE OF CONTENTS

LIST OF TABLES

1 DEFINITIONS OF STATISTICAL ANALYSIS PLAN

This statistical analysis plan (SAP) refers to the definition of terminologies, valid analytical methods and the detailed contents of statistical analysis for ONO-4538 Phase III study (protocol number: ONO-4538-52).

The SAP will be developed in accordance with the protocol, Core SAP (2017/05/26, Ver.1.0), and Core ADA-SAP (2017/05/26, Ver.1.0) for ONO-4538 study. The SAP Ver.1.0 will be finalized before the cutoff data lock for interim analysis. The analysis principles are outlined in Section 10 “Statistical Analysis” in the study-specific protocol.

If additional analyses not stated in the SAP are performed or endpoints not stated in the SAP are analyzed, the reasons for performing the analyses or analyzing the endpoints will be reported in the clinical study report, including the dates when the analyses were planned or the endpoints were derived.

2 SAMPLE SIZE

2.1 Planned Sample Size

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

<Rationale for sample size calculation>

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

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

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

Assuming an accrual period of 24 months and a minimum follow-up of 16 months, 530 subjects may be required to observe the required number of events taking into account the number of

censored subjects. Therefore, the target sample size was set at 530 subjects. The required number of events and the target sample size in the protocol were calculated by simulation with SAS statistical analysis software (version 9.4).

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

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

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

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

3 DETERMINATION OF SUBJECTS INCLUDED IN ANALYSIS

The analysis sets for efficacy endpoints are the Intention-to-Treat (ITT) and the PD-L1+ (≥ 1%) set (PD-L1 1% Positive Set: PDL1-PS).
The analysis set for safety endpoints is the Safety Set (SAF).
The analysis set for anti-drug antibody endpoints is the Anti-Drug Antibody Set (ADA).
Individual sets of subjects are defined below.

3.1 Definitions of Analysis Sets

1) Informed Consent Set (INF)

The INF will consist of all subjects who signed an informed consent.

2) Enrolled Set (ENR)

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

3) ITT/Randomized Set (RND)

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

4) SAF

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

5) PDL1-PS

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

6) Anti-Drug Antibody Set

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

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

3.2 Criteria for Handling of Subjects

Details of handling of subjects are shown below.

1) Non-enrolled Subjects

   Subjects who were not enrolled after signed to informed consent are defined as non-enrolled subjects.

2) Non-randomized Subjects

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

3) Untreated Subjects

   Subjects who have not received both of the investigational product and chemotherapy are defined as untreated subjects.

4) PD-L1 negative subjects

   Subjects who are PD-L1 negative (< 1%) are defined as PD-L1 negative subjects.

5) Incomplete Anti-Drug Antibody Subjects

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

For unexpected, problematic cases other than above, the Sponsor will examine such cases and decide how they will be handled in the analysis before database lock.

3.3 Criteria for Handling of Time Points

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

4 SIGNIFICANCE LEVEL TO BE USED

4.1 Efficacy

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

4.2 Safety

Not established because the test will not be performed.

5 GENERAL METHODS

Unless otherwise noted, analysis will be conducted based on treatment group randomized by IWRS. In the following sections, treatment group will refer to ONO-4538 group and placebo group. Investigational product will refer to ONO-4538 or placebo and chemotherapy will refer to carboplatin, paclitaxel and bevacizumab. The treatment group “As Randomized” will be retrieved from IWRS. The treatment group “As Treated” will be the same as the arm randomized by IWRS. However, if a subject received the incorrect treatment for the entire period of treatment, the subject’s treatment group will be defined as the incorrect treatment the subject actually received. Efficacy analysis will be conducted by “As Randomized” while safety analysis will be conducted by “As Treated”.

For evaluation by IRRC, if both the Reader 1 and Reader 2 complete assessment without discordance, it will be adopted for the Reader’s assessment that the value of 10.2 1) (8) Maximum percentage of change in the sum of diameters of target lesions (as assessed by the IRRC) will be larger. If both Reader 1 and Reader 2 do not evaluate target lesions including the case of unmeasurable or non-target lesions, the assessment of reader will be adopted in alphabetical order.

6 RELIABILITY OF THE STUDY

6.1 Analysis Set

INF will be the analysis set for Analytical Item (1).

SAF will be the analysis set for Analytical Item (2).

ITT will be the analysis set for Analytical Item (3), (4) and (5).

6.2 Analytical Items and Data Handling

1) Analytical Item

   (1) Reason for being excluded from each analysis set

   (2) Reason for discontinuation of the study treatment (Protocol 7.1.4)

   (3) Reason for withdrawals and dropouts from the study (Protocol 13)

   (4) The number of randomized subjects per study site

   (5) Important protocol deviation

2) Handling of data

The following deviations will be considered as important protocol deviations.

Eligibility:

- Subjects who failed to fulfill inclusion criteria #3
- Subjects who failed to fulfill inclusion criteria #4
- Subjects who failed to fulfill inclusion criteria #7
- Subjects who failed to fulfill exclusion criteria #10

On-study:

- Subjects receiving any concurrent anticancer therapy (ie. chemotherapy, hormonal therapy, immunotherapy, surgery, or radiation therapy) while on study therapy
- Subjects treated differently as randomized (subjects who received the wrong treatment excluding the never treated.)

6.3 Analytical Methods

1) Frequency of subjects who are included or excluded in each analysis set and frequency by reason for exclusion will be summarized by treatment group. Frequency of subjects who continuing or discontinued study treatment or study will also be summarized by treatment group.
2) Reason for discontinuations of study treatment will be summarized by treatment group.
3) Reason for lost to follow-up will be summarized by treatment group.
4) For the number of subjects randomized per study site, frequency distribution and summary statistics will be summarized by treatment group.
5) Frequency of important protocol deviation will be summarized by treatment group.

7 EXTENT OF EXPOSURE AND ADMINISTRATION OF STUDY TREATMENT

7.1 Analysis Set

The SAF will be the analysis set.

7.2 Analytical Items and Data Handling

1) Analytical Items

   (1) Duration of treatment period

   (2) Number of doses received

   (3) Duration of treatment

   (4) Number of cycles

   (5) Cumulative dose

   (6) Relative dose intensity

2) Handling of data

   (1) Duration of treatment period

   Duration of Treatment period = Last dose date of investigational product or each chemotherapy - First dose date of investigational product or each chemotherapy + 1

   (2) Number of cycles

   The number of cycles will be calculated for a cycle proceeding to the next cycle. A discontinued cycle or cycle in which no investigational products are administered will also be included for the number of cycles of investigational products. The same handling rules will be applied to each chemotherapy.

   (3) Duration of Treatment, Cumulative dose, Relative dose intensity

   To calculate duration of treatment, cumulative dose, and relative dose intensity for ONO-4538, refer to Table 7.2-1 and to calculate those for the chemotherapies (carboplatin, paclitaxel, and bevacizumab), refer to Table 7.2-2.

Table 7.2-1 Duration of Treatment, cumulative dose, relative dose intensity of ONO-4538

	ONO-4538
Cumulative dose	Cumulative dose (mg) is the sum of doses (mg) administered to a subject during the treatment period.
Relative dose intensity (%)	Cumulative dose (mg) / [Date of the last dose – Date of the first dose + 21] (days) x 360 (mg) / 21 (days) x 100
Duration of treatment (overall)	Date of the last dose – Date of the first dose + 1

Table 7.2-2 Duration of Treatment, cumulative dose, relative dose intensity of chemotherapies

	paclitaxel	**carboplatin**	**bevacizumab**
Cumulative dose	Cumulative dose (mg/m^2) is the sum of doses (mg/m^2) administered to a subject during the treatment period. Dose (mg / m^2) = Dose administered of Paclitaxel (mg) / Baseline BSA BSA (Body Surface Area) will be calculated by DuBois formula: [Body weight at screening (kg)]$^{0.425}$ x	Cumulative dose (AUC) is the sum of doses (AUC) administered to a subject during the treatment period. Dose (AUC) =Dose administered of Carboplatin (mg) / (Creatinine Clearance at screening + 25) Creatinine Clearance (CrCl) at screening will be calculated by	Cumulative dose (mg/kg) is the sum of doses (mg/kg) administered to a subject during the treatment period. Dose (mg/ kg) = Dose administered of Bevacizumab (mg) / Baseline Body weight (at screening)

	[Height at screening (cm)]$^{0.725}$ x 0.007184	Cockcroft-Gault formula. If value of the CrCl yields a result of > 125 mL/min, it should be used 125 mL/min for the dose calculation.	
Relative dose intensity (%)	Cumulative dose (mg/m^2) / [Date of the last dose – Date of the first dose + 21] (days) x 200 (mg/m^2) / 21 (days) x 100	Cumulative dose (AUC) / [Date of the last dose – Date of the first dose + 21] (days) x 6 (AUC) / 21 (days) x 100	Cumulative dose (mg/kg) / [Date of the last dose – Date of the first dose + 21] (days) x 15 (mg/kg) / 21 (days) x 100
Duration of treatment (overall)	Date of the last dose – Date of the first dose + 1	Date of the last dose − Date of the first date + 1	Date of the last dose − Date of the first dose + 1

7.3 Analytical Methods

1) For duration of treatment period, frequency distributions and summary statistics will be calculated by treatment group.
2) For number of doses received, summary statistics will be calculated by investigational product and each chemotherapy.
3) For duration of treatment, frequency distributions and summary statistics will be calculated by investigational product and each chemotherapy.
4) For number of cycles, frequency distributions and summary statistics will be calculated by investigational product and each chemotherapy.
5) For cumulative dose, summary statistics will be calculated by investigational product and each chemotherapy.

