Title: A phase 3, randomized, controlled study of mFOLFOX6 + bevacizumab combination therapy versus mFOLFOX6 + panitumumab combination therapy in chemotherapy-naïve patients with RAS (KRAS/NRAS) wild-type, unresectable, advanced/recurrent colorectal cancer

NCT Number: NCT02394795

Statistical analysis plan Approve Date: 03-Feb-2022

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- Patient identifiers within the text, tables, or figures or in by-patient data listings.
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Phase III Randomized Controlled Efficacy and Safety Study of mFOLFOX6 + Bevacizumab versus mFOLFOX6 + Panitumumab in Patients with Chemotherapy-Naïve Unresectable Advanced Recurrent Colorectal Cancer with Wild-Type *RAS* (*KRAS/NRAS*)

(PARADIGM study)

PAnitumumab and **RA**S, **DI**agnostically-useful **G**ene **M**utation for mCRC

Statistical Analysis Plan

Ver. 1.0

Study Protocol Number: Panitumumab-3001

Revision History

Version	Date	Author	Major change	Remark
1.0	February 3, 2022	[redacted]	First edition	

Approved by

[redacted]

[redacted]

Takeda Pharmaceutical Company Limited.

[redacted]

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1. Objectives

This statistical analysis plan was prepared prior to the database lock to clearly specify in detail the statistical methodologies used for the statistical analyses in the clinical study titled, "Phase III Randomized Controlled Efficacy and Safety Study of mFOLFOX6 + Bevacizumab versus mFOLFOX6 + Panitumumab in Patients with Chemotherapy-Naïve Unresectable Advanced Recurrent Colorectal Cancer with Wild-Type *RAS* (*KRAS/NRAS*)" (hereafter, this study). This statistical analysis plan is based on the study protocol version 5 (dated February 1, 2022).

2. Rationale for Target Sample Size

The target number of subjects to be randomized are 400 in each group, and 800 in total. The rationale is as follows (extracted from the study protocol).

In clinical studies of mFOLFOX6 + bevacizumab in patients with chemotherapy-naïve advanced recurrent colorectal cancer, the median overall survival (OS) was as shown in Table 6.a. The median OS ranged from 21.0 to 30.9 months as reported in three studies (NO16966, HORIZON III, and SOFT) that all enrolled patients with advanced recurrent colorectal cancer with and without wild-type *KRAS*. In the PEAK study, a phase 2 randomized controlled study of mFOLFOX6 + panitumumab and mFOLFOX6 + bevacizumab as first-line therapy for unresectable advanced recurrent colorectal cancer, the median OS was 24.3 months in patients with wild-type *KRAS*. In the CALGB/SWOG80405 study, a phase III randomized controlled study of chemotherapy + cetuximab and chemotherapy + bevacizumab as first-line therapy for unresectable advanced recurrent colorectal cancer[28], the median OS was 26.9 and 29.0 months in FOLFOX-treated patients with wild-type *KRAS* and wild-type *RAS*, respectively.

Based on the above, a median OS of 29 months may be expected with mFOLFOX6 + bevacizumab in the current study of patients with unresectable advanced recurrent colorectal cancer with wild-type *RAS*.

Table 2.a Median OS with mFOLFOX6 + Bevacizumab in Previous Reports

Study	Phase	Number of subjects	OS (median in month)	*KRAS*
NO16966	Phase III	349	21.0	Wild/variant
HORIZON III	Phase III	713	21.3	Wild/variant
SOFT	Phase III	159	30.9	Wild/variant
PEAK	Phase II	143	24.3	Wild
PEAK	Phase II	82	28.9	Wild (including *NRAS*)
CALGB/SWOG80405 (FOLFOX group)	Phase III	409	26.9	Wild
CALGB/SWOG80405 (FOLFOX group)	Phase III	192	29.0	Wild (including *NRAS*)

In the FIRE-3 study of cetuximab (which has the same mechanism of action as panitumumab), a phase III study of FOLFIRI + cetuximab versus FOLFIRI + bevacizumab as first-line therapy for unresectable advanced recurrent colorectal cancer with wild-type *KRAS*, the median OS in patients with wild-type *RAS* was 33.1 and 25.6 months in the FOLFIRI + cetuximab group and the FOLFIRI + bevacizumab group, respectively. Nonetheless, the survival curves of these treatment groups were mostly similar until Month 18, and varied afterward. In the CALGB/SWOG80405 study, the survival curves also varied at a later stage, as in FIRE-3.

