Certain information within this clinical study report has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
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If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

Note; This document was translated into English and the language in original document was Japanese.

SAPPHIRE study

(A phase II randomized study comparing the efficacy and **sa**fety of mFOLFOX6 + **p**anitumumab combination therapy and 5-FU/LV + **p**anitumumab combination t**h**erapy **i**n the patients with chemotherapy-naïve unresectable advanced **re**current colorectal carcinoma of *KRAS* wild-type after 6 cycles of combination therapy with mFOLFOX6 + panitumumab.)

Statistical Analysis Plan

Version 6.0

Created By:

[redacted]

Takeda Pharmaceutical Company Limited

[redacted]

Date of Creation: 20 December 2017

Table of Contents

1. History of creation and revision

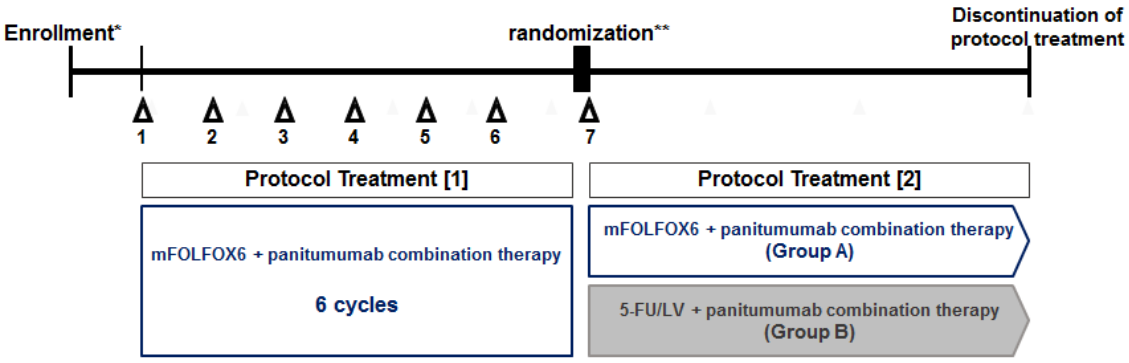
Version	Approval Date	Created By	Reason for Revision
1.0	October 8, 2014	[redacted]	Not applicable due to being the first version
1.1	November 25, 2014	[redacted]	Details for additional analyses were added
2.0	February 27, 2015	[redacted]	5.1. Data Handling (1) Description of continuous data was deleted; (2) Adverse event (AE) grade handling and final grade definitions were clarified. 7.1.2. Analysis of Demographics and Other Baseline Characteristics, and 7.1.3. Treatment Compliance: added Safety Data Analysis Set (SAS) to both sections. 7.1.3.1. Treatment Completion Status: added definition of relative dose intensity (RDI). Combined sections 7.1.3.2. Reasons for Discontinuation and 7.1.3.3. Reasons for Discontinuation and Other Details. 7.2.1. Primary Endpoint and Analysis Methods: added handling rules for patients without progression confirmed by imagining, and without disease progression beyond 9 months; added that the difference in PFS rate between treatment groups will be calculated as part of Primary Endpoint analysis. 7.2.2. Secondary Endpoints and Analysis Methods: added an analysis adjusting for stratification factors as explanatory variables in a Cox regression model. 7.3. Safety Analysis: (a) additional inclusion of two types of AE analyses that will be conducted, for AEs that occurred after enrolment (Set 1) and for AEs that after randomization (Set 2); (b) amended the AE tables to be consistent with the AE entry Form. 7.4. Sensitivity Analysis: inclusion of additional analysis to be performed when patients are censored at start of subsequent therapy.
3.0	April 18, 2017	[redacted]	6.4. In the definition of Full Analysis Set (FAS), added that patients in violation of ICH-GCP will