6) For relative dose intensity, frequency distributions and summary statistics will be calculated by investigational product and each chemotherapy.

8 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

8.1 Analysis Set

The ITT will be the analysis set.

8.2 Analytical Items and Data Handling

1) Analytical Items

(1) Demographic Variables

Location, gender (eCRF source), age, race, ethnicity, height, body weight and body mass index (BMI)

(2) Baseline Characteristics

Past history, complications, smoking history, ECOG Performance Status (eCRF source), period from the date of diagnosis of primary disease through randomization, staging (Stage) and Tumor Node Metastasis (TNM) classification (at first diagnosis of the primary disease), histology of non-squamous non-small cell lung cancer, primary site and metastatic site of non-squamous non-small cell lung cancer, site of recurrence (for recurrent non-squamous non-small cell lung cancer), and previous treatment for cancers (including history of surgery, radiotherapy, or medical treatment)

(3) Baseline Values of Observation

Sum of tumor diameters of target lesions (IRRC)

(4) Biomarkers

PD-L1 (test result source)

(5) Randomization factors

PD-L1 (IWRS source), Gender (IWRS source), ECOG Performance Status (IWRS source)

(6) Subsequent anticancer therapy

Surgery, radiotherapy, and medical treatment

(7) Concomitant medication

Immune modulating concomitant medication

2) Handling of data

(1) BMI

BMI (kg/m^2) = “Body weight (kg)” / “[Height (m)] ^{2}”

(2) Period from the date of diagnosis of primary disease through randomization

Period from the date of diagnosis of primary disease through randomization (months)

= (“Date of randomization” − “Date of diagnosis of the primary disease” + 1) / 30.4375

8.3 Analytical Methods and Classification

1) Each analytical item displayed in 8.2 Analytical Items and Data Handling will be summarized by treatment group according to Table 8.3-1. Also, each analytical item will be summarized for each treatment group by location.

2) Previous medical treatment for cancer will be summarized for each treatment group by generic name.

3) Details of subsequent anticancer therapy (surgery, radiotherapy, and medical treatment) will be summarized by treatment group.

4) For immune modulating concomitant medications, the number of subjects who received immune modulating concomitant medication for management of adverse event, management of concurrent disease, management of drug-related select adverse events classified by specific category (any grade, grade 3-5), management of IMAEs classified by specific category (any grade, grade 3-5), prevention, and other use will be calculated separately for each treatment group by medication class (WHODD: ATC Level 4) and generic name.

5) Cross-tabulation between stratification factors (IWRS source) and stratification factors (eCRF source or test result source) will be provided by treatment group.

   (1) PD-L1 expression level (IWRS source) vs PD-L1 expression level (test result source)

   (2) ECOG Performance Status (IWRS source) vs ECOG Performance Status (eCRF source)

   (3) Gender (IWRS source) vs Gender (eCRF source)

<Method of classification >

Classification for the ordinal scale or the continuous value will be determined based on clinical symptom or equipartition of the number of subjects (i.e., 1/3, 1/4, 1/5).
Each classification of analytical item is displayed in the following table.

Table 8.3-1 Classification of analytical item

Analytical Item	Stratum	Analytical Method
Location	Japan, Taiwan, South Korea	Frequency distributions
Gender (IWRS source)	Female, Male	Frequency distributions
Gender (eCRF source)	Female, Male	Frequency distributions
Age	・ Category1 <65, >=65 ・ Category2 <65, 65 - <75, >=75	Summary statistics, Frequency distributions
Race	Asian, American Indian or Alaska Native, African American, Native Hawaiian or Other Pacific Islander, White	Frequency distributions
Ethnicity	Not Hispanic or Latino, Hispanic or Latino	Frequency distributions
Height (cm)	<160, 160 - <165, 165 - <170, >=170	Summary statistics, Frequency distributions
Body weight (kg)	<50, 50 - <60, 60 - <70, >=70	Summary statistics, Frequency distributions
BMI (kg/m^2)	<18.5, 18.5 - <25.0, >=25.0	Summary statistics,

		Frequency distributions
Past history	No, Yes	Frequency distributions
Complications	No, Yes	Frequency distributions
Smoking history (smoking status)	Never, Current, Former, Unknown	Frequency distributions
Smoking history (years)	<15, 15 - <30, 30 - <45, >=45	Summary statistics, Frequency distributions
ECOG Performance Status (IWRS source)	0, 1, 2, 3, 4	Frequency distributions
ECOG Performance Status (eCRF source)	0, 1, 2, 3, 4	Frequency distributions
Period from the date of diagnosis of primary disease through randomization (months)	<1, 1 - <2, >=2	Summary statistics, Frequency distributions
Staging (Stage)	IIIB, IV, Recurrent	Frequency distributions
Tumor Node Metastasis (TNM) classification	T: TX, T1a, T1b, T2a, T2b, T3, T4 N: NX, N0, N1, N2, N3 M: MX, M0, M1a, M1b	Frequency distributions
Histology of non-squamous non-small cell lung cancer	Adenocarcinoma, Large cell carcinoma, Other	Frequency distributions
Primary site of non-squamous non-small cell	Right Upper Lobe, Right Middle Lobe, Right Lower Lobe, Left Upper	Frequency distributions

lung cancer	Lobe, Left Lower Lobe, Unknown, Other	
Metastatic site of non-squamous non-small cell lung cancer	Lung (Right Upper Lobe, Right Middle Lobe, Right Lower Lobe, Left Upper Lobe, Left Lower Lobe, Unknown, Other), Bone, Liver, Brain, Lymph Node, Bone Marrow, Pleura, Peritonea, Adrenal Gland, Skin, Other	Frequency distributions
Site of recurrence (for recurrent non-squamous non-small cell lung cancer)	Lung (Right Upper Lobe, Right Middle Lobe, Right Lower Lobe, Left Upper Lobe, Left Lower Lobe, Unknown, Other), Bone, Liver, Brain, Lymph Node, Bone Marrow, Pleura, Peritonea, Adrenal Gland, Skin, Other	Frequency distributions
Previous treatment for cancers (history of surgery)	No, Yes	Frequency distributions
Previous treatment for cancers (history of radiotherapy)	No, Yes	Frequency distributions
Previous treatment for cancers (history of medical treatment)	No, Yes	Frequency distributions
Sum of tumor diameters of target lesions	<40, 40 - <60, 60 - <80, >=80	Summary statistics, Frequency distributions

PD-L1 (IWRS source)	① <1% or indeterminate ② 1% - 49% ③ >= 50%	Frequency distributions
PD-L1 (test result source)	① <1% or indeterminate ② 1% - 49% ③ >= 50%	Frequency distributions

9 PRIMARY ENDPOINT

9.1 Analysis Sets

In the case of early efficacy stopping based on the results of the interim analysis, the ITT will be used as the analysis set.

If the study is continued based on the results of the interim analysis, the ITT and PDL1-PS will be used as the analysis sets for primary and sensitive analysis. Additionally, if the superiority of the ONO-4538 group over the placebo group is verified in the ITT in the primary analysis, the ITT will be used as the analysis set for secondary analysis. On the other hand, if the superiority of the ONO-4538 group over the placebo group is not verified in the ITT, the ITT and PDL1-PS will be used as the analysis sets for secondary analysis.

9.2 Analytical Item and Data Handling

1) Analytical Item
   PFS (per IRRC, primary definition).
2) Handling of data

Primary definition of PFS will be calculated by the following equation.

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

Overall response will not take into account any clinical deterioration and evaluable radiographic tumor assessment will be those without an overall response of “NE”.

Event/censored assessment in the primary definition of PFS will be performed according to Table 9.2-1, depending on the situation. If the date on which the overall response is assessed as PD for the first time and the date of the start of subsequent anticancer therapy are the same, the event will be handled at the date on which the overall response is assessed as PD. Additionally, if the date of radiographic tumor assessment which overall response is not PD or NE and the date of the start of subsequent anticancer therapy are the same, PFS will be censored at that date. When a subject corresponds to more than one situation, the shortest PFS will be handled as the PFS of the subject.