In the current study, if varied survival curves in the treatment groups are assumed from Month 18, as in the above discussion, the survival rates would be 75% in both treatment groups at Month 18 and 22% and 32% in the bevacizumab group and the panitumumab group, respectively, at Month 48, with the expectation of partially exponential distribution. Assuming that 800 subjects (400 subjects in each group) are enrolled at a constant rate for 24 months and followed for 36 months after the last subject enrollment, that 5% of subjects drop out, and a total of 570 events of death are accumulated, prolonged OS with FOLFOX + panitumumab versus FOLFOX + bevacizumab would be demonstrated with a power of approximately 80% in a log-rank test at a one-sided significance level of 0.025. Therefore, the planned number of subjects to be enrolled was 800 in total (400 in each group).

The sample size calculation was based on the assumption of median OS of 29 months in the bevacizumab group. Therefore, if OS is prolonged in the study overall, the target number of events may not be accumulated as planned in the study. Hence, it may be possible to recalculate the sample size in order to ensure the necessary number of events, depending on OS results in both treatment groups in periodic blinded monitoring reports.

[Revision of the main analysis of the primary endpoint, and powers after the revision] (Added in Version 2)

It is also assumed that 600 of 760 total subjects (assuming a 5% dropout rate of the original 800 subjects) will have left-sided disease, and that 400 death events will occur in left-sided subjects out of the target number of 570 events of death in subjects overall. In the revised study protocol, the primary objective is to demonstrate prolonged OS with mFOLFOX6 + panitumumab versus mFOLFOX6 + bevacizumab in at least one of the treatment groups, either subjects overall subjects or left-sided subjects. The powers for log-rank tests at a one-sided significance level of 0.0125 in each group of subjects overall and left-sided subjects are discussed below (Table 3), assuming hazard ratios of 0.68, 0.70, 0.72, and 0.74 in the mFOLFOX6 + bevacizumab group and the mFOLFOX6 + panitumumab group in left-sided subjects. In addition, the hazard ratio in the mFOLFOX6 + bevacizumab group was calculated based on the hazard ratio of the median survival in the TRICOLORE study (Table 1).

For right-sided subjects, the median survival in patients with right-side disease in the FIRE-3 study

was used (Table 2).

Efficacy by Primary Lesion Location in Previous Reports (Left-Sided Disease with Wild-Type *RAS*)

Study	CRYSTAL (Phase III)		PRIME (Phase III)		CALGB/SWOG 80405 (Phase III)		FIRE-3 (Phase III)		PEAK (Phase II)	
Treatment group	FOLFIRI	FOLFIRI +Cmab	FOLFOX	FOLFOX +Pmab	FOLFOX/FOLFIRI+Bmab	FOLFOX/FOLFIRI+Cmab	FOLFIRI +Bmab	FOLFIRI +Cmab	FOLFOX +Pmab	FOLFOX +Bmab
Number of subjects	138	142	159	169	152	173	149	157	53	54
OS (median in month)	21.7	28.7	23.6	30.3	32.6	32.9	28.0	38.3	43.4	32.0
HR	0.65		0.73		0.77		0.63		0.84	
95% CI	0.50-0.86		0.57-0.93		0.59-0.99		0.48-0.85		0.22-3.27	
P-Value	0.02		not reported		0.04		0.002		not reported	

Table 1. OS based on Median Survival in Study TRICOLORE

TRICOLORE	
Treatment group	mFOLFOX6 or CapeOX + bevacizumab
Number of subjects	243
OS (median in month)	33.6

Table 2. OS based on Median Survival in Treatment Groups in Study FIRE-3 (Right-Side Disease with Wild-Type *RAS*)

FIRE-3		
Treatment group	FOLFIRI + bevacizumab	FOLFIRI + cetuximab
Number of subjects	50	38
OS (median in month)	23.0	18.3

In subjects overall and left-sided subjects separately, a log-rank test will be performed at a one-sided significance level of 0.0125. A Monte Carlo simulation was performed, assuming that subjects are enrolled for 24 months and followed for 36 months after the last subject enrollment, and that 570 and 400 death events are accumulated in 800 subjects overall and 600 left-sided subjects, respectively. Based on these assumptions, a significant difference should be demonstrated in a log-rank test in at least one group, either subjects overall or left-sided subjects, at the following powers (Table 3).

