



Title: A phase I/II study for the safety and efficacy of Panitumumab in combination with TAS-102 for patients with RAS (KRAS, NRAS) wild-type, unresectable, advanced/recurrent colorectal cancer

NCT Number: NCT02613221

Statistical analysis plan Approve Date: 10-Jul-2018

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Note: This document was translated into English as the language on original version was Japanese.

APOLLON study

(A phase I/II study for the safety and efficacy of Panitumumab in combination with TAS-102 for patients with *RAS* wild-type metastatic colorectal cancer refractory to standard chemotherapy)

(Protocol number: Panitumumab-1501)

Statistics Analysis Plan

Version 4.0



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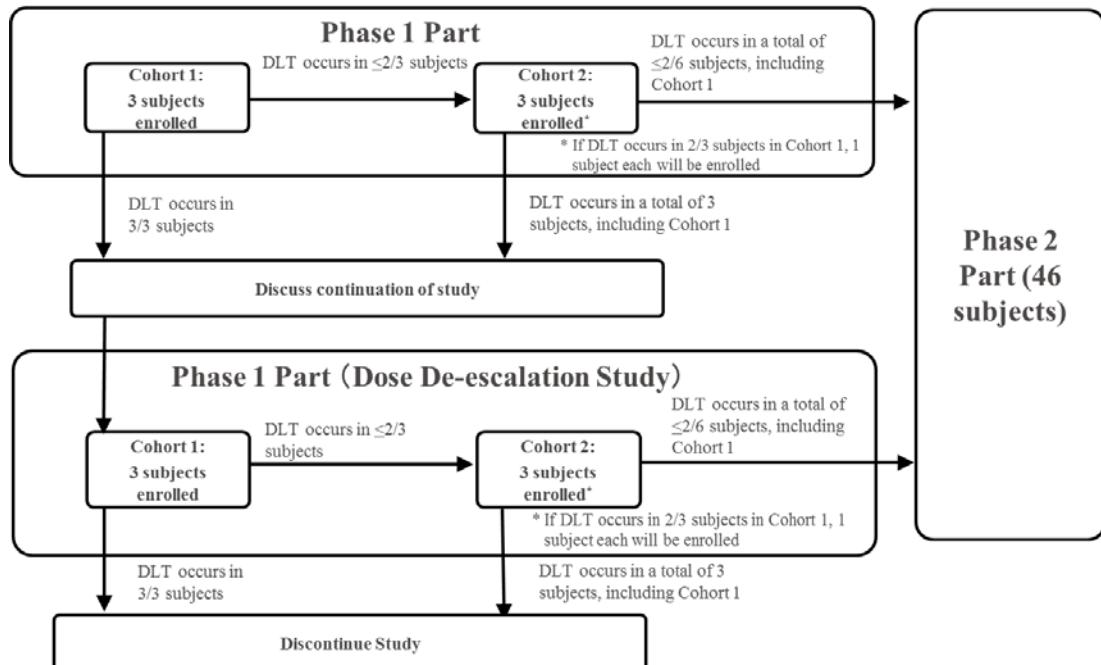
1. History of preparation and revision

Version	Date of approval	Author	Reason for revision
1.0	June 3, 2016	PPD	Not applicable, because it is the first version
2.0	February 28, 2017	PPD	(1) Addition of definition of protocol treatment and acceptable range (2) Addition of analysis plan for phase II part
3.0	December 28, 2017	PPD	(1) Addition of analysis items associated with the protocol revision (ver. 2.0) (2) 7.2.3 Completion of administration (3) 7.2.3.3 Dose reduction status
4.0	July 10, 2018	PPD	(1) 3. Time Period for Analysis is clarified. (2) MedDRA version is stated. (3) Addition of following analysis items: 7.2.3.2 7.2.3.3 7.2.4.3 1) and 2) 7.2.4.4 7.2.6.3 7.2.6.4 7.2.6.5

2. Analysis Plan Objectives

This analysis plan specifies how the initial and final analyses of the clinical study are planned to be conducted in accordance with the “Clinical Study Protocol of A phase I/II study for the safety and efficacy of Panitumumab in combination with TAS-102 for patients with RAS wild-type metastatic colorectal cancer refractory to standard chemotherapy” (hereinafter, protocol).

The study design is shown below.



3. Time period for Analysis

Phase I part: Analysis will be performed after completion of enrollment for phase I, after completion of the Dose Limiting Toxicity (DLT) evaluation period for all enrolled subjects, and after completion of DLT evaluation. A statistical analysis plan for conference presentation will be prepared separately, and analysis will be performed accordingly. Similarly, analysis will be performed again at completion of the period for all observations (final analysis).

Phase II part: Analysis will be performed after completion of enrollment for phase II part and when evaluation has been performed in all the enrolled subjects at 6 months after the start of protocol treatment (initial analysis) and at completion of period for all observations (final analysis).

Protocol treatment

With protocol treatment, in principle, combination therapy with panitumumab and TAS-102 will be conducted, and even if any of the criteria for suspension or discontinuation of either drug is met, treatment with other drugs will be continued unless any of the criteria for discontinuation of protocol

treatment is met (Section 8.7 of protocol). Protocol treatment in principle will be initiated within 14 days of entry.

4. Analysis data set

4.1 Handling of cases/data

(1) Handling of laboratory values/subjective and objective findings of adverse events

Adverse events recorded on the adverse event form will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (ver.21.0) and summarized by system organ class (SOC) and preferred terms (PTs). Skin disorders will be regarded as events classified into “Skin and subcutaneous tissue disorders” of SOC or “Paronychia” by PT. The PTs classified as skin toxicity (Rash acneiform, Paronychia, Dry skin, Pruritus) are defined in Table 4.1.

Table 4.1 Events classified as skin toxicity

Rash acneiform	Acne, Dermatitis acneiform, Folliculitis, Rash, Dermatitis, Drug eruption, Rash pruritic, Eczema, Skin disorder, Rash generalized, Seborrhoeic dermatitis
Paronychia	Paronychia, Nail avulsion, Onychoclasia, Onychomadesis, Nail disorder, Ingrowing nail, Excessive granulation tissue, Pyogenic granuloma
Dry skin	Dry skin, Skin fissures, Xeroderma, Skin exfoliation, Skin chapped, Eczema asteatotic, Hyperkeratosis
Pruritus	Pruritus, General pruritus

(2) Handling of adverse event grade

If an AE is assessed multiple times in the same subject, the highest grade among all AE assessments shall be reported as the worst grade of the AE.

(3) Handling of missing/ejected data

Missing data will not be complemented unless the details of individual analysis items are specified. When rejecting data, the corresponding data will be indicated and the reason for rejection clarified in a table. However, handling of patients with no occurrence of events related to Progression-Free Survival (PFS), Overall Survival (OS), or Time to Treatment Failure (TTF) will be described in each section.