Table 9.2-1 Definition of event and censoring for the primary definition of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline radiographic tumor assessments	Date of randomization	Censored
No death without an overall response of PD	Date of the last evaluable radiographic tumor assessment[*1]	Censored
No death without evaluable radiographic tumor assessment	Date of randomization	Censored
Assessment of overall response will not be done for more than 98 days before overall response of PD or death	Date of the last evaluable radiographic tumor assessment[*1, *2] before overall response of PD or death	Censored
Subsequent anticancer therapy before an overall response of PD or death	Date of the last evaluable radiographic tumor assessment[*1] on or before initiation of subsequent anticancer therapy	Censored
End of investigating subsequent anticancer therapy before an overall response of PD or death	Date of the last evaluable radiographic tumor assessment[*1] on or before end of investigating subsequent anticancer therapy	Censored
No subsequent anticancer	Date of the last evaluable	Censored

therapy before an overall response of PD or death	radiographic tumor assessment[*1] on or before no subsequent anticancer therapy	
Death without evaluable radiographic tumor assessment after randomization	Date of death	Event
Death	Date of death	Event
Overall response of PD	Date of the first overall response of PD	Event

*1 The date of randomization will be used as the date of censoring when the subject does not have any evaluable radiographic tumor assessment after randomization.
*2 The date of randomization will be used instead of date of the last evaluable radiographic tumor assessment when the subject does not have any evaluable radiographic tumor assessment between the date of randomization and the date of assessment of PD or death.

9.3 Analytical Methods (when the study stopped for superiority based on the results of Interim Analysis)

9.3.1 Primary Analysis

To preserve the overall type I error rate at ≤ 5% (two-sided), a significance level α for analysis will be calculated using the Lan-DeMets α spending function (O'Brien-Fleming).

The distribution of PFS-will be compared between the two treatments groups using the two-sided stratified log-rank test with the three stratification factors (IWRS source) presented below.

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

9.3.2 Sensitivity Analysis for Primary Analysis

1) The distribution of PFS-will be compared between the two treatment groups using the unstratified log-rank test.

2) The distribution of PFS will be compared between the two treatment groups by using the stratified log-rank test adjusted by the three stratification factors (Gender and ECOG Performance Status from eCRF source and PD-L1 expression from test result source), if there exist more than 10% discrepancy in at least one factor between stratification factors (IWRS source) and stratification factors (eCRF source / test result source).

9.3.3 Secondary Analysis

1) The number of events and censors will be tabulated for each treatment group. The status of subjects who are censored in the Kaplan-Meier analysis will also be tabulated by treatment groups using the following categories:

   a) Censored on date of randomization

   b) Censored on date of last evaluable tumor assessment

      a. To confirm to receive subsequent anticancer therapy before an overall response of PD or death

      b. To confirm the end of investigating subsequent anticancer therapy before an overall response of PD or death

      c. To confirm that assessment of overall response will not be done for more than 98 days before an overall response of PD or death

      d. On-study: Not meet the above condition a, b and c and continuing the treatment period or follow-up period (excluding the case to confirm the alive in outcome survey even if the subject requested that the study be discontinued)

      e. Off-study: Lost to follow-up and not meet all the above condition a, b, c and d

2) The hazard ratio and the corresponding two-sided 100 (1-α) % confidence interval (CI) (adjusted using Lan-DeMets alpha spending function (O'Brien-Fleming type) based on the number of observed PFS events) for the ONO-4538 group relative to the placebo group will

be estimated using a stratified Cox proportional hazard model with the stratification factors (IWRS source) presented above and with the treatment group as the single covariate. The hazard ratio and the corresponding two-sided 95 % CI for ONO-4538 group relative to the placebo group for each stratification factor will be estimated using an unstratified Cox proportional hazard model with the treatment group as the single covariate.

3) The Kaplan-Meier curve will be plotted for each treatment group.

4) Using the Kaplan-Meier method, the median PFS and the corresponding two-sided 100 (1-α) % CI (adjusted using Lan-DeMets alpha spending function (O'Brien-Fleming type) based on the number of observed PFS events) will be estimated for each treatment group. CI for median PFS will be calculated using the Brookmeyer and Crowley method based on a log-log transformed CI for the survivor function.

5) For each treatment group, PFS rates at Months 6, 12, 18, 24, 30 and 36 after randomization will be derived from the Kaplan-Meier method and the corresponding two-sided 95% CI will be derived based on Greenwood's formula for variance derivation and on log-log transformation applied on the survivor function.

6) The analyses described in 9.3.3 Secondary Analysis 1), 3) and 4) will be performed by the three stratification factors (IWRS source) presented 9.3.1 Primary Analysis 1) to 3).

9.4 Analytical Methods (when the study continued based on the results of Interim Analysis)

9.4.1 Primary Analysis

The analysis will be performed by adjusting multiplicity using the Hochberg's method according to the following procedures 1 to 4. A significance level α for analysis will be calculated using the Lan-DeMets α spending function (O'Brien-Fleming).

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

2) For PFS, comparison between treatment groups will be performed in the PDL1-PS via the stratified log-rank test stratified by randomization factors (PD-L1 expression level, ECOG Performance Status, and gender).
3) If the p value in the ITT and the p value in the PDL1-PS obtained from the stratified log-rank tests in 1 and 2 above are referred to as $p_{(1)}$ and $p_{(2)}$ in ascending order, then its corresponding null hypotheses referred to as $H_{0(1)}$ and $H_{0(2)}$, respectively.
4) Superiority of the ONO-4538 group to the placebo group will be verified using $p_{(1)}$ and $p_{(2)}$.
   (1) If $p_{(2)} < \alpha$, both null hypotheses $H_{0(1)}$ and $H_{0(2)}$ will be rejected.
   (2) If $p_{(2)} \geq \alpha$ and $p_{(1)} < \alpha/2$, only null hypothesis $H_{0(1)}$ will be rejected.

9.4.2 Sensitivity Analysis for Primary Analysis

The analyses described in 9.3.2 Sensitivity Analysis for Primary Analysis will be performed.

9.4.3 Secondary Analysis

The analyses described in 9.3.3 Secondary Analysis will be performed.

10 EFFICACY SECONDARY ENDPOINT

10.1 Analysis Set

In the case of early efficacy stopping based on the results of the interim analysis, the ITT will be used as the analysis set.

If the study is continued based on the results of the interim analysis and the superiority of the ONO-4538 group over the placebo group is verified in the ITT in the final analysis for primary endpoint, the ITT will be used as the analysis set. On the other hand, if the superiority of the ONO-4538 group over the placebo group is not verified in the ITT, the ITT and PDL1-PS will be used as the analysis sets.

10.2 Analytical Items and Data Handling

1) Analytical Item

   (1) Overall Survival (OS)

   (2) PFS (as assessed by the study site's investigator)

   (3) Objective response rate (ORR as assessed by the IRRC and study site's investigator)

   (4) Disease control rate (DCR as assessed by the IRRC and study site's investigator)

   (5) Duration of response (DOR as assessed by the IRRC)

   (6) Time to response (TTR as assessed by the IRRC)

   (7) Best overall response (BOR as assessed by the IRRC and study site's investigator)

   (8) Maximum percentage of change in the sum of diameters of target lesions (as assessed by the IRRC)

2) Handling of data

   (1) PFS (per study site's investigator)

   i. Primary definition of PFS (per study site's investigator)
   Refer to 9.2 1) Analytical Item and 9.2 2) Handling of data

   ii. Secondary definition of PFS (per study site's investigator)

PFS (per study site's investigator, secondary definition) will be calculated by the following equation.

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

Evaluable radiographic tumor assessment will be those without an overall response of "NE".

Event/censored assessment in the secondary definition of PFS will be performed according to Table 10.2-1, depending on the situation. If the date on which the overall response is assessed as PD or clinical deterioration for the first time and the date of the start of subsequent anticancer therapy are the same, the event will be handled at the date on which the overall response is assessed as PD or clinical deterioration. Additionally, if the date of radiographic tumor assessment which overall response is not PD or NE and the date of the start of subsequent anticancer therapy are the same, PFS will be censored at that date. When a subject corresponds to more than one situation, the shortest PFS will be handled as the PFS of the subject.