Table 3. Results of Monte Carlo Simulation

Number of subjects	Significance level	Between-group HR in left-sided subjects	Power
760 (380/group) for overall subjects 600 (300/group) for left-sided subjects	One-sided 0.0125*	0.68	91%
		0.70	86%
		0.72	79%
		0.74	71%

* A significant difference between the mFOLFOX6 + bevacizumab group and the mFOLFOX6 +

panitumumab group will be demonstrated when a significant difference between these groups is demonstrated in either subjects overall or left-sided subjects.

[Significance levels and powers of the main analysis of the primary endpoint] (Added in Version 3)
The main analysis was revised as follows.
Main analysis:
For overall survival (OS) in left-sided subjects, a stratified log-rank test will be performed, where the stratification factors include all stratification factors other than study site. When the analysis in left-sided subjects demonstrates a significant difference between treatment groups, the stratified log-rank test will proceed with overall subjects as a hierarchical procedure.
Significance level of the main analysis:
Assuming that 420 death events have been accumulated in left-sided subjects at the time of the final analysis planned in 2021, the significance level in the final main analysis will be as discussed below.

The previous study protocol (version 2) planned to have interim analyses in both overall subjects and left-sided subjects. The information time and alpha used at the interim analyses as well as the resultant nominal significance levels planned for the final analyses were as follows.
Nominal Significance Level for Overall Subjects (Protocol Version 2):

Analysis	Percentage of events	Nominal significance level (one-sided)
Interim analysis	71.2%	0.00308
Final analysis	100.0%	0.01154*

Nominal Significance Level for Left-Sided Subjects (Protocol Version 2):

Analysis	Percentage of events	Nominal significance level (one-sided)
Interim analysis	70.5%	0.00293
Final analysis	100.0%	0.01159*

*: The nominal significance level planned for the final analyses in study protocol version 2, which was based on alpha used in the interim analysis in study protocol version 2.

In the revised study protocol, the final main analysis was changed to be performed in a hierarchical manner. A stratified log-rank test will be performed first in left-sided subjects and subsequently in subjects overall only when a significant difference was demonstrated. The nominal significance level of analysis in left-sided subjects is;
$(0.0125 - 0.00308) + 0.01159 = 0.02101$
That is, the nominal significance level will be 0.02101 (one-sided; equivalent to two-sided 0.04202).
The rationale is as follows. In the revised study protocol, the final main analysis was changed to be

performed in left-sided subjects only. Nonetheless, the interim analysis had already been performed in both subjects overall and left-sided subjects. Because it might be impracticable to explicitly calculate the correlation between the test statistics in left-sided subjects in the final analysis and the test statistics in overall subjects in the interim analysis, the value of 0.0125 − 0.00308 was adopted, despite it being a conservative value. To that value, the nominal significance level of 0.01159, which may be used in left-sided subjects, was added, yielding the significance level of the final main analysis.

Powers of main analysis:

The powers for log-rank tests at a one-sided significance level of 0.02101 (two-sided 0.04202) in left-sided subjects are discussed below. Assuming hazard ratios based on the median survival (33.6 months) in the mFOLFOX6 + bevacizumab group in the TRICOLORE study and 420 death events in left-sided subjects, a Monte Carlo simulation was performed to obtain the power for each log-rank test.

Table 2. Results of Monte Carlo Simulation

Number of subjects	Significance level	Between-group HR in left-sided subjects	Power
604 for left-sided subjects	One-sided 0.02101%	0.70	91%
		0.72	87%
		0.74	80%
		0.76	71%

3. Analysis Populations

The analysis populations are defined below.

3.1. Full Analysis Set (FAS)

The FAS will include enrolled subjects who were randomized, received at least one dose of the protocol treatment, and met the major eligibility criteria.

3.2. Safety Analysis Set (SAS)

The SAS will include all enrolled subjects who initiated the protocol treatment.

3.3. Efficacy Analysis Population

The efficacy analysis population is the FAS.

Additionally, the following two populations are defined for analysis of disposition of subjects, although not defined in the study protocol.

1) Consented subjects

This will include all subjects who gave informed consent.

2) All enrolled subjects

This will include all consented subjects who were actually enrolled in this study.