(4) Protocol treatment and acceptable range for tests

Performed items	Protocol specification	Allowance range
Protocol treatment	From the date of treatment of the previous course (Day 1) to after 4 weeks (Day 29)	Scheduled day \pm 3 days

4.2 Number of significant figures in analysis results

Percentages (%) expressing frequency distribution will be rounded to one decimal place unless the details of individual analysis items are specified.

Among summary statistics (number of cases, the mean, standard deviation, minimum, maximum, and inclusive quartiles), the mean, standard deviation, and quartiles will be rounded to one decimal place lower than the original data.

P-values will be indicated to 4 decimal places rounded from the 5th decimal. However, a p-value less than 0.0001 will be expressed as “p < 0.0001.” Hazard ratios and their 95% confidence intervals will be indicated to 2 decimal places rounded from the 3rd decimal.

5. Software used for analysis

The statistical software used for analysis will be CCI

6. Statistical analysis of the phase I part of the study

6.1 Analysis set

Two analysis sets will be created for the phase I part of the study: “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria” and the “DLT evaluation set.” The DLT evaluation set will be based on the following definition from the protocol, Section 8.9.2:

Subjects enrolled in the phase I part of the study will be included in the DLT evaluation set. Subjects will be excluded from the DLT evaluation if at least the designated dose of protocol treatment is not administered by the end of Course 1 (except when the protocol treatment is discontinued due to DLT), if there are major protocol deviations such as the use of contraindicated drugs, or if the subject is determined to be unsuitable for the DLT evaluation. The designated dose is 75% (15 doses) of the total number of doses (20 doses) of panitumumab (2 doses of 6 mg/kg) and TAS-102 (2 doses daily of 35 mg/m²) on Days 1-5 and Days 8-12.

6.2 Analysis of demographic and other baseline characteristics

The following analyses will be conducted in the “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria” and the “DLT evaluation set.”

(1) Discrete data:

A frequency distribution for the discrete data will be computed indicating the percentage (%) with the analysis set as a denominator. Aggregation items are as follows:

- Age (≥ 20 to < 30 years, ≥ 30 to < 40 years, ≥ 40 to < 50 years, ≥ 50 to < 60 years, ≥ 60 to < 70 years, ≥ 70 to < 75 years; ≥ 20 to < 65 years, ≥ 65 to < 75 years), sex, information on primary organ tumor (solitary, multiple), primary tumor location [colon (cecum, ascending colon, transverse colon, descending colon, sigmoid colon), rectum (rectosigmoid, rectum)], [right side, left side], information on metastasis (number of organs with metastasis) (0, 1, ≥ 2), organs with metastasis (liver, lung, peritoneum, lymph node, bone, adrenal gland, skin, and others), ECOG Performance status (P.S.) [before treatment on Day 1 of Course 1 (0, 1)], resection of primary tumor (yes, no), adjuvant chemotherapy (yes, no), number of previous treatments (1, 2, 3), complications (absence, presence)

Determination of primary tumor location:

Right side: in the case of solitary or multiple lesions in the cecum, ascending colon, and transverse colon

Left side: in the case of solitary or multiple lesions in the descending colon, sigmoid colon, rectosigmoid, and rectum

(2) Continuous data:

Summary statistics (number of cases, mean, standard deviation, minimum, maximum, and

inclusive quartiles) will be calculated for continuous data.

- Age (years), height (cm), body weight (kg) (at enrollment), BMI (kg/m^2) (at enrollment), period from the start date of first-line treatment to the date of enrollment (months) (One month is considered as 28 days in calculations).

6.3 Safety analysis

6.3.1 Incidence of DLT events with panitumumab + TAS-102 combination therapy

In accordance with the protocol, Section 8.9.3., the number of cases determined as DLTs among subjects in the DLT evaluation set will be shown and the percentage (%) will be indicated with the total number of cases in the DLT evaluation set as a denominator.

6.3.2 Listing of DLT events

A table listing events determined as DLTs in the DLT evaluation set will be prepared.

Display items:

Subject No., sex, age (years), BMI (kg/m^2) (at enrollment), protocol treatment initiation date, DLT event name (event name recorded by physician, Lowest Level Terms [LLT] code, LLT (English, Japanese), PT code, PT (English, Japanese), SOC code, SOC (English, Japanese), date of onset, severity, causal relationship of adverse event with protocol treatment, causal relationship with panitumumab, seriousness, discontinuation of protocol treatment, outcome, date of resolution

6.3.3 Frequency tabulation of adverse events

The following analyses regarding treatment-emergent adverse events (TEAEs) will be performed on the “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria” and the “DLT evaluation set.”

TEAEs are adverse events that develop after initiation of protocol treatment.

Skin toxicity are events meeting the definitions of TEAEs in [Table 4.1](#).

TEAEs will be coded using MedDRA and summarized by SOC and PTs.

A subject with multiple events in the same SOC will be counted once for that SOC. A subject with multiple events with the same PT will be counted once for that PT.

6.3.3.1 Frequency tabulation of all TEAEs

6.3.3.2 Frequency tabulation of TEAEs for which the causal relationship with protocol treatment was “related”

6.3.3.3 Frequency tabulation of TEAEs for which the causal relationship with panitumumab was “related”

- 6.3.3.4 Frequency tabulation of all TEAEs by severity
- 6.3.3.5 Frequency tabulation of TEAEs by severity for which the causal relationship with protocol treatment was “related”
- 6.3.3.6 Frequency tabulation of TEAEs by severity for which the causal relationship with panitumumab was “related”
- 6.3.3.7 Frequency tabulation of TEAEs for action taken for protocol treatment was “discontinuation”
- 6.3.3.8 Frequency tabulation of TEAEs by severity for action taken for protocol treatment was “discontinuation”
- 6.3.3.9 Frequency tabulation of serious TEAEs
- 6.3.3.10 Frequency tabulation of serious TEAEs for which the causal relationship with protocol treatment was “related”
- 6.3.3.11 Frequency tabulation of serious TEAEs for which the causal relationship with panitumumab treatment was “related”
- 6.3.3.12 Frequency tabulation of non-serious TEAEs with $> 5\%$ incidence
- 6.3.3.13 Frequency tabulation of non-serious TEAEs with $> 5\%$ for which the causal relationship with protocol treatment was “related”
- 6.3.3.14 Frequency tabulation of non-serious TEAEs with $> 5\%$ for which the causal relationship with panitumumab was “related”
- 6.3.3.15 Frequency tabulation of TEAEs with \geq Grade 3
- 6.3.3.16 Frequency tabulation of TEAEs of Grade ≥ 3 for which the causal relationship with protocol treatment was “related”
- 6.3.3.17 Frequency tabulation of TEAEs of Grade ≥ 3 for which the causal relationship with panitumumab was “related”
- 6.3.3.18 The incidence rate of TEAEs of Grade ≥ 3
- 6.3.3.19 The incidence rate of TEAEs of Grade ≥ 3 for which the causal relationship with protocol treatment was “related”
- 6.3.3.20 The incidence rate of TEAEs of Grade ≥ 3 for which the causal relationship with panitumumab was “related”

The following analyses will be performed on the “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria” and the “DLT evaluation set.”