Table 10.2-1 Definition of event and censoring for the secondary definition of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline radiographic tumor assessments	Date of randomization	Censored
No death without an overall response of PD and clinical deterioration	Date of the last evaluable radiographic tumor assessment[*1]	Censored
No death without evaluable radiographic tumor assessment and clinical deterioration	Date of randomization	Censored

Assessment of overall response will not be done for more than 98 days before overall response of PD, clinical deterioration or death	Date of the last evaluable radiographic tumor assessment[*1,*2] before overall response of PD, clinical deterioration or death	Censored
Subsequent anticancer therapy before an overall response of PD, clinical deterioration or death	Date of the last evaluable radiographic tumor assessment[*1] on or before initiation of subsequent anticancer therapy	Censored
End of investigating subsequent anticancer therapy before an overall response of PD, clinical deterioration or death	Date of the last evaluable radiographic tumor assessment[*1] on or before end of investigating subsequent anticancer therapy	Censored
No subsequent anticancer therapy before an overall response of PD, clinical deterioration or death	Date of the last evaluable radiographic tumor assessment[*1] on or before no subsequent anticancer therapy	Censored
Death without evaluable radiographic tumor assessment after randomization	Date of death	Event
Death	Date of death	Event
Overall response of PD	Date of the first overall response of PD	Event

Clinical deterioration	Date of the first clinical deterioration	Event

*1 The date of randomization will be used as the date of censoring when the subject does not have any evaluable radiographic tumor assessment after randomization.
*2 The date of randomization will be used instead of date of the last evaluable radiographic tumor assessment when the subject does not have any evaluable radiographic tumor assessment between the date of randomization and the date of assessment of PD, clinical deterioration or death

(2) DOR

DOR will be calculated by the following equation. The target of the evaluation is a subject whose best overall response is CR or PR.

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

Event/censored assessment in DOR will be performed according to Table 10.2-2, depending on the situation. If the date on which the overall response is assessed as PD for the first time and the date of the start of subsequent anticancer therapy are the same, the event will be handled at the date on which the overall response is assessed as PD. Additionally, if the date of radiographic tumor assessment which overall response is not PD or NE and the date of the start of subsequent anticancer therapy are the same, DOR will be censored at that date. Also, when a subject corresponds to more than one situation, the shortest DOR will be handled as the DOR of the subject.

Table 10.2-2 Definition of event and censoring in DOR

Situation	Date of Response or Censoring	Outcome
No death without an overall response of PD	Date of the last evaluable radiographic tumor assessment	Censored
No death without evaluable radiographic tumor	Date of the confirmation of	Censored

assessment after the confirmation of response	response	
Assessment of overall response will not be done for more than 98 days before overall response of PD or death	Date of the last evaluable radiographic tumor assessment before overall response of PD or death	Censored
Subsequent anticancer therapy before an overall response of PD or death	Date of the last evaluable radiographic tumor assessment on or before initiation of subsequent anticancer therapy	Censored
End of investigating subsequent anticancer therapy before an overall response of PD or death	Date of the last evaluable radiographic tumor assessment on or before end of investigating subsequent anticancer therapy	Censored
No subsequent anticancer therapy before an overall response of PD or death	Date of the last evaluable radiographic tumor assessment on or before no subsequent anticancer therapy	Censored
Death without evaluable radiographic tumor assessment after the confirmation of response	Date of death	Event
Death	Date of death	Event
Overall response of PD	Date of the first overall response of PD	Event

(3) OS, ORR, DCR, TTR, and Maximum percentage of change in the sum of diameters of target lesions

Refer to Core SAP section 3.

Last confirmed to be alive in Core SAP section 3.1 means last date of data confirmed to be alive from all of date of data (visit date, performed or assessed) in this study.

10.3 Analytical Methods

1) For item 1, the analyses in Core SAP section 5.1 1) to 5) will be performed.
2) For items 2, the analyses in Core SAP section 5.2 1) to 5) will be performed. Description of Core SAP section 5.2 1) refer to 9.3.3 Secondary Analysis 1).
3) For item 3 and 4, the analyses in Core SAP section 5.4 1) and 3) and section 5.5 1) and 3) will be performed, respectively. Also, the relative risk and the corresponding two-sided 95% CI of the ONO-4538 group relative to the placebo group adjusted with the same stratification factor will be calculated using the Cochran-Mantel-Haenszel method.
4) For items 5 and 6, the analyses in Core SAP section 5.6 1) and 2) and section 5.7 1) and 2) will be performed, respectively. Description of Core SAP section 5.6 1) refer to 9.3.3 Secondary Analysis 1) b).
5) For item 7, the analysis in Core SAP section 5.10 1) will be performed.
6) For item 8, the analysis in Core SAP section 5.9 will be performed.

Note: the confidence level will be 95%. PFS rate and OS rate will be calculated at 6, 12, 18, 24, 30, and 36 months after randomization.

10.4 Subgroup Analyses for the Efficacy Endpoints

10.4.1 Analysis Sets

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

10.4.2 Analytical Item and Data Handling

1) Analytical Items

   (1) PFS (per IRRC and study site's investigator, primary definition)

   (2) OS

   (3) ORR (per IRRC and study site's investigator)

2) Handling of data

   (1) Stratification factor and Method of classification

   The stratification factors will be chosen from Section 8.2 Analytical Items and Data Handling. The stratification factors will be classified as the following Table 10.4-1. Unless otherwise noted, ECOG Performance Status and Gender which are used for randomization will be extracted from IWRS. The others except for PD-L1 expression level will be extracted from eCRF. PD-L1 expression will be extracted from test result. Subsequent anticancer therapy (Immunotherapy) will only be used for OS.

Table 10.4-1 Classification of analytical item

Analytical Item	Stratum
Location	Japan, Taiwan, South Korea
Gender (IWRS source)	Female, Male
Gender (eCRF source)	Female, Male
Age	・ Category 1 <65, >=65 ・ Category 2 <65, 65 - <75, >=75
Body weight (kg)	<50, 50 - <60, 60 - <70, >=70

BMI (kg/m^2)	<18.5, 18.5 - <25.0, >=25.0
Smoking history (smoking status)	Never, Current, Former, Unknown
Smoking history (years)	<15, 15 - <30, 30 - <45, >=45
ECOG Performance Status (IWRS source)	0, 1, >=2
ECOG Performance Status (eCRF source)	0, 1, >=2
Period from the date of diagnosis of primary disease through randomization (months)	<1, 1 - <2, >=2
Histology of non-squamous non-small cell lung cancer	Adenocarcinoma, Large cell carcinoma, Other
Brain metastases	No, Yes
Liver metastases	No, Yes
Bone metastases	No, Yes
Staging (Stage)	IIIB, IV, Recurrent
Previous treatment for cancers (history of surgery)	No, Yes
Previous treatment for cancers (history of	No, Yes

radiotherapy)	
Previous treatment for cancers (history of medical treatment)	No, Yes
Subsequent anticancer therapy (Immunotherapy)	No, Yes
PD-L1 (IWRS source)	① <1% or indeterminate ② 1% - 49% ③ >= 50%
PD-L1 (test result source)	① <1% or indeterminate ② 1% - 49% ③ >= 50%

10.4.3 Analytical Methods

1) For OS and PFS, forest plots will be created to present the number of events, the median and the corresponding 95% CI for each treatment group and the hazard ratio and the corresponding 95% CI for the ONO-4538 group relative to placebo group. Number of events, the median and the corresponding 95% CI will be calculated using Kaplan Meier method for each treatment group. Also, the hazard ratio and the corresponding 95% CI for the ONO-4538 group relative to placebo group will be calculated using the unstratified Cox proportional hazard model with the treatment group as the single covariate in each subgroup.
2) For ORR, forest plots will be created to present the percentage and the corresponding two-sided 95% CI, and the associated odds ratio and the corresponding two-sided 95% CI. The percentage and the corresponding two-sided 95% CI will be calculated using the Clopper-Pearson method for each treatment group. Also, the associated odds ratio and corresponding two-sided 95% CI for ONO-4538 group relative to placebo group will be calculated using the unstratified logistic regression model with the treatment group as the single covariate in each subgroup.

10.5 Interaction Analysis

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

Analyses specified in the Core SAP 5.11 1) will be performed using the unstratified Cox proportional hazard model.

10.6 Adjusted Analysis

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

Analyses specified in the Core SAP 5.12 1) will be performed. The confidence level will be 95%.

10.7 Exploratory Analysis

The ITT will be used as the analysis set.

1) For OS and PFS (per IRRC and study site's investigator, primary definition), the point estimate of Restricted Mean Survival time (RMST) [1), 2)] at months 6, 12, 18, 24, 30 and 36 after randomization and the corresponding two-sided 95% CI will be calculated by the treatment group. Also, the difference between the RMST of ONO-4538 group and placebo group and the corresponding 95% CI at each time point will be calculated.