			be excluded. 7.1.2. Inclusion of additional analyses. 7.1.3.1. Inclusion of graphs to be created. 7.1.2. Clarified criteria for determining the absence of disease progression at 9 months after randomization. Specifically, patients without image data will be handled as follows: "Patients without image data at 9 months after randomization will be treated as progression free if the absence of progression is confirmed by imaging immediately before and after 9 months. Patients who discontinue treatment before 9 months, withdraw their consent, or become intractable, will be included in the denominator, but will not be treated as progression free." 7.2.2. Specified study site as a stratification factor. 7.2.3. Clarified that performance status (PS) at the the seventh cycle is defined as PS at time of randomization. 7.2.4. Added analysis according to primary tumor site to subgroup analysis. 7.2.5. Specified the handling of censoring for analysis of oxaliplatin (OXA) and panitumumab duration. 7.3.1. Added methods for tabulating AEs.
4.0	August 1, 2017	[redacted]	4. Clarified that SAS is a subset of FAS. Added a citation to a separate document entitled "Inclusion and Exclusion Criteria and Data Handling Rules" to definition of analysis sets and handling rules for analyses of patient data within each analysis set. 7.1.2. (1) Added "others" to the classification of primary tumor site. Defined the proximal 2/3 of the transverse colon as the right side, and the distal 1/3 of the transverse colon as the left side. Added a handling rule for patients where the primary tumor site exists astride the right and left sides. 7.3.1 Revised "Frequency table of non-serious AEs with incidence rate of ≥5% in either

			treatment group" to "Frequency table of non-serious AEs with incidence rate of >5% in either treatment group." 7.4.2. Revised start date to Protocol treatment [1] start date. 7.4.3. Revised start date to Protocol treatment [1] start date.
5.0	November 10, 2017	[redacted]	7.2.1 Added the decision by SAPPHIRE study steering committee meeting on February 22, 2017 on the handling of patients without imaging data at 9 month, but who had imaging data from 3 days earlier than allowance.
6.0	December 20, 2017	[redacted]	The following analyses were added as a new section, 7.5. 7.5.1 Creation of waterfall plot 7.5.2 Depth of Response (DpR) evaluation 7.5.3 Early tumor shrinkage (ETS) evaluation 7.5.4 Additional definitions for right and left classification of primary tumor sites

2. Purpose of Statistical Analytical Plan

"A phase II randomized study comparing the efficacy and safety of mFOLFOX6 + panitumumab combination therapy and 5-FU/LV + panitumumab combination therapy in patients with chemotherapy-naïve, unresectable, advanced recurrent colorectal carcinoma of *KRAS* wild-type after 6 cycles of combination therapy with mFOLFOX6 + panitumumab Statistical Analysis Plan" specifies the plan of the final statistical analysis of "A phase II randomized study comparing the efficacy and safety of mFOLFOX6 + panitumumab combination therapy and 5-FU/LV + panitumumab combination therapy in patients with chemotherapy-naïve unresectable, advanced, recurrent colorectal carcinoma of *KRAS* wild-type after 6 cycles of combination therapy with mFOLFOX6 + panitumumab Clinical Study Implementation Plan".



*: Perform the first administration within 14 days after enrollment.
**: If possible, conduct immediately before administration of the 7th cycle.

3. Time Point of Analysis

This analysis will be conducted when patient enrolment has been completed and when all enrolled patients have completed evaluation at 9 months post-randomization (initial analysis), and when all observations are complete (final analysis).

4. Population for Analysis

In this study, there will be two analysis sets, referred to as the Full Analysis Set (FAS) and the Safety Data Analysis Set (SAS). The FAS is defined as “all randomized patients, excluding patients in violation of ICH-GCP”, and the SAS is defined as “all patients who receive at least one protocol treatment following randomization”. In addition, all patients enrolled in this study are defined as “all enrolled patients”. However, if the same patient is re-enrolled after discontinuing the study before receiving a treatment, the patient will be treated as one case and will not be duplicated.

Prior to database lock, the statistical analysis officer and analyst will confirm the validity of the handling rules for analyses of patient data within each analysis set (see Attached document, “Inclusion and Exclusion Criteria, and Data Handling Rules”), and will provide any supplementary information required regarding the handling of issues not specified in the planning stage, prior to finalizing the statistical analysis plan.

5. Data Handling

5.1. Handling of Patient Data

(1) Clinical laboratory test values, and subjectively or objectively observed adverse events (AEs)

AEs described in the AE Form will be renamed according to MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT). “Peripheral neuropathy” includes AEs in the PT “peripheral neuropathy” in the Standardized MedDRA Query, and “skin disorders” includes AEs

within the SOC “Skin and subcutaneous tissue disorders” or PT “paronychia”.

(2) AE grading

If more than one occurrence of an AE is recorded in the same patient, the highest grade and earliest onset date will be utilized for analysis of each AE.