The worst grade in each subject will be calculated. The incidence rate of TEAEs of Grade ≥ 3 and the 95% confidence intervals using Agresti-Coull methods will be calculated. Similarly, incidence rate and the 95% confidence interval of TEAEs will be calculated in the number of TEAE incidence

with \geq Grade 3 as the numerator, and the TEAE collecting periods as the denominator. The 95% confidence intervals will be calculated using the following formula:

$$95\% \text{ confidence interval of incidence rate} = \text{incidence rate} \pm 1.96 \sqrt{\frac{\text{incidence rate}}{\text{TEAE collecting period}}}$$

Skin toxicity will be analyzed similarly as described above (6.3.3.1 to 6.3.3.20)

7. Statistical analysis of the phase II part of the study

7.1 Analysis set

In the phase II part of the study, statistical analysis will be performed on a “full analysis set” and “safety analysis set.” The “full analysis set” will be the main efficacy analysis set, and is defined as “subjects enrolled in phase I and II who received at least one dose of protocol treatment (RD) and satisfied all of the enrollment criteria.” RD is the recommended dose that is confirmed in the phase I part. The “safety analysis set” is defined as “subjects enrolled in phase I and II who received at least one dose of either panitumumab or TAS-102.” Additionally, the set of all subjects who are enrolled in this study is defined as “all enrolled subjects.”

The statistics representative and analysis personnel should finalize a statistical analysis plan before data fixation based on confirmation of the definition of analysis sets and appropriateness of analytical handling rules of the subject data in the analysis sets, and additional handling rules for the issues that are not determined at planning before data fixation.

7.2 Evaluation of analysis set

7.2.1 Eligibility and analysis set

A flow chart showing the breakdown of “all enrolled subjects,” “full analysis set,” and “safety analysis set,” and reasons for patients not being included in the analysis set will be tabulated and shown with a flow chart.

Reason for exclusion of safety analysis set:

- Never received panitumumab or TAS-102

Reason for exclusion of the full analysis set

- Not meeting enrollment criteria
- Never received protocol treatment (RD)

7.2.2 Analysis of demographic and other baseline characteristics

7.2.2.1 Demographic and other baseline characteristics

The following analyses will be performed on “all enrolled subjects,” the “full analysis set,” and the “safety analysis set”:

(1) Discrete data

A frequency distribution will be tabulated for discrete data, and the percentage (%) will be indicated with the analysis set as a denominator. Tabulation items are as follows:

- Age (≥ 20 to < 30 years, ≥ 30 to < 40 years, ≥ 40 to < 50 years, ≥ 50 to < 60 years, ≥ 60 to < 70 years, ≥ 70 to < 75 years; ≥ 20 to < 65 years, ≥ 65 to < 75 years), sex, information on primary organ tumor (solitary, multiple), primary tumor location [colon (cecum, ascending colon, transverse colon, descending colon, sigmoid colon), rectum (rectosigmoid, rectum)], [right side, left side], information on metastasis (number of organs with metastasis) (0, 1, ≥ 2), organs with metastasis (liver, lung, peritoneum, lymph node, bone, adrenal gland, skin, and others), ECOG Performance status (P.S.) [before treatment on Day 1 of Course 1 (0, 1)], resection of primary tumor (yes, no), adjuvant chemotherapy (yes, no), number of previous treatments (1, 2, 3), complications (absence, presence).

(2) Continuous data

Summary statistics (number of cases, the mean, standard deviation, minimum, maximum, quartiles) will be calculated for continuous data.

- Age (years), height (cm), body weight (kg) (at enrollment), BMI (kg/m^2) (at enrollment), period from the start date of first-line treatment to the date of enrollment (months) (One month is considered as 28 days in calculations).

7.2.2.2 Breakdown of complications

The frequency distribution of complications in “all enrolled subjects,” “full analysis set,” and “safety analysis set” will be tabulated, and the percentage (%) will be indicated with the analysis set as the denominator. Complications will be coded using MedDRA and summarized by SOC and PTs.

7.2.3 Medication status

7.2.3.1 Completion of administration

The summary statistics (number of cases, mean, median, standard deviation, minimum, maximum, quartiles) of the cumulative dose and relative dose intensity (RDI) up to 6 months after the start of protocol treatment (168 days) or until the completion date of the course over the period of 6 months (168 days) will be calculated by drug for the “full analysis set” and “safety analysis set.” The RDI will be calculated using the following formulae:

$$\text{Total RDI (\%)} = (\text{all actual dose/all planned dose}) \times (168/\text{actual number of days of all courses}) \times 100$$

7.2.3.2 Completion of administration by worst grade of stomatitis

The cumulative dose and summary statistics of RDI (number of cases, mean, SD, minimum, maximum, quartile) will be calculated for the “full analysis set” and “safety analysis set” by the presence/absence of stomatitis, worst grade, and by drug up to 6 months (168 days) after the start of protocol treatment or to the date of completion of the course across 6 months (168 days).

7.2.3.3 Initial onset of stomatitis and cumulative dose

Kaplan-Meier method will be used to estimate survival curve until the onset of event in the “safety analysis set,” and the point estimation value of incidence and its 95% confidence interval (two-sided) will be calculated at the quartile of the cumulative dose to the initial onset of event and specified time points.

Cumulative dose is to be the dose accumulated by the time of initial onset of event for each drug. For cases without event occurrence, the cumulative dose to the date of death, date of discontinuation/dropout, date of last survival confirmation, or the date of data cut-off, whichever is earlier, will be used.

First onset of event: \geq Grade 1 stomatitis, \geq Grade 2 stomatitis, \geq Grade 3 stomatitis

7.2.3.4 Reason for discontinuation of protocol treatment

Reasons for discontinuation of patients who withdraw up to 6 months (168 days) and during the entire study period in the “full analysis set” and “safety analysis set” will be tabulated, and the percentage (%) will be indicated with the respective analysis set as the denominator.

Reasons for discontinuation of protocol treatment:

- Lack of efficacy (progression)
- Adverse event
- Voluntary discontinuation
- Death during protocol treatment
- Significant deviation from the protocol
- Lost to follow-up
- Discontinuation of the entire study
- Pregnancy
- Others

7.2.3.5 Dose reduction status

The frequency and percentage (%) of the subjects with dose reduction from the initial dose of the treatment period up to 6 months after the start of protocol treatment (168 days), or until the completion date of the course over the period of 6 months (168 days), and over the entire study period will be tabulated for each drug for the “full analysis set” and “safety analysis set.” Drug withdrawal or treatment discontinuation will not be regarded as dose reduction.