   For treatment group i (i = 1, 2; 1=ONO-4538 group, 2=placebo group) and time point j (j = 6, 12, 18, 24, 30 and 36), RMST and its standard error are expressed as $RMST_{ij}$ and SE_{ij}

respectively and these values will be derived by TIMELIM option of SAS's LIFETEST procedure. Using these values, 95% CI of $RMST_{ij}$ will be calculated by the following equation where $z_{2.5}$ denotes the upper 2.5% critical value for the standard normal distribution.

$$\mathrm{RMST}_{ij} \pm z_{2.5} SE_{ij}$$

Also, difference of RMST between ONO-4538 group and placebo group and its 95% CI will be calculated by the following equation respectively.

$$\mathrm{RMST}_{1j} - \mathrm{RMST}_{2j},$$

$$\mathrm{RMST}_{1j} - \mathrm{RMST}_{2j} \pm z_{2.5} \sqrt{SE_{1j}^2 + SE_{2j}^2}$$

2) For OS, to evaluate the effect of subsequent anticancer therapy (immunotherapy), the adjusted hazard ratio and the corresponding two-sided 95% CI for the ONO-4538 group relative to the placebo group will be estimated using the two-stage accelerated failure time model (two-stage model) [3]. The Weibull model will be used as the accelerated failure time model. The following factors are considered as those related to the use of subsequent anticancer therapy (immunotherapy), and are included in the model as covariates when estimating acceleration factor. Note that the value at the closest measurement point at the time of discontinuation of all treatments and at the measurement point before the date of discontinuation of all treatments will be used as covariates values except for PD-L1 expression level (test result source).

- PD-L1 expression level (test result source : <1% or indeterminate, 1% - 49% and >= 50%)
- Value of LDH at the time of discontinuation of all treatments
- Value of CRP at the time of discontinuation of all treatments
- Value of NLR at the time of discontinuation of all treatments

  NLR = Neutrophil count / Lymphocyte count

The specific procedure for estimating the adjusted hazard ratio and the corresponding two-sided 95% CI for the ONO-4538 group relative to the placebo group in OS using the accelerated failure time model is as follows.

(1) Classify the subjects in the placebo group into the following three groups:

A) Subjects who are continuing the treatment period

B) Subjects who discontinued the treatment period and received a subsequent anticancer therapy (immunotherapy) once or more

C) Subjects who discontinued the treatment period and have not received any subsequent anticancer therapy (immunotherapy)

(2) Compare a survival time after the date of discontinuation in group B and C using the accelerated failure time model (Weibull model) with group (B or C) and factors related to the use of subsequent anticancer therapy (immunotherapy) described above as covariates and estimate the acceleration factor. The acceleration factor will be calculated by $e^{\text{coefficient of group}}$.

(3) Using the acceleration factor estimated in (2), calculate an adjusted overall survival for each subject in group B if the subjects had not received any subsequent anti-cancer therapy (immunotherapy). The adjusted overall survival will be calculated as follows:

The adjusted overall survival (month) = "time from randomization to discontinuation of all treatments" + "(survival time after discontinuation of all treatments) / value of the acceleration factor"

3) Using the overall survival in ONO-4538 group and group A, C and the adjusted over survival in group B, the hazard ratio and the corresponding two-sided 95 % CI for ONO-4538 group relative to the placebo group will be estimated using the stratified Cox proportional hazard model with the stratification factors (IWRS source) presented above and with the treatment group as the single covariate.

11 ANALYSIS OF SAFETY

11.1 Analysis Sets

The SAF will be the analysis set.

11.2 Analytical Items and Data Handling

1) Analytical Items

(1) Adverse events, drug-related adverse events and deaths

(2) Select adverse events and drug-related select adverse events

(3) Time to onset or resolution/resolving of select adverse events and drug-related select adverse events

(4) Immune-mediated adverse events and drug-related immune-mediated adverse events

(5) Time to onset or resolution/resolving of immune-mediated adverse events and drug-related immune-mediated adverse events

(6) Laboratory tests

a) Hematology Tests

Hemoglobin, White blood cell count, Neutrophil count, Lymphocyte count, Platelet count

b) Serum chemistry Tests

ALP, AST (GOT), ALT (GPT), Total bilirubin, Creatinine

(7) Hormone Tests

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

(8) 12-lead ECG

Heart Rate (HR), PR Interval, RR Interval, QRS Complex, QT Interval, QTcF Interval

2) Handling of data

(1) For analytical items (1), (2), (3), (6), (7) and (8), handling of data refers to the Core SAP section 6. All of the items (1), (2) and (3) occurring between the start date of the first administration of the investigational product or each chemotherapy and 30 days after the last dose of investigational product or each chemotherapy (30-day safety window) / 100 days after the last dose of investigational product or each chemotherapy (100-day safety window) will be tabulated by treatment group.

Drug-related AEs will be defined as any AEs for which a causal relationship to the investigational product or chemotherapies is “Related” or missing.

AEs and drug-related AEs leading to discontinuation of treatment group will be defined as any AEs and drug-related AEs leading to discontinuation of the last treatment in treatment group, refer to 19 Appendix.

AEs leading to discontinuation of investigational product will be defined as any AEs with action taken with investigational product = “Drug Withdrawn”.

Drug-related AEs leading to discontinuation of investigational product will be defined as any AEs leading to discontinuation of investigational product with causal relationship to the investigational product assessed as “Related” or missing.

AEs leading to discontinuation of 4 drugs will be defined as any AEs with action taken with investigational product and all chemotherapies = “Drug Withdrawn”.

Drug-related AEs leading to discontinuation of 4 drugs will be defined as any AEs leading to discontinuation of 4 drugs with causal relationship to the investigational product or chemotherapies assessed as “Related” or missing.

AEs leading to dose delay of treatment group will be defined as any AEs with action taken with any of treatment(s) = “Drug Delayed”.

Drug-related AEs leading to dose delay of treatment group will be defined as any AEs leading to dose delay of treatment group with causal relationship to that treatment assessed as “Related” or missing.

The observation period of AEs for the tabulation by period will be from the date of the start of the administration of the investigational product to the date of 1) - 3) shown below, whichever comes first.

1) 30 days after the final administration of the investigational product and each chemotherapy (For 100-day safety window analysis, 100 days after the final administration of the investigational product and each chemotherapy)

2) The date of death or the last date of survival confirmation

3) The date of data cutoff

Definition of select AEs will be described in clinical study report.

For the items (6), (7) and (8), test results measured between the start date of the first administration of the investigational product or each chemotherapy and 30 days after the last dose of investigational product or each chemotherapy will be used for tabulation. As baseline, the value at the time point closest to the start date of the first administration of the investigational product or each chemotherapy during the screening period (including unscheduled) will be used for summarization. If the assessment date and start date of the first administration are the same date and if it is confirmed that the assessment was conducted before the first administration, the value on the date will be handled the data as baseline. On the other hand, if it is unknown that the assessment was conducted before the first administration, the value on the date will be handled the data as post dose of administration. Also, for the item (8), QTcF Interval will be calculated by the following equation.

$$QTcF = QT / RR^{0.33}$$

(2) Deaths

For subjects who died due to Grade 5 drug-related adverse events, the cause of death will be defined as ‘Drug toxicity’ as priority. Otherwise, the reason of death in outcome survey will be used for summary.

(3) Multiple events of adverse events

Analyses that take into account the multiple occurrences of a given adverse event will be conducted. This data will be presented as the rate per 100 person-years of exposure. The analyses will take into account all on-treatment events (allowing more than 1 event per subject) and the total exposure time. The person-year exposure will be computed as the sum over the subject’s exposure expressed in years where the exposure time is defined as

"(Min (30 days after last dose of study treatment (100 days for 100-day safety window) or date of death or last known date alive or data cutoff date － date of first dose of study treatment) + 1) / 365.25"

(4) Immune-mediated adverse events (IMAEs)

IMAEs occurring between the start date of the first administration of the investigational product or each chemotherapy and 100 days after the last dose of investigational product or each chemotherapy (100-day safety window) will be tabulated. Analyses for IMAEs will be limited to subjects who are included in SAF and received immunosuppressive medication for treatment of the event, with the exception of endocrine events that are defined as specific category of ADRENAL INSUFFICIENCY, HYPOTHYROIDISM/THYROIDITIS, HYPERTHYROIDISM, DIABETES MELLITUS and HYPOPHYSITIS, which will be included in the analysis regardless of treatment since endocrine events are often managed without immunosuppression. For analytical items (5), handling of data is the same as time to onset or resolution/resolving of selected AEs.

Definition of IMAEs will be described in clinical study report.

11.3 Analytical Methods

1) Adverse events, drug-related adverse events

Analyses specified in the Core SAP 8.1 except for 2) and the following analyses will be performed using 30-day / 100-day safety window. Note that a cutoff value of incidence rate used for summarizing AEs and drug-related AEs which incidence rate is greater than or equal to certain level will be set as 5%.