(3) Missing or unused data

Unless otherwise specified for individual analyses, missing data will not be interpolated. In addition, if data are removed, the relevant data and reasons for removal will be clarified in a listing. However, handling of patients without events for progression-free survival (PFS), overall survival (OS), time to treatment failure (TTF), and performance status (PS) maintenance period is described in Section 7.2.5.

5.2. Significant Digits

Unless otherwise specified for individual analyses, the proportion (%) of the frequency distribution will be rounded to one decimal place.

For descriptive statistics, both the mean and standard deviation will be rounded to one less digit than that of the original data.

P-value will be expressed to four decimal places by rounding the fifth decimal place. However, when the p-value is less than 0.0001, it will be expressed as “p <0.0001.” The hazard ratio (HR) and its 95% confidence interval will be expressed to two decimal places by rounding the third decimal place.

6. Statistical Software

SAS Version 9.4 (SAS Institute, Cary, NC, USA) will be used for the statistical analysis.

7. Statistical Methodology

7.1. Patient Analysis

7.1.1. Eligibility and Analysis Sets

All enrolled patients, patients allocated to treatment arms, the breakdown of analysis sets, as well as patients who were excluded from the analysis sets and the reasons for exclusion, will be compiled into a CONSORT (**CON**solidated **S**tandards **O**f **R**eporting **T**rials) diagram.[1]

7.1.2. Analysis of Demographics and Other Baseline Characteristics

For the key patient demographics and baseline characteristics, the following values will be tabulated for each treatment group, and all the groups combined. Values for all enrolled patients,

FAS and SAS will be tabulated.

(1) Discrete data

Frequency distribution and proportion (%) calculated using the target population as the denominator will be reported for discrete data. Items to be tabulated are as follows.

- Age (≥70 years or <70 years), gender, histologic type at Stage IV diagnosis (including: well-differentiated adenocarcinoma [papillary adenocarcinoma and tubular adenocarcinoma (well differentiated type)]; moderately differentiated adenocarcinoma [tubular adenocarcinoma (well differentiated type)]; poorly differentiated adenocarcinoma [poorly differentiated adenocarcinoma (solid type) or poorly differentiated adenocarcinoma (non-solid type)]; mucinous carcinoma; signet-ring cell carcinoma, etc.), history of previous surgery (yes or no), history of radiotherapy (yes or no), history of preoperative and/or postoperative adjuvant chemotherapy (yes or no), number of metastatic sites (0, 1, or ≥2), site of metastases (liver, lung, peritoneum, distant lymph nodes, bone, adrenal glands, skin, etc.), ECOG PS at enrolment, single or multiple tumor sites, the site of the primary lesion (right side, left side, or other; "right side" includes cecum, ascending colon, proximal 2/3 of the transverse colon; "left side" includes distal 1/3 of the transverse colon, descending colon, sigmoid colon, recto-sigmoid and rectum; "other" is defined as unknown lesion location, etc. If there are multiple primary lesions across right side, left side, or other, the steering committee will decide the location for each patient).
- Treatment status for Protocol treatment [1] (presence or absence of any dose reduction, presence or absence of any dose delays), clinical laboratory test values and observations during Protocol treatment [1] (Grade 1, 2, or ≥3), peripheral neuropathy (Grade 1, 2 or ≥3), RECIST category at randomization (complete response [CR], partial response [PR], or stable disease [SD]), *NRAS* and *KRAS* mutation status (mutation positive or wild type), curative resection during Protocol treatment [1] (yes or no) (for all enrolled patients), reasons for discontinuation of Protocol treatment [1] (for all enrolled patients), ECOG PS at the seventh cycle.

(2) Continuous data

Descriptive statistics (number of patients, mean, median, standard deviation, minimum value, maximum value) will be reported for continuous data.

- Age

7.1.3. Treatment Status

7.1.3.1. Treatment Completion Status

The number of completed treatments in the FAS and SAS will be tallied according to treatment

group, for cycles designated for each drug (up to cycle 6, cycles 7, 8, 9, 10, 11, and 12), and frequency distribution with proportion (%) will be calculated using the number of patients in each analysis set as the denominator. In addition, for cycles designated for each drug (up to cycle 6, cycle 7, 8, 9, 10, 11, and 12), the cumulative dose as well as the relative dose intensity (RDI) will be calculated for each drug; the changes in mean RDI (%) with time will be plotted in a graph. Descriptive statistics will be calculated for total cumulative dose and total RDI over all 12 cycles, including the number of patients, mean, median, standard deviation, minimum value, and maximum value. Total cumulative dose and total RDI will be calculated in two ways: including the Protocol treatment period [1]; or from randomization (and excluding treatment period for Protocol treatment [1]). RDI will be derived using the following formula.