7.2.3.6 Follow-up status

The quartiles of follow-up period will be calculated in the “full analysis set” and “safety analysis set.” The follow-up period is the period from the day of enrollment until the day of completion of follow-up. The reverse Kaplan-Meier method will be used to calculate the quartiles of the follow-up period.¹⁾ The final date of follow-up is the date before the date of death for the case of death, and on the final day on which survival is confirmed for surviving subjects

7.2.4 Efficacy analysis

7.2.4.1 Primary endpoint and analysis method

[Primary endpoint]

Progression-free survival (PFS rate) at 6 months after enrollment

The PFS rate 6 months after enrollment, the primary endpoint, is the gross proportion of surviving subjects without documented progression up to 6 months after enrollment (date of enrollment + 24 weeks \pm 2 weeks), counting from the day of enrollment. Subjects with no imaging data on progression at 6 months after enrollment and subjects lost to follow-up will be included in the denominator, but will not be handled as progression-free.

Definition of progression:

Progression will include both progressive disease (PD) based on diagnostic imaging assessed according to RECIST ver. 1.1 and primary disease progression that cannot be confirmed by diagnostic imaging (clinical progression). When progression is documented by diagnostic imaging, the day on which the diagnostic imaging is performed will be the progression date. For clinical progression, the day of the clinical determination will be the progression date. In a case in which, for example, tumor diameter has become extremely small, if the status is determined to be “not definite progression” clinically, although the assessment is PD according to the response criteria, the assessment of PD according to the response criteria will take precedence and the status will be considered progression. (In this case, the clinical determination on continuing protocol treatment will take precedence.) Even if the assessment is not PD according to the response criteria, if there is

definite clinically documented progression, the clinical determination will take precedence and the status will be considered progression. For surviving subjects without documented progression, the period will be cut off on the final day when a progression-free status is confirmed (final day of progression-free survival confirmation). Confirmation of progression-free status by imaging test or sample test is not mandatory, and clinical confirmation by outpatient medical examination, etc., will be allowed. Contact by telephone only will not be allowed. Events and the cut-off will also be handled the same way in subjects who have discontinued protocol treatment for reasons such as toxicity and refusal of treatment, even if another (follow-up) therapy is added. Thus, the time of treatment discontinuation or the day of follow-up treatment initiation will not be the cut-off.

[Main analysis]

The following analysis will be performed on the “full analysis set.”

PFS rate at 6 months is calculated by counting of subjects with progression, without progression, and unconfirmed at 6 months. Based on the observed PFS rate at 6 months from the day of enrollment, binomial test will be conducted on the null hypothesis “value will be determined invalid at PFS rate $\leq 29\%$.” Significant level will be 2.5% (one-sided) in the main analysis. For interval estimation, accurate 90% confidence interval (two-sided) based on binomial distribution will be used.

7.2.4.2 Secondary endpoints and analysis method

[Secondary endpoints]

1) Progression-free survival (PFS)

PFS is the period from the day of enrollment until the day of documented PD (radiological decision or clinical decision) or the day of death due to any cause, whichever comes earlier.

For surviving subjects without documented progression, the period will be cut off on the final day on which progression-free status is confirmed (final day of progression-free survival confirmation). Events and the cut-off will also be handled the same way in subjects who have discontinued protocol treatment for reasons such as toxicity and refusal of treatment, even if another (follow-up) therapy is added. Thus, the time of treatment discontinuation or the day of follow-up treatment initiation will not be the cut-off.

[Analysis method]

Kaplan-Meier method will be used to illustrate survival curve until the onset of event in the “full analysis set,” and the point estimation value of survival rate and its 95% confidence interval (two-sided) will be calculated at the quartile of PFS and specified time points. The

Log-Log conversion of Brookmeyer and Crowley will be used to calculate the 95% confidence intervals of the quartiles for PFS.

2) Overall survival (OS)

OS is the period from the day of enrollment until death by any cause. For surviving subjects, the period is terminated on the final day of survival confirmation or data cut-off date, whichever occurs earlier.

[Analysis method]

Kaplan-Meier method will be used to illustrate survival curve until the onset of event in the “full analysis set,” and the point estimation value of survival rate and its 95% confidence interval (two-sided) will be calculated at the quartile of OS and specified time points. The Log-Log conversion of Brookmeyer and Crowley will be used to calculate the 95% confidence intervals of the quartiles for OS.

3) Response rate (RR)

RR is the percentage of subjects whose best overall response after enrollment according to RECIST ver. 1.1 is either complete response or partial response. Overall response will be graded by favorability in the order of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE). Best overall response is the best response recorded throughout all courses.

[Analysis method]

RR of target lesion and its 95% confidence interval (two-sided) will be calculated in the “full analysis set.”

Further, the maximum tumor reduction rate will be calculated for each subject, and a waterfall plot will be created by arranging the maximum tumor reduction rate in ascending order. Lines of reference at -30% indicating PR and at + 20% indicating PD will be drawn.

$$\text{Reduction ratio of SoD} = \frac{\text{SoD at evaluation point} - \text{SoD before treatment}}{\text{SoD before treatment}} \times 100\%$$

4) Duration of response (DOR)

DOOR is the period from the day when either CR or PR is first confirmed until the day of documented PD or the day of death due to any cause, whichever occurs earlier. For surviving subjects without documented PD, the period will be cut off on the final day of progression-free survival confirmation.

[Analysis method]

The Kaplan-Meier survival curve will show the subject status until the onset of event for the subjects who showed response among the “full analysis set,” and the point estimation value of survival rate and its 95% confidence interval (two-sided) will be calculated at the quartile of DOOR and specified time points.

5) Disease control rate (DCR)

DCR is the percentage of subjects whose best overall response after enrollment according to RECIST ver. 1.1 is CR, PR, or SD.

[Analysis method]

DCR and its 95% confidence interval (two-sided) will be calculated in the “full analysis set.”

6) Time to treatment failure (TTF)

TTF is the period from the day of enrollment until the day of the decision to discontinue protocol treatment, the day of documented progression during protocol treatment (day of decision on clinical PD or radiological PD), or the day of death due to any cause, whichever comes earlier. Subjects not included in the above criteria will be censored at the dose starting date in the final course.

[Analysis method]

Kaplan-Meier method will be used to illustrate survival curve until the onset of event in the “full analysis set,” and the point estimation value of survival rate and its 95% confidence interval (two-sided) will be calculated at the quartile of TTF and specified time points. The Log-Log conversion of Brookmeyer and Crowley will be used to calculate the 95% confidence intervals of the quartiles for TTF.