(1) Drug-related AEs and drug-related SAEs by the worst CTCAE grade (grade 1, 2, 3, 4, and 5) in each investigational product will be summarized by SOC and PT.

(2) AEs leading to discontinuation of investigational product and drug-related AEs leading to discontinuation of investigational product by the worst CTCAE grade (grade 1, 2, 3, 4, and 5) in each investigational product will be summarized by SOC and PT.

(3) Drug-related AEs and drug-related SAEs by the worst CTCAE grade (any grade, grade 3-4, and grade 5) in each investigational product will be summarized by SOC and PT.

(4) AEs leading to discontinuation of investigational product and drug-related AEs leading to discontinuation of investigational product by the worst CTCAE grade (any grade, grade 3-4, and grade 5) in each investigational product will be summarized by SOC and PT.

(5) Analyses specified in the Core SAP 8.1 3) will also be performed for SAEs, drug-related SAEs, AEs leading to discontinuation of treatment group and drug-related AEs leading to discontinuation of treatment group.

(6) AEs leading to discontinuation of 4 drugs and drug-related AEs leading to discontinuation of 4 drugs in each treatment group will be summarized by SOC and PT.

2) Deaths

Number of all deaths and deaths within 30 days/100 days after the last dose of investigational product or each chemotherapy as well as the frequency by the reason of death will be summarized by treatment group.

3) Multiple events of AEs and drug-related AEs

The total number and rate (exposure adjusted) of occurrences for all AEs and drug-related AEs in each treatment group will be summarized by SOC and PT using 30-day / 100-day safety window.

4) Select adverse events and drug-related select adverse events

Analyses specified in the Core SAP 8.2 and the following additional analyses will be performed using 30-day / 100-day safety window replacing ‘SOC’ with ‘specific category and subcategory’. For Core SAP 8.2 1), it will be tabulated by specific category and subcategory.

(1) Drug-related select AEs and serious drug-related select AEs by the worst CTCAE grade (grade 1, 2, 3, 4 and 5) in each investigational product will be summarized by specific category, subcategory and PT.

(2) Select AEs leading to discontinuation of investigational product and drug-related select AEs leading to discontinuation of investigational product by the worst CTCAE grade (grade 1, 2, 3, 4 and 5) in each investigational product will be summarized by specific category, subcategory and PT.

(3) Drug-related select AEs and serious drug-related select AEs by the worst CTCAE grade (any grade, grade 3-4 and grade 5) in each investigational product will be summarized by specific category, subcategory and PT.

(4) Select AEs leading to discontinuation of investigational product and drug-related select AEs leading to discontinuation of investigational product by the worst CTCAE grade (any grade, grade 3-4 and grade 5) in each investigational product will be summarized by specific category, subcategory and PT.

(5) Analyses specified in the Core SAP 8.2 2) will also be performed for serious select AEs, serious drug-related select AEs, select AEs leading to discontinuation of treatment group and drug-related select AEs leading to discontinuation of treatment group.

5) Time to onset or resolution/resolving of select adverse events and drug-related select adverse events

Analyses specified in the Core SAP 8.3 and 8.4 will be performed using 30-day /100-day safety window.

Additionally, following analyses will be performed for the time to resolution / resolving of any select AEs, any drug-related select AEs, CTCAE grade 3 or more select AEs and CTCAE grade 3 or more drug-related select AEs by specific category and subcategory using 30-day / 100-day safety window.

(1) Subjects who received immune modulating medication will be calculated.

(2) Subjects in whom events are resolved / resolving will be calculated.

(3) Subjects with immune modulating medication in whom events are resolved / resolving will be calculated.

6) Immune-mediated adverse events and drug-related immune-mediated adverse events

Same analyses specified in the Core SAP 8.2 and the following additional analyses will be performed using 100-day safety window replacing "select AEs" with IMAEs and ‘SOC’ with ‘specific category’. For Core SAP 8.2 1), it will be tabulated by specific category.

(1) Drug-related IMAEs and serious drug-related IMAEs by the worst CTCAE grade (grade 1, 2, 3, 4 and 5) in each investigational product will be summarized by specific category and PT.

(2) IMAEs leading to discontinuation of investigational product and drug-related IMAEs leading to discontinuation of investigational product by the worst CTCAE grade (grade 1, 2, 3, 4 and 5) in each investigational product will be summarized by specific category and PT.

(3) Drug-related IMAEs and serious drug-related IMAEs by the worst CTCAE grade (any grade, grade 3-4 and grade 5) in each investigational product will be summarized by specific category and PT.

(4) IMAEs leading to discontinuation of investigational product and drug-related IMAEs leading to discontinuation of investigational product by the worst CTCAE grade (any grade, grade 3-4 and grade 5) in each investigational product will be summarized by specific category and PT.

(5) Analyses specified in the Core SAP 8.2 2) will also be performed for serious IMAEs, serious drug-related IMAEs, IMAEs leading to discontinuation of treatment group and drug-related IMAEs leading to discontinuation of treatment group.

7) Time to onset or resolution/resolving of immune-mediated adverse events and drug-related immune-mediated adverse events

Same analyses described in 11.3 5) Time to onset or resolution/resolving of select adverse events and drug-related select adverse events will be performed using 100-day safety window replacing "select AEs" with IMAEs and “specific category and subcategory” with “specific category”.

8) Laboratory tests

Analyses specified in the Core SAP 8.5 1) and 2) will be performed using the data occurring between the start date of the first administration of the investigational product or each chemotherapy and 30 days after the last dose the investigational product or each chemotherapy.

9) Hormone Tests

Analyses specified in the Core SAP 8.7 1) will be performed using the data occurring between the start date of the first administration of the investigational product or each chemotherapy and 30 days after the last dose the investigational product or each chemotherapy.

10) 12-lead ECG

Analyses specified in the Core SAP 8.9 1) will be performed using the data occurring between the start date of the first administration of the investigational product or each chemotherapy and 30 days after the last dose the investigational product or each chemotherapy.

11.4 Subgroup Analyses for the Safety Endpoints

For each treatment group as well as for the stratification factors presented in 10.4 Subgroup Analyses for the Efficacy Endpoints, the overall summary table of any AEs, drug-related AEs, serious AEs and drug-related serious AEs by the worst CTCAE grade (any grade, grade 3-4, grade 5) will be presented by SOC and PT using 30-days safety window.

12 PATIENT REPORTED OUTCOMES

12.1 Analysis Sets

The ITT will be the analysis set.

12.2 Analytical Items and Data Handling

1) Analytical Items

(1) Patient with questionnaire completion

(2) EuroQol 5 Dimension (EQ-5D)

(3) EQ-5D index scores (Japan based scoring)

(4) Change from baseline of EQ-5D index scores (Japan based scoring)

(5) EuroQol visual analogue scale (EQ-VAS) scores

(6) Change from baseline of EQ-VAS scores

(7) LCSS questionnaire completion rate

(8) The LCSS disease-related symptom improvement rate at week 12

(9) Change from baseline of the average symptom burden scale index score at each LCSS assessment

2) Handling of data

(1) EQ-5D index scores (Japan based scoring)

EQ-5D questionnaire asks the patients to describe their current health state on 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with each dimension having 3 response choices (1 = no problem, 2 = some problem, and 3 = extreme problem). For example, if mobility = 2, self-care = 2, usual activities = 1, pain/discomfort = 1, and anxiety/depression = 1, then “Health State” would be “22111”.
(At least one 3 (N3), M2 (Mobility = 2), M3 (Mobility = 3), SC2 (Self Care = 2), SC3 (Self Care = 3), UA2 (Usual Activities = 2), UA3 (Usual Activities = 3), PD2 (Pain/Discomfort = 2), PD3 (Pain/Discomfort = 3), AD2 (Anxiety/Depression = 2), AD3 (Anxiety/Depression = 3))

If Full health “11111”, the value set is equal to 1. In other cases, the below mathematical representation is used.

Japan Value Set: 1 - 0.152 - 0.075MO2 - 0.418MO3 - 0.054SC2 - 0.102SC3 - 0.044UA2 - 0.133UA3 - 0.080PD2 - 0.194PD3 - 0.063AD2 - 0.112AD3

If there is any question for which the answer is not given for these 5 questions, the EQ-5D index score will also not be available.

(2) LCSS questionnaire completion rate

LCSS questionnaire completion rate is defined as the proportion of questionnaires actually received out of the expected number (i.e., the number of patients still on treatment or in follow up).

(3) The LCSS disease-related symptom improvement rate at week 12

Disease-related symptom improvement rate by Week 12 is defined as the proportion of randomized patients who had a 10 point or greater decrease from baseline in average symptom burden scale index score at any time between baseline and Week 12.