4. Disposition of Subjects

4.1. Analysis Variables

1) Disposition of subjects
2) Protocol deviations
3) Reason for protocol treatment discontinuation
4) Extent of exposure to the protocol treatment

4.2. Analysis Populations

Among the analysis variables in Section 4.1, analyses of variable 1 will be performed in consented subjects, analyses of variables 2 and 3 will be performed in all enrolled subjects, and analyses of variable 4 will be performed in the SAS.

4.3. Analysis Methods

1) Disposition of subjects

Disposition of subjects will be tabulated and presented in figures.

2) Protocol deviations

Protocol deviation in subjects will be tabulated.

3) Reason for protocol treatment discontinuation

Reasons for protocol treatment discontinuation in the study will be tabulated by reason.

4) Extent of exposure to the protocol treatment

For extent of exposure to the protocol treatment in the study, summary statistics of duration of treatment and number of treatment courses will be calculated for the protocol treatment overall and for each drug. Frequencies and proportions (%) of subjects who had dose reduction, dose interruption, or drug discontinuation will be calculated in each treatment group.

5. Demographic and Other Baseline Characteristics

5.1. Analysis Variables

1) Subject Characteristics

Variable	Nature of variable
Age at enrollment (year)	Continuous
Primary lesion location (right-side/left-sided/other) [see section 5.3 for the definitions]	Categorical
Sex (male/female)	Categorical
Age at enrollment (≤64 years/≥65 years)	Categorical
Primary organ(s) (single/multiple)	Categorical
Lesion(s) (cecum/ascending/transverse/descending/sigmoid/rectosigmoid/rectum) *	Categorical
Number of metastatic organs (0/1/≥2)	Categorical
Metastatic organ(s) (liver/lung/peritoneum/lymph node/bone/adrenal gland/skin/other)*	Categorical
Metastatic organ (liver only/other)	Categorical
Resection of the primary lesion (yes/no)	Categorical
Resection of the metastatic lesion (yes/no)	Categorical
Palliative colostomy (yes/no)	Categorical
Bypass surgery (yes/no)	Categorical
Radiotherapy (radical radiotherapy) (yes/no)	Categorical
Preoperative/postoperative adjuvant chemotherapy (preoperative/postoperative/pre+postoperative/never)	Categorical
RAS gene analysis	
Sampling site (primary lesion/liver/lung/lymph node/other)	Categorical
Sample type (biopsy/intraoperative)	Categorical
Histology (papillary adenocarcinoma/tubular adenocarcinoma [well/moderately-differentiated]/poorly-differentiated adenocarcinoma [solid/nonsolid]/mucinous adenocarcinoma/signet-ring cell carcinoma/adenocarcinoma [NOS]/other)	Categorical
Analytical method (RASKET/Other)	Categorical
KRAS result	
EXON2 codon12 (wild/variant/not determined or indeterminate)	Categorical
EXON2 codon13 (wild/variant/not determined or indeterminate)	Categorical
EXON3 codon59 (wild/variant/not determined or indeterminate)	Categorical
EXON3 codon61 (wild/variant/not determined or indeterminate)	Categorical
EXON4 codon117 (wild/variant/not determined or indeterminate)	Categorical
EXON4 codon146 (wild/variant/not determined or indeterminate)	Categorical
NRAS result	
EXON2 codon12 (wild/variant/not determined or indeterminate)	Categorical
EXON2 codon13 (wild/variant/not determined or indeterminate)	Categorical
EXON3 codon59 (wild/variant/not determined or indeterminate)	Categorical
EXON3 codon61 (wild/variant/not determined or indeterminate)	Categorical
EXON4 codon117 (wild/variant/not determined or indeterminate)	Categorical
EXON4 codon146 (wild/variant/not determined or indeterminate)	Categorical
Previous disease (yes/no)	Categorical
Concurrent disease (yes/no)	Categorical
ECOG PS at enrollment (0/1/2/3/4)	Categorical
Duration of follow-up (year)	Continuous

*: For those variables in which a subject may meet multiple categories, tabulation and analysis will be performed for each category.

5.2. Analysis Populations

Analyses will be performed in the efficacy analysis population and the safety analysis population.

5.3. Analysis Methods

1) Subjects' Characteristics

The above-mentioned variables of subject characteristics will be summarized with descriptive statistics. Minimums, medians, maximums, first quartiles, third quartiles, interquartile ranges, means, and standard deviations will be calculated for continuous variables, and frequencies and proportions will be calculated for categorical variables. In analyses to make summaries in the subsequent sections, variables will be analyzed descriptively in the same manner. For subject characteristics, analyses will be performed by primary lesion location (i.e., for subjects overall, left-sided subjects, and right-sided subjects) in each treatment group. The definitions of primary lesion location (left-sided/right-side/other) are as shown below.