7.2.4.3 Subgroup analysis of efficacy

1) Subgroup analysis on the following items will be performed for each background factor described below. The same analysis method will be used as in Sections 7.2.4.1 and 7.2.4.2. Using all background factors as explanatory variables, multivariate analysis will be performed using the Cox proportional hazard model for PFS, OS, and TIF. Similarly, using all background factors as explanatory variables, logistic regression analysis will be performed for PFS rate and DCR.

7.2.4.3.1.1 PFS rate

7.2.4.3.1.2 PFS

7.2.4.3.1.3 OS

7.2.4.3.1.4 RR

7.2.4.3.1.5 DCR

7.2.4.3.1.6 TTF

Background factors:

Age (≥ 20 years < 65 years, ≥ 65 years < 75 years), sex, ECOG Performance status (P.S.) [before dosing on Day 1 of Course 1 (0, 1)], information on primary tumor location [right, left], adjuvant chemotherapy (yes, no), resection of primary lesion (yes, no), number of days since the start of first-line treatment (< 600 days, ≥ 600 days)

2) A landmark analysis for PFS, OS, and TIF will be performed for each landmark point after enrollment. Patients developing applicable events by the landmark point after enrollment and those who have been discontinued will be excluded from the analysis. The same analysis method will be used as in Section 7.2.4.2.

7.2.4.3.2.1 PFS

7.2.4.3.2.2 OS

7.2.4.3.2.3 TTF

Factor	Landmark point	Category
Skin Toxicity,	Week 6	$\leq G1, \geq G2$
Skin Toxicityr	Week 10	$\leq G1, \geq G2$

Factor	Landmark point	Category
Stomatitis	Week 6	$\leq G1, \geq G2$
Stomatitis	Week 10	$\leq G1, \geq G2$
Neutropenia	Week 6	$\leq G0, \geq G1$
Neutropenia	Week 6	$\leq G2, \geq G3$
Early Tumor Shrinkage (ETS)*	Week 8	Yes, No

*ETS refers to the case of tumor shrinkage by at least 20% within 8 weeks after enrollment.

7.2.4.4 Other efficacy analysis items

1) ETS

The presence/absence of cases with tumor shrinkage by at least 20% within 8 weeks after enrollment, the number of patients who dropped out (discontinued protocol treatment) within 8 weeks after enrollment in the full analysis set, and the dropout rate will be shown.

2) Administration of each drug and the change from the onset of response to death or completion of observation

Swimmers plot will be created to illustrate the change from the onset of response to death or completion of observation.

Date of response onset: the date CR or PR is first confirmed

Vertical axis: case

Horizontal axis: duration (days)

Administration status: A bar graph showing the duration of TAS administration (from Day 1 of TAS-102 to the date of last administration of TAS-102, with “x” indicating administration of panitumumab.

▲ will indicate the date of discontinuation of protocol treatment.

Therapeutic effect: ○ will indicate the date of response onset

■ will indicate the confirmation date of PD.

Survival: The OS part after discontinuation of protocol treatment will be indicated as ---- (survivors will be distinguished by color)

Post treatment: ● will indicate the start date of post treatment.

3) Time-course change in the reduction rate of the sum of target lesion diameters

A spider plot will be created to describe the reduction rate of the sum of target lesion diameters in all patients by best overall response of PR, SD, and PD.

7.2.4.5 Level of significance, confidence coefficient

Significance level: Main analysis only, 5% (one-sided); other analyses, 5% (two-sided)

Confidence coefficient: Main analysis only, 90% (two-sided); other analyses, 95% (two-sided)

7.2.5 Safety analysis

The following analyses regarding TEAEs will be performed on the “full analysis set” and “safety analysis set.”

TEAEs will be coded using MedDRA and summarized by SOC and PTs.

A subject with multiple events in the same SOC will be counted once for that SOC. A subject with multiple events with the same PT will be counted once for that PT.

7.2.5.1 Frequency tabulation of all TEAEs

7.2.5.2 Frequency tabulation of TEAEs for which the causal relationship with protocol treatment was “related”

7.2.5.3 Frequency tabulation of TEAEs for which the causal relationship with panitumumab was “related”

7.2.5.4 Frequency tabulation of all TEAEs by severity

7.2.5.5 Frequency tabulation of TEAEs by severity for which the causal relationship with protocol treatment was “related”

7.2.5.6 Frequency tabulation of TEAEs by severity for which the causal relationship with panitumumab was “related”

7.2.5.7 Frequency tabulation of TEAEs for action taken for protocol treatment was “discontinuation”

7.2.5.8 Frequency tabulation of TEAEs by severity for action taken for protocol treatment was “discontinuation”

7.2.5.9 Frequency tabulation of serious TEAEs

7.2.5.10 Frequency tabulation of serious TEAEs for which the causal relationship with protocol treatment was “related”

7.2.5.11 Frequency tabulation of serious TEAEs for which the causal relationship with panitumumab treatment was “related”

7.2.5.12 Frequency tabulation of non-serious TEAEs with > 5% incidence

- 7.2.5.13 Frequency tabulation of non-serious TEAEs with $> 5\%$ for which the causal relationship with protocol treatment was “related”
- 7.2.5.14 Frequency tabulation of non-serious TEAEs with $> 5\%$ for which the causal relationship with panitumumab was “related”
- 7.2.5.15 Frequency tabulation of TEAEs with \geq Grade 3
- 7.2.5.16 Frequency tabulation of TEAEs with \geq Grade 3 for which the causal relationship with protocol treatment was “related”
- 7.2.5.17 Frequency tabulation of TEAEs with \geq Grade 3 for which the causal relationship with panitumumab was “related”
- 7.2.5.18 The incidence rate of TEAEs with \geq Grade 3
- 7.2.5.19 The incidence rate of TEAEs with \geq Grade 3 for which the causal relationship with protocol treatment was “related”
- 7.2.5.20 The incidence rate of TEAEs with \geq Grade 3 for which the causal relationship with panitumumab was “related”

The following analyses will be performed on the “full analysis set” and “safety analysis set”:

The worst grade in each subject will be calculated. The incidence rate of TEAEs of Grade ≥ 3 and the 95% confidence intervals using Agresti-Coull methods will be calculated. Similarly, incidence rate and the 95% confidence interval of TEAEs will be calculated in the number of TEAE incidence with \geq Grade 3 as the numerator, and the TEAE collecting periods as the denominator. The 95% confidence intervals will be calculated using the following formula:

$$\text{The 95\% confidence intervals of incidence rate} = \text{incidence rate} \pm 1.96 \sqrt{\frac{\text{incidence rate}}{\text{TEAE collecting period}}}$$

Skin toxicity will be analyzed similarly as described above (7.2.5.1 to 7.2.5.20)

7.2.6 Other safety analysis items

7.2.6.1 ECOG P.S.

The frequency distribution of ECOG P.S. in the “full analysis set” and “safety analysis set” will be tabulated for each course, and the percentage (%) will be indicated with the analysis set at Day 1 of each course (excluding withdrawal cases) as the denominator.