RDI (%) = (actual dose / first scheduled dose) × (14 / actual number of days taken to complete the specified cycle) × 100

Total RDI (%) = (actual total dose / expected total dose) × (expected total number of cycle days[†] / actual total number of cycle days[‡]) × 100

[†]14 × 12 cycles when protocol treatment [1] is included, 14 × 6 cycles if not.

[‡]Actual total number of cycle days:

- when including Protocol treatment period [1], defined as (start date of drug administration for the final cycle) - (start date of drug administration for the 1st cycle) + 14
- when not including Protocol treatment period [1], defined as (start date of drug administration for the final cycle) - (start date of drug administration for the 7th cycle) + 14

7.1.3.2. Reasons for Discontinuation

For the FAS and SAS, reasons for discontinuation for each treatment group will be collected for each cycle (up to cycle 6, cycles 7, 8, 9, 10, 11, and 12), and the proportion (%) calculated using the number of patients in each analysis set as a denominator. For patients whose reasons for discontinuation is “other”, the reasons for discontinuation by treatment completion status will be summarized and tabulated.

7.1.3.3. Dose Reduction Status

For the FAS and SAS, the frequency distribution and proportion (%) of patients who required dose reduction will be tabulated according to drug and treatment group. Similarly, the and proportion (%) of patients who undergo dose reduction at each specified cycles (up to cycle 6, cycle 7, 8, 9, 10, 11, and 12) will be calculated, and the frequency distribution according to reasons of dose reduction will be calculated.

7.1.3.4. Follow-up Status

For the FAS and SAS, the quartiles of follow-up period will be calculated either according to treatment groups, or all treatment groups combined. The follow-up period is calculated from the day of randomization to the end of follow-up. For calculating quartiles, the reverse Kaplan-Meier method will be used.[2]

7.2. Efficacy Analysis

7.2.1. Primary Endpoint and Analysis Methods

〔Primary endpoint〕

- PFS rate at 9 months

The primary endpoint is PFS rate at 9 months, defined as the proportion of subjects who are alive and for whom progression of disease at 9 months after randomization was absent. The presence or absence of progression will be evaluated based on information from diagnostic imaging, clinical decision, or survival up to 9 months after randomization. Patients without image data at 9 months after randomization will be treated as progression free if the absence of progression is confirmed by imaging immediately before and after 9 months. Patients who discontinued treatment before 9 months, withdraw their consent, or become intractable, will be included in the denominator but will not be treated as progression free.

In the SAPPHIRE study Steering Committee meeting on February 22, 2017, it was determined that a patient (case no. 1044-003) without image data at 9 months but with imaging data from 3 days before the allowance date, that the latter image data will be used as the 9-month imaging data. The minutes of the meeting are attached for reference.

Disease progression is defined as follows.

[Definition of Disease Progression]

Disease worsening includes both progressive disease (PD), based on diagnostic imaging and defined by RECIST v1.1, as well as clinical deterioration, defined as progression of the original disease that cannot be confirmed by diagnostic imaging. If disease worsening is determined based on diagnostic imaging, the examination date on which the imaging test was performed is to be designated as the worsening date, and if disease worsening is determined based on clinical deterioration, the date on which clinical deterioration was determined is to be designated the worsening date. In cases in which tumor diameter becomes extremely small but PD is determined according to RECIST, even if the patient is clearly not deteriorating clinically, priority will be given to determination of PD according to RECIST and the patient will be deemed as having disease worsening (clinical judgement will be prioritized as to whether protocol treatment should be

continued). Conversely, in patients who are not determined as PD according to RECIST but who are clearly deteriorating clinically, clinical judgement will be prioritized and the patient will be deemed as having disease worsening.