- ✓ Left-sided: Single lesion or multiple lesions in the descending colon, sigmoid colon, rectosigmoid region, or rectum
- ✓ Right-sided: Single lesion or multiple lesions in the cecum, ascending colon, or transverse colon
- ✓ Other: Multiple primary lesions in both the right side and the left side.

6. Efficacy Results

6.1. Analysis Variables

1) Primary endpoint

Overall survival (OS)

2) Secondary endpoints

(1) Progression-free survival (PFS)

(2) Response rate (RR)

(3) Duration of response (DOR)

(4) Proportion of subjects with curative resection

3) Exploratory endpoints

[redacted]

6.2. Analysis Populations

All analyses will be performed in the efficacy analysis population. However, analyses may be performed in the safety analysis population if specified separately.

6.3. Analysis Methods

1) Primary endpoint

OS is defined as the time from the date of randomization (Day 1) until the date of death from any cause. Survival subjects will be censored at the last confirmed date of survival or the date of data cutoff, whichever is earlier.

For overall survival (OS) in left-sided subjects, a stratified log-rank test will be performed, where the stratification factors include all stratification factors other than study site. Kaplan-Meier curves of event-free survival will be presented for each treatment group. For survival time, quartiles will be calculated for each treatment group. For survival rates in Months 12, 24, 36, 48, and 60, point estimates will be calculated for each treatment group along with the confidence intervals (determined by the Greenwood formula; the same shall apply hereafter) and the confidence intervals at the significance level chosen for the analysis. Two-sided 95% confidence intervals will be calculated for reference. Moreover, a Cox model stratified using all stratification factors other than study site will be used to calculate between-group hazard ratios along with two-sided confidence intervals and the confidence intervals at the significance level chosen for the analysis. Two-sided 95% confidence intervals will be calculated for reference. Apart from the above, an unstratified log-rank test and an unstratified Cox model analysis will be performed for reference. When a significant difference is observed between treatment groups in any analysis in left-sided subjects, the analysis will proceed with overall subjects as a hierarchical procedure. That is, when a significant difference is demonstrated between treatment groups in any analysis in left-sided subjects, the same analysis will be performed for subjects overall. In these analyses, significance levels and confidence coefficients will be as follows.

[Significance level]

0.02101 (two-sided, 4.202%) for left-sided subjects

0.025 (two-sided, 0.05) for overall subjects

[Confidence coefficient]

95.798% (two-sided) for left-sided subjects

95% (two-sided) for overall subjects

If non-normal distribution is indicated for any major covariates, a Cox model to correct the confounding will be used to calculate between-group hazard ratios along with the two-sided 95% confidence intervals.

2) Secondary endpoints

Analyses (1) to (4) below will be performed in both subjects overall and left-sided subjects.

(1) Progression-free survival (PFS)

PFS is defined as the time from the date of randomization (Day 1) until the date of progression of disease (PD) assessment or the date of death from any cause, whichever is earlier. Survival subjects without PD assessment will be censored on the last confirmed date of no clinical progression (the last confirmed date of progression-free survival). (The absence of progression may be confirmed clinically in an outpatient setting and not necessarily confirmed by imaging or sample analysis. It is not allowed to confirm a subject's status simply via telephone. For subjects for whom the presence or absence of progression was confirmed in another hospital to which the subject had been transferred or referred, the written medical information with rationale for the diagnosis will be obtained and retained. In this case also, it is not allowed to confirm a subject's status simply via telephone). Survival subjects without PD assessment, who became eligible for curative resection during the protocol treatment, will be censored on the last date of no PD as confirmed by predefined preoperative imaging (the last confirmed date of progression-free survival).

Kaplan-Meier curves of progression (event)-free survival will be presented for each treatment group. For survival time, quartiles will be calculated for each treatment group. For progression-free survival rates in Months 12, 24, 36, 48, and 60, point estimates will be calculated for each treatment group along with two-sided 95% confidence intervals. A stratified log-rank test will be performed, where the stratification factors include all stratification factors other than study site. Moreover, a stratified Cox model, where the stratification factors include all stratification factors other than study site, will be used to calculate between-group hazard ratios along with two-sided 95% confidence intervals. Apart from the above, an unstratified log-rank test and an unstratified Cox model analysis will be performed for reference.