7.2.6.2 Laboratory tests

A shift table will be prepared by performing a cross tabulation (number of cases and the percentages) of the results of CTCAE grading based on laboratory values for each test item in the “full analysis set” and “safety analysis set,” using the worst grade at the start and after the start of treatment. The percentage (%) will be indicated with the respective analysis set as the denominator.

Test items:

Neutrophil count, platelet count, hemoglobin level, total bilirubin, ALT (GPT), AST (GOT), creatinine, Mg, albumin, Na, K, Ca

7.2.6.3 Number of days to the onset of specific event

Summary statistics will be calculated for the number of days from the start date of protocol treatment to the onset of the events below in the “full analysis set” and “safety analysis set.”

Target events:

≥ Grade 1 stomatitis, worst Grade stomatitis, ≥ Grade 3 stomatitis, ≥ Grade 3 dermatitis acneiform,
≥ Grade 3 hypomagnesaemia, ≥ Grade 2 skin toxicity

7.2.6.4 Subsequencet therapy

With regard to the implementation status of Subsequencet therapy in the “full analysis set” and “safety analysis set,” the frequency distribution of the following items will be shown, as well as the percentages (%) with analysis set as the denominator:

Implementation status of Subsequencet therapy

No	Patients with continuous treatment
	Deaths within 4 weeks of discontinuation of protocol treatment
	BSC after 4 weeks of discontinuation of protocol treatment
Yes	Regorafenib
	Other

7.2.6.5 Effects between specific events

Cross-tabulation by the presence/absence of occurrence and cross-tabulation by grade will be performed for events 1 and 2, below, in the “full analysis set” and “safety analysis set.” Cases of no event will be counted as Grade 0. The percentages (%) will be shown with analysis set as the denominator.

Event 1	Event 2
Neutropenia	Stomatitis
Dermatitis acneiform	Stomatitis

7.2.7 Table listing

The following tables will be created for the “enrolled subjects” in section 7.2.7.2 and for the “safety analysis set” in other sections

7.2.7.1 List of subjects who discontinued protocol treatment

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, date of discontinuation, reason for discontinuation, adverse event name (event name recorded by physician, LLT code, LLT (English, Japanese), PT code, PT English, Japanese), SOC code, SOC (English, Japanese), date of onset, severity, causal relationship of adverse event with protocol treatment, causal relationship with panitumumab, seriousness, discontinuation of protocol treatment, outcome, date of resolution

7.2.7.2 List of subjects/data excluded from analysis

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, reason for exclusion

7.2.7.3 List of fatal cases

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, date of death, reason for death, adverse event name (event name recorded by physician, LLT code, LLT (English, Japanese), PT code, PT (English, Japanese), SOC code, SOC (English, Japanese), date of onset, seriousness, causal relationship of adverse event with protocol treatment, causal relationship with panitumumab, seriousness, discontinuation of protocol treatment, outcome, date of resolution

7.2.7.4 List of treatments

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, primary lesion (information on primary organ, site, with/without resection, date of surgery), metastatic lesion (number of organs with metastases, site, with/without resection, date of surgery), performing a palliative colostomy (with/without, date of surgery), bypass surgery (with/without, date of surgery), radiation therapy (radical irradiation) (with/without, date of surgery, date of final dose), first-line treatment (start date, treatment details), second-line treatment (treatment details), third-line treatment (with/without, treatment details), preoperative/postoperative adjuvant chemotherapy (with/without, time period, oxaliplatin-containing regimen, date of final dose)

7.2.7.5 List of protocol treatment status

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, start date of TAS-102 by course, dose, number of doses, date of panitumumab administration, dose, presence or absence of discontinuation of protocol treatment, date of discontinuation, reason for discontinuation

7.2.7.6 List of complications

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, name of complication (name of complication recorded by physician, LLT code, LLT (English, Japanese), PT code, PT (English, Japanese), SOC code, SOC (English, Japanese)

7.2.7.7 Table of MedDRA-coded AEs

Display items:

Name of AE recorded by physician LLT code, LLT (English, Japanese), PT code, PT (English, Japanese), SOC code, SOC (English, Japanese)

7.2.7.8 List of TEAEs

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, adverse event name (event name recorded by physician, LLT code, LLT (English, Japanese), PT code, PT (English, Japanese), SOC code, SOC (English, Japanese), date of onset, severity, causal relationship with protocol treatment, causal relationship with panitumumab, seriousness, discontinuation of protocol treatment, outcome, date of resolution.

7.2.7.9 List of Deaths and other serious adverse events

Display items:

Same as "List of TEAEs"

7.2.7.10 List of skin toxicity

Display items:

Same as "List of TEAEs"

7.2.7.11 List of RECIST response evaluations

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, evaluation period, sum of target lesion diameter (before treatment, at evaluation), reduction rate of sum of target lesion diameter, results of response evaluation of target lesion, results of response evaluation of non-target lesion, development of new lesion, site of new lesion, results of overall response evaluation

$$\text{Reduction ratio of SoD} = \frac{\text{SoD at evaluation point} - \text{SoD before treatment}}{\text{SoD before treatment}} \times 100\%$$

7.2.7.12 List of determinations of PD

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, day of decision on clinical PD, day of decision on radiological PD, final day of imaging test, final day on which progression-free survival is confirmed, start date of follow-up treatment

7.2.7.13 List of survival survey results

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, survival survey results, last confirmed date of survival, date of death, reason of death (other details)

7.2.7.14 List of laboratory test values

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, laboratory test items, test date, measured values (SI), Unit (SI), site reference values (SI) (lower limit – upper limit)

Test items: Same as 7.2.6.2.

7.3 Criteria for interim analysis and premature discontinuation

No interim analyses are scheduled.

7.4 Sensitivity analysis

Sensitivity analysis of primary endpoint

For the PFS rate at 6 months (the primary endpoint), results will be calculated for the case in which the period is terminated at the point follow-up treatment is initiated, and the difference between major analysis results will be confirmed.

Kaplan-Meier method will be used to illustrate survival curve until the onset of event in the “full analysis set,” and the point estimation value of survival rate and its 95% confidence interval (two-sided) will be calculated at the quartile of PFS and specified time points. The Log-Log conversion of Brookmeyer and Crowley will be used to calculate the 95% confidence intervals of the quartiles for PFS.

In evaluating PFS, results will be calculated for the case of termination at the point follow-up treatment is initiated (start date of follow-up treatment), and the difference between that and the results for the case in which the period is cut off on the last confirmed date of progression-free status.