(4) The average symptom burden scale index score

The average symptom burden index score at each assessment is defined as the mean of the 6 symptom-specific questions of the LCSS.

(5) Time window for QOL evaluations

All questionnaires completed at baseline and on-study will be assigned to a time-point according to the windowing criteria in Table 12.2-1 Time windows for QOL evaluations.

Table 12.2-1 Time windows for QOL evaluations

Nominal Time-Point	Time Window
Screening Period	The response closest to the first administration of investigational product or each chemotherapy during screening period including unscheduled will be adopted.
Treatment Period	
Week 6 (Day 43)	
Week 12 (Day 85)	Day 2 to Day 64

Week 18 (Day 127)	Day 65 to Day 106
…Every 6 weeks thereafter while on treatment	Day 107 to Day 148
At the completion of the treatment period (at discontinuation)	Scheduled assessed time point (+21 days / -20 days)
Follow-up Period	At the completion of the treatment period (at discontinuation) or 28 days after completion of the treatment period incl. unscheduled.
·Follow-up 1 (((date at the completion of the treatment period or date at the 28 days after the completion of the treatment period, whichever comes last) +1) + 92)	(Max (date at the completion of the treatment period or date at 28 days after the completion of the treatment period incl. unscheduled) +1) to Day 137
·Follow-up 2 (((date at the completion of the treatment period or date at the 28 days after the completion of the treatment period, whichever comes last) +1) + 183)	(Max (date at the completion of the treatment period or date at 28 days after the completion of the treatment period incl. unscheduled) +1) + 138 to Day 229
·Follow-up 3 (((date at the completion of the treatment period or date at the 28 days after the completion of the treatment period, whichever comes last) +1) + 274)	(Max (date at the completion of the treatment period or date at 28 days after the completion of the treatment period incl. unscheduled) +1) + 230 to Day 320
·Follow-up 4 (((date at the completion of the treatment period or date at the 28 days after the completion of the treatment period, whichever comes last) +1) + 366)	(Max (date at the completion of the treatment period or date at 28 days after the completion of the treatment period incl. unscheduled) +1) + 321 to Day 457
·Follow-up 5 ((d(ate at the completion of the treatment period or date at the 28 days after the completion of the treatment period, whichever comes last) +1) + 548)	(Max (date at the completion of the treatment period or date at 28 days after the completion of the treatment period incl. unscheduled) +1) + 458 to Day 640
·Follow-up 6 (((date at the completion of the treatment period or date at the 28 days after the completion of the treatment period, whichever comes last) +1) + 731)	(Max (date at the completion of the treatment period or date at 28 days after the completion of the treatment period incl. unscheduled) +1) + 641 to Day 822

12.3 Analytical Methods

1) Patient with questionnaire completion

The percentage of patients with questionnaire completion in each treatment group will be summarized at each time point. Percentages will be calculated based on the number of patients assessed by treatment group at each assessment time point.

2) EQ-5D

The percentages of patients with no health problems, moderate health problems and extreme health problems will be calculated for each EQ-5D dimension at each time point by treatment group.

Percentages will be calculated based on the number of patients assessed by treatment group at each assessment time point for each EQ-5D dimension.

3) EQ-5D index scores (Japan based scoring)

(1) For EQ-5D index scores at each time point in each treatment group will be summarized using summary statistics. 95% CI for mean scores of EQ-5D index scores at each time point in each treatment group will also be calculated.

(2) For change from baseline of EQ-5D index scores at each time point in each treatment group will be summarized using summary statistics. 95% CI for mean scores of change from baseline of EQ-5D index scores at each time point in each treatment group will also be calculated.

4) EQ-VAS scores

(1) For EQ-VAS scores at each time point in each treatment group will be summarized using summary statistics. 95% CI for mean scores of EQ-VAS scores at each time point in each treatment group will also be calculated.

(2) For change from baseline of EQ-VAS scores at each time point in each treatment group will be summarized using summary statistics. 95% CI for mean scores of change from baseline of EQ-5D index scores at each time point in each treatment group will also be calculated.

5) LCSS questionnaire completion rate

LCSS questionnaire completion rate will be calculated and summarized by treatment group at each assessment point.

6) The LCSS disease-related symptom improvement rate

The disease-related symptom improvement rate at week 12 and its corresponding 95% exact CI will also be calculated by Clopper-Pearson method for each treatment group.

7) Change from baseline of the average symptom burden scale index score

Baseline and change from baseline of the average symptom burden scale index score at each LCSS assessment point will be summarized using summary statistics (N, mean, median, SD, the 25- and 75-percent points) by treatment group.

13 ANTI-DRUG ANTIBODY ANALYSIS

13.1 Analysis Sets

The ADA will be the analysis set.

13.2 Analytical Item and Data Handling

1) Analytical Item

Anti-ONO-4538 antibody up-regulated expression.

2) Handling of data

Refer to Core ADA-SAP section 3.

13.3 Analytical Methods

Refer to Core-ADA SAP section 5.1.

14 INTERIM STATISTICAL ANALYSIS

One interim analysis for PFS per IRRC will be performed in the ITT population to determine whether to stop the study early for superiority based on the stratified log-rank test with allocation factors (PD-L1 expression level, ECOG PS, and gender) as stratification factors when approximately 82.4% (n = 280) of the target number of PFS events over the entire study (n = 340) have occurred. To control the overall type I error rate at no more than 5% (two-sided), the significance levels used in the interim and final analyses will be calculated by the Lan-DeMets α spending function (O'Brien-Fleming type) based on the actual number of events.
During the interim analysis, the Independent Data Monitoring Committee (IDMC) will determine early efficacy stop. The details of the interim analysis are described separately in IDMC procedures and an interim analysis plan.

When the superiority of the ONO-4538 group over the placebo group is verified with PFS (per IRRC, primary definition) at the interim analysis or final analysis, analysis for OS (1st time) will be performed at that time. Additionally, analysis of OS (2nd time) will be performed based on a cut-off data which cut-off date is one year after a cut-off date of the interim analysis or final analysis.

The following analysis will be performed in 2nd time analysis of OS on the ITT.

1) The analysis in Core SAP section 5.1 1), 2), 3) and 5) will be performed.
2) The analysis in 10.4.3 Analytical Methods 1) will be performed.

15 BLINDED REVIEWS

15.1 Objectives

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

15.2 Analysis Sets

The ITT will be the analysis set.

15.3 Analytical Items and Data Handling

1) Analytical Items
   (1) Patient background factors
   (2) Subsequent anticancer therapy (surgery, radiotherapy, medical treatment)
   (3) Efficacy endpoints
      a) PFS (per IRRC, primary definition)
      b) PFS (per study site's investigator, primary definition)
      c) OS
      d) ORR (per IRRC)
   (4) Adverse events and drug-related adverse events
2) Handling of data

Each item will be analyzed according to the method defined above.

15.4 Analytical Methods

1) Frequency distributions and summary statistics will be calculated for section 8.2 1) Analytical Items (1) to (5) except for (4), and the classification in 8.3 Analytical Methods and Classification will be determined.
2) Details of subsequent anticancer therapy (surgery, radiotherapy, and medical treatment) will be summarized.
3) To verify the validity of the analysis method or handling of data, the number of events, censored and reason for censors of PFS will be tabulated. Additionally, the median PFS and the corresponding 95% CI by using Kaplan-Meier method will be estimated. 95% CI for the

median PFS will be calculated using the Brookmeyer and Crowley method based on a log-log transformed confidence interval for the survivor function.

4) To verify the validity of the analysis method or handling of data, the number of events and censors of OS will be tabulated. Additionally, the median OS and the corresponding 95% CI by using Kaplan-Meier method will be estimated. 95% CI for the median OS will be calculated using the Brookmeyer and Crowley method based on a log-log transformed confidence interval for the survivor function.
5) To verify the validity of the analysis method, ORR and the corresponding exact (Clopper-Pearson method) 95% CI will be calculated. As necessary, the missing condition will be verified.
6) Numbers of patients with AEs and drug-related AEs will be summarized as a whole, or by System Organ Class (SOC), Preferred Term (PT) and Grade.

16 TECHNICAL MATTERS

Refer to Core SAP section 12

16.1 SAS Programming in Analyses

1) Cochran-Mantel-Haenszel test

   The Cochran-Mantel-Haenszel test will be performed using the CMH option of the FREQ procedure of SAS.

   PROC FREQ DATA = [Analysis data set];

      TABLES [the stratification variable] * [treatment group] * [response variable] / CMH RISKDIFF (COMMON COLUMN=1) ALPHA = 0.05;

   RUN;

2) The accelerated failure time model (Weibull model)

   When estimating the acceleration factor using the accelerated failure time model (Weibull model) in 10.7 2), the following SAS sample program code of LIFEREG procedure will be used.