(2) Response rate (RR)

Response rate (RR) is defined as the proportion of subjects with CR or PR as best overall response.

For subjects in the FAS with an evaluable lesion, frequency analyses will be performed to calculate point estimates along with two-sided 95% confidence intervals for each treatment group. Moreover, a Cochran-Mantel-Haenszel test will be performed, where the stratification factors include all stratification factors other than study site. For between-group differences (Group P - Group B), point estimates along with two-sided 95% confidence intervals will be calculated.

(3) Duration of response (DOR)

Duration of response (DOR) is defined as the time from the date of first confirmed complete response (CR) or partial response (PR) until the date of PD assessment or death from any cause, whichever is earlier. Survival subjects without PD assessment will be censored on the last date of no PD as confirmed by predefined imaging (the last confirmed date of progression-free survival). Survival subjects without PD assessment, who became eligible for curative resection during the protocol treatment, will be censored on the last date of no PD as confirmed by predefined preoperative imaging (the last confirmed date of progression-free survival).
For subjects with response in the FAS, Kaplan-Meier curves of event-free survival will be presented for each treatment group. For survival time, quartiles will be calculated for each treatment group. For survival rates until Months 12, 24, 36, 48, and 60, point estimates will be calculated for each treatment group along with two-sided 95% confidence intervals.

(4) Proportion of subjects with curative resection

This is defined as the proportion of subjects who had curative resection (complete resection = R0 resection).
For each treatment group, frequency analysis will be performed to calculate point estimates along with two-sided 95% confidence intervals. For between-group differences (Group P - Group B), point estimates along with two-sided 95% confidence intervals will be calculated.

3) Exploratory Endpoints

[redacted]

[redacted]

[redacted]

8. Safety Analyses

8.1. Analysis Variables

1) Adverse events

8.2. Analysis Populations

Safety analyses will be performed in the safety analysis population.

8.3. Analysis Methods

1) Treatment-Emergent Adverse Events (TEAEs)

A TEAE is defined as an adverse event that occurred after the first dose of the protocol treatment and during the protocol treatment.

For each treatment group, the numbers of subjects with TEAEs, the numbers of TEAEs, and the incidences of TEAEs will be calculated by event and by severity. Adverse events will be coded using the system organ classes (SOCs) and preferred terms (PTs) of the MedDRA for analyses. In calculating the numbers of subjects with TEAEs, a subject who had the same event more than once will be counted as 1 subject in the applicable category or term. In calculating the numbers of TEAEs, an event that occurred in the same subject more than once will be counted as 1 event in the applicable category or term for every time it occurred. In calculating severity, a subject who had the same event more than once will be counted as 1 subject in the severest category. The MedDRA version used will be the latest version available at the time of database lock. The above analyses will be performed for the following variables.

- TEAEs related to any drug of the protocol treatment
- TEAEs leading to discontinuation of the protocol treatment
- Serious TEAEs related to the protocol treatment

9. General Specification

1) Significance levels in testing will be 0.05 (two-sided) in principle. For confidence intervals, two-sided 95% confidence intervals will be calculated unless otherwise specified.
2) In listing, units and digits used will be those as recorded. In tabulation, the number of digits will be as specified below. Proportions (%) will be given to the first decimal place.
   - Minimum and maximum: Reference number of digits
   - Mean, median, first quartiles, third quartiles, and interquartile ranges: Reference number of digits + 1 digit
   - Standard deviation and confidence interval: Reference number of digits + 2 digits

   The reference numbers of digits are those defined for or reported (shown) in case report forms. Nonetheless, some values, including confidence intervals of hazard ratios, may be shown with an appropriate number of digits.
3) The following formulae will be applied in calculating year, month, week, and day.
   1 year = 365.25 days
   1 month = 30.4375 days
   1 week = 7 days

10. Data Handling

1) Missing Data
   No imputation of missing data will be performed in principle.
2) Quantitation Limit
   Laboratory values reported as "quantitation limit" will be deemed values of the quantitation limits for analyses.

11. Interim analysis

An interim analysis is planned in this study, as detailed in the study protocol and in the interim analysis plan.

12. Software

Analyses will be performed and figures will be created using the following software.

1) Microsoft Office Excel 2016 or later
2) SAS version 9.3 or later, or R version 3.6.2 or later

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