8. References

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

APOLLON study

(A phase I/II study for the safety and efficacy of Panitumumab in combination with TAS-102 for patients with *RAS* wild-type metastatic colorectal cancer refractory to standard chemotherapy)

(Protocol number: Panitumumab-1501)

Statistics Analysis Plan

Version 3.0

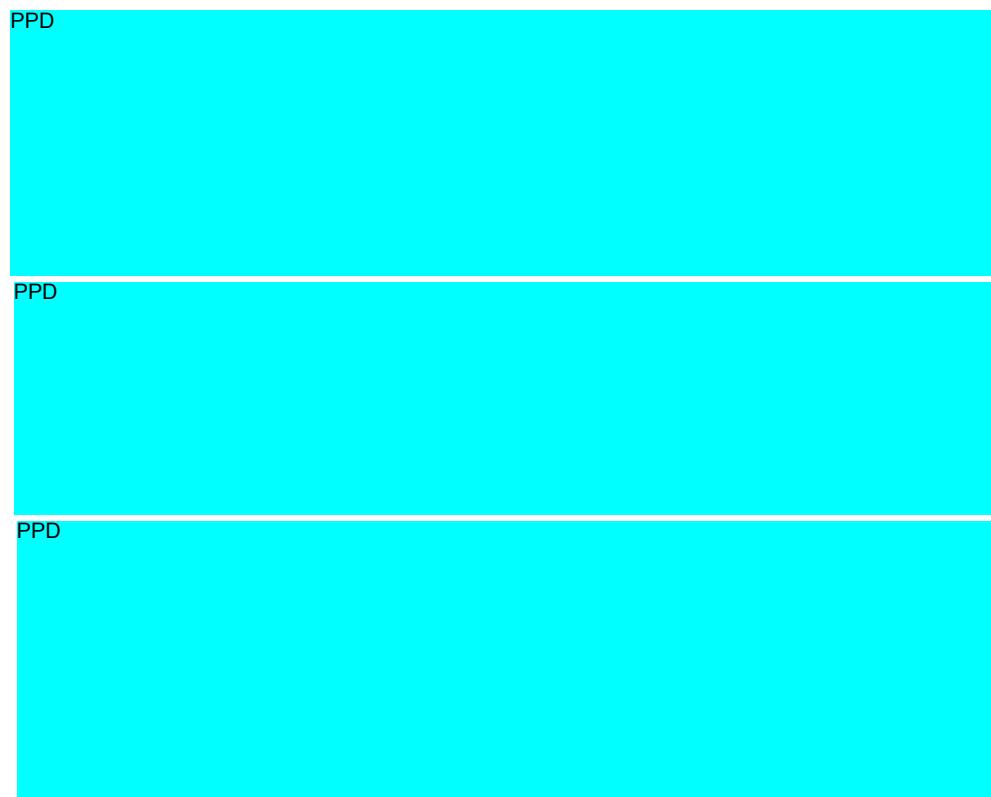


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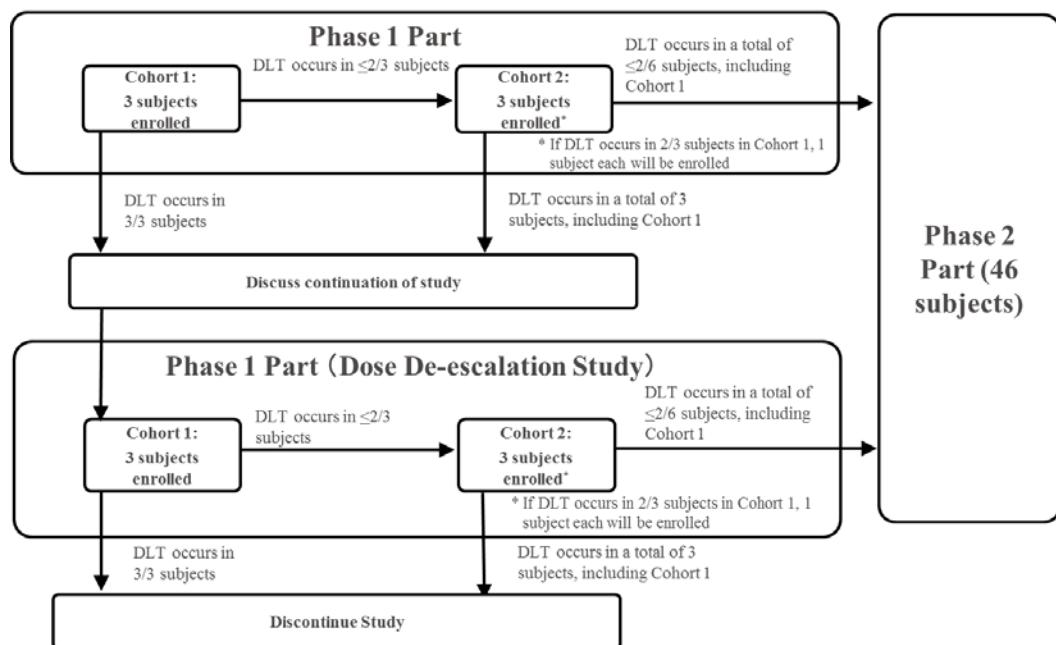
1. History of preparation and revision

Version	Date of approval	Author	Reason for revision
1.0	June 3, 2016	PPD ██████████	Not applicable, because it is the first version
2.0	February 28, 2017	PPD ██████████	(1) Addition of definition of protocol treatment and acceptable range (2) Addition of analysis plan for phase II part
3.0	December 28, 2017	PPD ██████████	(1) Addition of analysis items associated with the protocol revision (ver. 2.0) (2) 7.2.3 Completion of administration (3) 7.2.3.3 Dose reduction status

2. Analysis Plan Objectives

This analysis plan specifies how the initial and final analyses of the clinical study are planned to be conducted in accordance with the “Clinical Study Protocol of A phase I/II study for the safety and efficacy of Panitumumab in combination with TAS-102 for patients with RAS wild-type metastatic colorectal cancer refractory to standard chemotherapy” (hereinafter, protocol).

The study design is shown below.



3. Time period for Analysis

Phase I part: Analysis will be performed after completion of enrollment for phase I part and after completion of Dose Limiting Toxicity (DLT) evaluation period for all enrolled subjects, and when DLT has been evaluated.

Phase II part: Analysis will be performed after completion of enrollment for phase II part and when evaluation has been performed in all the enrolled subjects at 6 months after the start of protocol treatment (initial analysis) and at completion of period for all observations (final analysis).

Protocol treatment

With protocol treatment, in principle, combination therapy with panitumumab and TAS-102 will be conducted, and even if any of the criteria for suspension or discontinuation of either drug is met, treatment with other drugs will be continued unless any of the criteria for discontinuation of protocol treatment is met (Section 8.7 of protocol). Protocol treatment in principle will be initiated within 14 days of entry.

4. Analysis data set

4.1 Handling of cases/data

(1) Handling of laboratory values/subjective and objective findings of adverse events

Adverse events recorded on the adverse event form will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred terms (PTs). Skin disorders will be regarded as events classified into “Skin and subcutaneous tissue disorders” of SOC or “Paronychia” by PT. The PTs classified as skin toxicity (Rash acneiform, Paronychia, Dry skin, Pruritus) are defined in Table 4.1.