Censoring will occur on the final date that PD or clinical deterioration was confirmed to be absent (final PFS confirmation date) for surviving subjects without disease worsening (confirmation of lack of progression by imaging or biopsy is not required, and may be done via clinical examinations during outpatient visits, etc; communication by telephone is not acceptable). If patients received additional subsequent treatment having discontinued protocol therapy due to e.g. toxicity or patient refusal, PFS events and censoring will be handled in the same way; i.e. patients will not be censored at the time of treatment discontinuation or the start of subsequent treatment.

[Primary analysis]

The following analysis will be performed using the FAS.

For each treatment group, the total number of patients with, without, or unknown progression of disease at 9 months will be tabulated, and the proportion of patients without progression will be calculated as the PFS rate at 9 months. The numerator is the number patients without progression, and the denominator is the total number of patients with, without, or unknown progression of disease. A binomial test will be performed on the PFS rates at 9 months for each treatment group under the null hypothesis that "the true PFS rate is less than the threshold rate of 30% and the treatment judged as ineffective." The significance level in the main analyses shall be 10% on each side. For interval estimation, a two-sided 80% confidence interval (CI) using the Agresti-Coul method will be used.[3] In addition, a two-sided 95% CI of the intergroup differences (group B - group A) of PFS rate at 9 months will be calculated using the method of Agresti-Caffo.[4]

7.2.2. Secondary Endpoints and Analysis Methods

[Secondary endpoints]

- Progression-free survival (PFS)

PFS is defined as the time from date of randomization (day 0) to the date of disease progression or death from any cause, whichever is earlier. The definition for disease progression is described in 7.2.1.

[Analysis method]

For the FAS, PFS curves for each treatment group will be developed using the Kaplan-Meier method, and quartiles and 95% CI on both sides will be calculated. The 95% CI of the quartiles of PFS will be calculated using Log-Log transformation by the method of Brookmeyer and Crowley.[3] For reference, the hazard ratio (HR) for group B versus group A and the 95% CI on both sides based

on the Cox regression model will be calculated, and a log-rank test will be performed. Analysis will also be conducted adjusting for stratification factors other than study site as variables in the Cox regression model, and the adjusted HR for group B versus group A and the 95% CI on both sides will be calculated.

- Overall Survival (OS)

OS is defined as the time from the date of randomization (day 0) to the date of death by any cause.

[Analysis method]

Analyses similar to those specified for PFS will be performed for OS using the FAS.

- Response Rate (RR)

RR is defined as the proportion of patients who have a best overall response of a CR or a PR according to RECIST v1.1 after randomization. Quality of response per RECIST, from highest to lowest, is in the order of CR, PR, SD, PD, and inability to evaluate.

[Analysis method]

RR and 95% CI on both sides will be calculated for each treatment group using the FAS. The differences in RR between the treatment groups, i.e. group B – group A, and the 95% CI on both sides of difference in RR will also be calculated. For calculating the CI of the RR, the Agresti-Coull method will be used; for calculating the CI of the difference in RR between treatment groups, the Agresti-Caffo method will be used.[6]

- Time to Treatment Failure (TTF)

TTF is defined as the time from the date of randomization (day 0) to the date on which a decision to discontinue protocol treatment was made, disease worsening was acknowledged, or death due to any cause, whichever occurred earliest.

[Analysis method]

Analyses similar to those specified for PFS will be performed for TTF using the FAS.

7.2.3. Other Efficacy Evaluation Endpoints

- Performance Status (PS) Maintenance Period

The PS maintenance period is defined as the time from the date of randomization (day 0) to the date on which PS worsened by 1 point or more, discontinuation of protocol treatment, disease worsening was acknowledged, or death due to any cause, whichever occurred earliest. However, PS

at the seventh cycle is regarded as being equivalent to PS at randomization.

[Analysis method]

Analyses similar to those specified for PFS will be performed using the FAS.

- Duration of oxaliplatin (OXA) treatment in mFOLFOX6 + Panitumumab Group

Duration of OXA is defined as the time from the date of randomization (day 0) to the date of discontinuation of OXA from protocol treatment for patients enrolled in Group A, disease worsening was acknowledged, or death due to any cause, whichever occurred earliest.

[Analysis method]

Analyses similar to those specified for PFS will be performed using the FAS.

- Duration of Panitumumab Treatment in Both Groups

Duration of panitumumab treatment is defined as the time from the date of randomization (day 0) to the date of discontinuation of panitumumab, disease worsening was acknowledged, or death due to any cause, whichever occurred earliest.