   PROC LIFEREG DATA = [Analysis data set];

      MODEL [survival time variable] = [treatment group] / DIST = WEIBULL;

      OUPUT OUT = [Output data set] CDF=CDF;

   RUN;

16.2 Imputation of Missing Value

16.2.1 Imputing the Date of Death and Date of Severity CTCAE Grade5 (AE grade 5 start date)

If the day of death is missing, “01” will be imputed for the day. After that, the derived date of death will be derived from the following conditions;

1) If the imputed date of death < the date of the last survival confirmed, the date of last survival confirmed will be the derived date of death.
2) If the imputed date of death >= the date of the last survival confirmed, the imputed date of death will be the derived date of death.

If the year or month of death will be missing, the date of the last survival confirmed will be the derived date of death.

16.2.2 Imputing Other Date

Define the derived minimum date as the earliest date within the possible date and the derived maximum date as the latest date within the possible date.

If day and month are missing, minimum date and maximum date to be derived is following;

1) Derived minimum date; 01 JAN
2) Derived maximum date; 31 DEC

If day is missing, minimum date and maximum date to be derived is following;

1) Derived minimum date; first date of that month
2) Derived maximum date; last date of that month

For AE start date (AE grade start date except for Grade 5) with completely missing, the first administration date of investigational product or each chemotherapy will be the derived date.

For AE start date (AE grade start date except for Grade 5) with partially missing (day and month are unknown or day is unknown), the derived date will be derived from the following conditions;

1) If the derived minimum date >= the first administration date of investigational product or each chemotherapy, the derived minimum date will be the derived date.
2) If the derived minimum date < the first administration date of investigational product or each chemotherapy <= the derived maximum date, the first administration date of investigational product or each chemotherapy will be the derived date.
3) If the first administration date of investigational product or each chemotherapy > the derived maximum date, the derived maximum date will be the derived date.
4) If the first administration date of investigational product or each chemotherapy is missing, the derived minimum date will be the derived date.

For the date of diagnosis of primary disease with partially missing (day and month are unknown), the derived date will be derived from the following conditions;

1) If the year of diagnosis of primary disease = the year of previous treatment for cancers (including history of surgery, radiotherapy, or medical treatment), the date performed previous treatment for cancers will be the derived date.
2) If the year of diagnosis of primary disease is not equal to the year of previous treatment for cancers, the derived minimum date will be the derived date.

17 REFERENCE

1) Royston P, Parmar MK. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. Stat Med. 2011;30:2409-2421.

2) Uno H, Claggett B, Tian L, et al. Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. J Clin Oncol . 2014;32:2380-2385.

3) Latimer NR, Henshall C, Siebert U, et al. Treatment Switching: statistical and decision making challenges and approaches. Int J Technol Assess Health Care. 2016;32:160-166.

18 CHANGES IN THE STATISTICAL ANALYSIS PLAN FROM THE STUDY SPECIFIC PROTOCOL

18.1 Changes in the Statistical Analysis Plan from the Study Specific Protocol

1) Safety analysis items

(1) Changes

Vital signs, Chest X-ray and ECOG Performance Status were deleted from safety analysis items

(2) Reason for changes

The above safety analysis items will be examined exclusively to secure the safety of subjects.

18.2 Changes in the Statistical Analysis Plan from the Statistical Analysis Plan version 1.0

1) 5. General methods

(1) Changes

Description of reader adoption for evaluation by IRRC was added.

(2) Reason for changes

It needs to clarify how to adopt the reader for evaluation by IRRC.

2) 6. Reliability of the study

(1) Changes

Description of handling data for important protocol deviations was added.

(2) Reason for changes

It needs to clarify how to handle important protocol deviations.

3) 8. Demographics and other baseline characteristics

(1) Changes

Description of analytical methods and classification was modified.

(2) Reason for changes

It needs to clarify analytical methods.

4) 9. Primary endpoint

(1) Changes

Description of categories to tabulate the censors was added.

(2) Reason for changes

It needs to define the categories to tabulate the censors.

5) 10. Efficacy secondary endpoint

(1) Changes

a) Handling of data about OS was added.

b) Stratification factors for subgroup analysis were defined.

c) Exploratory analysis for OS was added.

(2) Reason for changes

a) It needs to define the handling of data for last confirmed to be alive.

b) It needs to define the stratification factors and classification for subgroup analysis.

c) It needs to evaluate more details of the efficacy especially OS.

6) 11. Analysis of safety

(1) Changes

a) Definition of baseline for safety analysis items except for AEs was added.

b) Some analyses for time to resolution / resolving were added.

(2) Reason for changes

a) It needs to define the baseline for safety analysis items except of AEs.

b) It needs to evaluate more details of the safety especially Select AEs and IMAEs.

7) 12. Patient reported outcomes

(1) Changes

More details of time windows for QOL evaluations were added.

(2) Reason for changes

It needs to make clear the time windows for QOL evaluations.

8) 14. Interim Statistical Analysis

(1) Changes

The 2nd time analysis plan of OS were added.

(2) Reason for changes

It needs to evaluate the OS follow-up data.

9) 15. Blinded Reviews

(1) Changes

Description of analytical methods was modified.

(2) Reason for changes

It needs to clarify analytical methods.

10) 16. Technical matters

(1) Changes

Descriptions for SAS programming in analyses and imputation of missing date of the date of diagnosis of primary disease were added.

(2) Reason for changes

It needs to define the used SAS programming for 10.7 Exploratory Analysis and imputation of missing date of the date of diagnosis of primary disease.

19 APPENDIX

Definition of AE and Drug-related AE leading to discontinuation of treatment group / investigational product

- AEs and drug-related AEs leading to discontinuation of treatment group
  - Identify the treatment(s) discontinued last in treatment group (investigational product and chemotherapy) with their reason of discontinuation for AEs whose action taken is "Drug Withdrawn".
    - 1. Identify treatment(s)* with last date of withdrawal in treatment group.

      Max (date of withdrawal for investigational product, paclitaxel, carboplatin, bevacizumab)

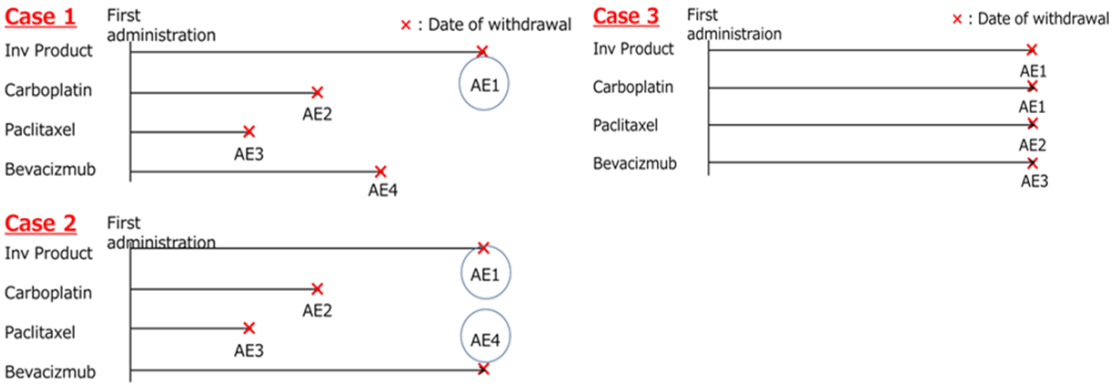
      * There may be more than one treatment.
    - 2. Identify AEs with action taken as "Drug Withdrawn" for the treatment(s) identified in 1. Corresponding AEs are identified as AEs leading to discontinuation of treatment group.
    - 3. Identify drug-related AEs with causal relationship to the investigational product or chemotherapy as “Related” or missing for the AEs identified in 2. Corresponding drug-related AEs are identified as drug-related AEs leading to discontinuation of treatment group.

Handling are shown in the following example cases.

In Case 1, AE1 is identified as the AE leading to discontinuation of treatment group which caused discontinuation of investigational product that is the treatment discontinued last in treatment group.

In Case 2, AE1 and AE4 are identified as the AEs leading to discontinuation of treatment group which caused discontinuation of investigational product and Bevacizumab that are treatment discontinued last in treatment group at the same date.

In Case 3, all AEs (AE1, AE2 and AE3) are identified as the AEs leading to discontinuation of treatment group because all the treatments are discontinued due to expression of AEs (AE1, AE2 and AE3) at the same date.



- AEs and drug-related AEs leading to discontinuation of investigational product
  - AEs leading to discontinuation of investigational product will be defined as any AEs with action taken with investigational product = “Drug Withdrawn”.
  - Drug-related AEs leading to discontinuation of investigational product will be defined as any AEs leading to discontinuation of investigational product to causal relationship with the investigational product assessed as “Related” or missing.