[Analysis method]

Analyses similar to those specified for PFS will be performed using the FAS.

7.2.4. Predefined Subgroup Analysis

In this study, analyses described in sections 7.2.1 and 7.2.2. will be carried out on the following subgroups.

- Subgroup analysis based on *NRAS/KRAS* status (‘mutant’ or ‘wild type’)
- Subgroup analysis based on stratification factors other than study site: age at the time of registration (≥20 years and ≤69 years or ≥70 years), number of metastatic sites at the time of registration (0 and 1 or ≥2), RECIST response status at randomization (CR, PR or SD)
- The location of the primary lesion (‘right side’, ‘left side’, or ‘other’)

7.2.5. Method of Data Conversion and Handling of Missing Data

In the PFS, OS and TTF analyses, patients who do not develop events described in 7.2.2. and 7.2.3. by the end of the study are censored.

The date of censorship is defined as the final PFS confirmation date confirming the absence of disease progression in the analysis of PFS, the final survival confirmation date in the analysis of the OS, the final protocol treatment start date in the analysis of TTF, the final ECOG PS confirmation

date for analysis of PS maintenance. In addition, in the analysis of treatment duration for OXA and panitumumab, censorship will occur on completion of study if treatment is continued beyond the study; the date of censorship is defined as the first day of drug administration of the last cycle of treatment.

7.3. Safety Analysis

AEs occurring after enrolment (Set 1) or after randomization (Set 2) will be tabulated using the SAS.

7.3.1. Treatment-emergent AEs (TEAEs)

The frequency and proportion for the following items will be reported for each treatment group.

- Frequency of each TEAE and the total sum of frequencies
- Frequency of TEAEs having a causal relationship (“related”) with any study drug
- Frequency of TEAEs having a causal relationship (“related”) with each study drug
- Frequency of TEAEs requiring discontinuation (“discontinue administration") of any study drug
- Frequency of TEAEs requiring discontinuation (“discontinue administration") of each study drug
- Frequency of all TEAEs by severity
- Frequency of TEAEs having a causal relationship (“related”) with any study drug by severity
- Frequency of TEAEs having a causal relationship (“related”) with each study drug by severity
- Frequency of TEAEs requiring discontinuation (“discontinue administration") of any study drug by severity
- Frequency of TEAEs requiring discontinuation (“discontinue administration") for each study drug by severity
- Frequency of serious TEAEs
- Frequency of serious TEAEs having a causal relationship (“related”) with any study drug
- Frequency of serious TEAEs having a causal relationship (“related”) with each study drug
- Frequancy of non-serious TEAE with occurrence in > 5% of patients in any of the treatment groups

In addition, the worst Grades for each patient will be calculated, and incidence of TEAE Grade ≥3 (or Grade ≥2 for peripheral neuropathy) and 95% CI using the Agresti-Coul method will be calculated. Similarly, the incidence rate and 95% CI will be calculated using the TEAE recording periods as the denominator, and the incidence of Grade ≥3 TEAEs (or Grade ≥2 for peripheral neuropathy) as the numerator. The 95% CI will be calculated using the following formula.

$$95\%\ \text{CI of incidence rate} = \text{Incidence rate} \pm 1.96\sqrt{\frac{\text{Incidence rate}}{\text{Collection period of TEAEs}}}$$

7.3.2. Follow-up Analysis of TEAEs

For TEAEs of Grade ≥3 (or Grade ≥2 for peripheral neuropathy), a graph of the cumulative incidence will be prepared using the Kaplan-Meier method. Occurrence of a Grade ≥3 TEAE (or Grade ≥2 peripheral neuropathy) will be defined as an event, and the day from randomization to the occurrence of the TEAE will be defined as the time to event. In the absence of a Grade ≥3 TEAE (or Grade ≥2 peripheral neuropathy), the patient will be censored at the end of the AE collection period. For TEAEs classified as peripheral neuropathy and skin disorder, the cumulative expression rates will be plotted as above.

In addition, the cumulative incidence of peripheral neuropathy and skin disorder will be plotted over the cumulative dosage of OXA or panitumumab, respectively, on the horizontal axis. Grade ≥2 peripheral neuropathy or Grade ≥3 skin disorder are deemed as events and the cumulative dosages are the time to event will be plotted as Kaplan-Meier graphs. If there are no events, the patients will be censored at the cumulative dosage at the end of protocol treatment.

7.4. Sensitivity Analysis

7.4.1. Sensitivity Analysis of Primary Endpoint

For calculation of the primary endpoint of PFS rate at 9 months, results obtained after censoring patients at the start of subsequent therapy will be compared with results from the main analysis, to confirm any differences between the results.

7.4.2. Sensitivity Analysis of Secondary Endpoints

For the analyses described in section 7.2.2, results calculated using the start date of Protocol Treatment [1] as day 0 will be compared to the main analysis results.

In addition, comparisons between results will be calculated as described in 7.4.1, to confirm any differences between the results.

7.4.3. Sensitivity Analysis of Other Efficacy Evaluation Items

For “Treatment duration of OXA in mFOLFOX6 + panitumumab group” and “Treatment duration of panitumumab in both groups”, results calculated using the start date of Protocol Treatment [1] as day 0 will be compared with the results from the main analysis.

7.5. Additional Analysis

7.5.1. Creation of Waterfall plot

For patients in the FAS, calculation of the (a) ratio of the sum of diameters of target lesion at enrolment, to the sum of the shortest diameters of target lesion at its minimum value from the time of enrolment, and (b) ratio in the sum of diameters of target lesion at enrolment, to the sum of the target lesion diameters at its minimum value after randomization, will be analyzed as follows.

[Analysis method]

- A waterfall plot will be prepared for each treatment group, and the descriptive statistics of depth of response (DpR) including number of patients, mean, median, standard deviation, maximum value and minimum value, will be calculated.
- A waterfall plot for each treatment group will be created separately according to the primary site of the tumor (right or left) and the descriptive statistics including number of patients, mean, median, standard deviation, maximum value and minimum value, will be calculated.

7.5.2. Evaluation of Depth of Response (DpR)

For patients in the FAS, calculation of the (a) ratio of the sum of diameters of target lesion at enrolment, to the sum of the shortest diameters of target lesion at its minimum value from the time of enrolment, and (b) ratio of the sum of diameters of target lesion at enrolment, to the sum of the target lesion diameters at its minimum value after randomization, will be analyzed as follows.

[Analysis method]

- Mann-Whitney test will be performed for comparisons between treatment groups.
- Mann-Whitney test will be separately performed for comparisons between treatment groups, according to the site of primary tumor (right or left).

7.5.3. Evaluation of Early Tumor Shrinkage (ETS)

For patients in the FAS, the change in the diameter of the target lesion at 8 weeks after enrolment will be calculated, and the patient classified as achieving ‘ETS’ if the change is ≥20%, and ‘no ETS’ if <20%, and used for the following analysis. If the change in diameter of the target lesion at 8 weeks after enrolment cannot be calculated, ETS will be classified as unknown.

[Analysis method]

- The analyses described in 7.2.1. and 7.2.2 will be performed separately for ‘ETS’ and ‘no ETS’ groups. The confidence interval will be 95% for both groups.

7.5.4. Additional Definition of Primary Tumor Location: Right and Left

Although primary tumor location is defined in section 7.1.2, the following additional definitions are used to perform the analyses in sections 7.2.1 and 7.2.2.

(1) Definition 2: The transverse colon is classified as “right”

1) Right Side
   - cecum, ascending colon, proximal 2/3 of transverse colon and distal 1/3 of transverse colon
2) Left Side
   - descending colon, sigmoid colon, rectal sigmoid and rectum
3) Other
   - multiple primary sites across the left and right side
   - unknown primary tumor location

(2) Definition 3: The transverse colon is classified as “other”

1) Right Side
   - cecum and ascending colon
2) Left Side
   - descending colon, sigmoid colon, rectal sigmoid and rectum
3) Other
   - proximal 2/3 of transverse colon, distal 1/3 of transverse colon
   - multiple primary sites across the left and right side
   - unknown primary tumor location

8. References

1）Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c869.

2）Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996; 17: 343–46.

3）Agresti A, Coull BA. Approximate is better than 'exact' for interval estimation of binomial proportions. American Statistician 1998; 52: 119–126.

4）Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982; 38: 29–41.

5）Agresti A, Caffo B. Simple and effective confidence intervals for proportions and differences of proportions result from adding two successes and two failures. American Statistician 2000; 54:

280–288.