Table 4.1 Events classified as skin toxicity

Rash acneiform	Acne, Dermatitis acneiform, Folliculitis, Rash, Dermatitis, Drug eruption, Rash pruritic, Eczema, Skin disorder, Rash generalized, Seborrhoeic dermatitis
Paronychia	Paronychia, Nail avulsion, Onychoclasia, Onychomadesis, Nail disorder, Ingrowing nail, Excessive granulation tissue, Pyogenic granuloma
Dry skin	Dry skin, Skin fissures, Xeroderma, Skin exfoliation, Skin chapped, Eczema asteatotic, Hyperkeratosis
Pruritus	Pruritus, General pruritus

(2) Handling of adverse event grade

If an AE is assessed multiple times in the same subject, the highest grade among all AE assessments shall be reported as the worst grade of the AE.

(3) Handling of missing/ejected data

Missing data will not be complemented unless the details of individual analysis items are specified. When rejecting data, the corresponding data will be indicated and the reason for rejection clarified in a table. However, handling of patients with no occurrence of events related to Progression-Free Survival (PFS), Overall Survival (OS), or Time to Treatment Failure (TTF) will be described in each section.

(4) Protocol treatment and acceptable range for tests

Performed items	Protocol specification	Allowance range
Protocol treatment	From the date of treatment of the previous course (Day 1) to after 4 weeks (Day 29)	Scheduled day \pm 3 days

4.2 Number of significant figures in analysis results

Percentages (%) expressing frequency distribution will be rounded to one decimal place unless the

details of individual analysis items are specified.

Among summary statistics (number of cases, the mean, standard deviation, minimum, maximum, and inclusive quartiles), the mean, standard deviation, and quartiles will be rounded to one decimal place lower than the original data.

P-values will be indicated to 4 decimal places rounded from the 5th decimal. However, a p-value less than 0.0001 will be expressed as “p < 0.0001.” Hazard ratios and their 95% confidence intervals will be indicated to 2 decimal places rounded from the 3rd decimal.

5. Software used for analysis

The statistical software used for analysis will be **CCI**

6. Statistical analysis of the phase I part of the study

6.1 Analysis set

Two analysis sets will be created for the phase I part of the study: “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria” and the “DLT evaluation set.” The DLT evaluation set will be based on the following definition from the protocol, Section 8.9.2:

Subjects enrolled in the phase I part of the study will be included in the DLT evaluation set. Subjects will be excluded from the DLT evaluation if at least the designated dose of protocol treatment is not administered by the end of Course 1 (except when the protocol treatment is discontinued due to DLT), if there are major protocol deviations such as the use of contraindicated drugs, or if the subject is determined to be unsuitable for the DLT evaluation. The designated dose is 75% (15 doses) of the total number of doses (20 doses) of panitumumab (2 doses of 6 mg/kg) and TAS-102 (2 doses daily of 35 mg/m²) on Days 1-5 and Days 8-12.

6.2 Analysis of demographic and other baseline characteristics

The following analyses will be conducted in the “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria” and the “DLT evaluation set.”

(1) Discrete data:

A frequency distribution for the discrete data will be computed indicating the percentage (%) with the analysis set as a denominator. Aggregation items are as follows:

- Age (≥ 20 to < 30 years, ≥ 30 to < 40 years, ≥ 40 to < 50 years, ≥ 50 to < 60 years, ≥ 60 to < 70 years, ≥ 70 to < 75 years; ≥ 20 to < 65 years, ≥ 65 to < 75 years), sex, information on primary organ tumor (solitary, multiple), primary tumor location [colon (cecum, ascending colon, transverse colon, descending colon, sigmoid colon), rectum (rectosigmoid, rectum)], [right side, left side], information on metastasis (number of organs with metastasis) (0, 1, ≥ 2), organs with metastasis (liver, lung, peritoneum, lymph node, bone, adrenal gland, skin, and others), ECOG Performance status (P.S.) [before treatment on Day 1 of Course 1 (0, 1)], resection of primary tumor (yes, no), adjuvant chemotherapy (yes, no), number of previous treatments (1, 2, 3), complications (absence, presence)

Determination of primary tumor location:

Right side: in the case of solitary or multiple lesions in the cecum, ascending colon, and transverse colon

Left side: in the case of solitary or multiple lesions in the descending colon, sigmoid colon, rectosigmoid, and rectum

(2) Continuous data:

Summary statistics (number of cases, mean, standard deviation, minimum, maximum, and

inclusive quartiles) will be calculated for continuous data.

- Age (years), height (cm), body weight (kg) (at enrollment), BMI (kg/m²) (at enrollment), period from the start date of first-line treatment to the date of enrollment.

6.3 Safety analysis

6.3.1 Incidence of DLT events with panitumumab + TAS-102 combination therapy

In accordance with the protocol, Section 8.9.3., the number of cases determined as DLTs among subjects in the DLT evaluation set will be shown and the percentage (%) will be indicated with the total number of cases in the DLT evaluation set as a denominator.

6.3.2 Listing of DLT events

A table listing events determined as DLTs in the DLT evaluation set will be prepared.

Display items:

Subject No., sex, age (years), BMI (kg/m²) (at enrollment), protocol treatment initiation date, DLT event name (event name recorded by physician, Lowest Level Terms [LLT] code, LLT (English, Japanese), PT code, PT (English, Japanese), SOC code, SOC (English, Japanese), date of onset, severity, causal relationship of adverse event with protocol treatment, causal relationship with panitumumab, seriousness, discontinuation of protocol treatment, outcome, date of resolution

6.3.3 Frequency tabulation of adverse events

The following analyses regarding treatment-emergent adverse events (TEAEs) will be performed on the “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria” and the “DLT evaluation set.”

TEAEs are adverse events that develop after initiation of protocol treatment.

Skin toxicity are events meeting the definitions of TEAEs in Table 4.1.

TEAEs will be coded using MedDRA and summarized by SOC and PTs.

A subject with multiple events in the same SOC will be counted once for that SOC. A subject with multiple events with the same PT will be counted once for that PT.

6.3.3.1 Frequency tabulation of all TEAEs

6.3.3.2 Frequency tabulation of TEAEs for which the causal relationship with protocol treatment was “related”

6.3.3.3 Frequency tabulation of TEAEs for which the causal relationship with panitumumab was “related”

6.3.3.4 Frequency tabulation of all TEAEs by severity

- 6.3.3.5 Frequency tabulation of TEAEs by severity for which the causal relationship with protocol treatment was “related”
- 6.3.3.6 Frequency tabulation of TEAEs by severity for which the causal relationship with panitumumab was “related”
- 6.3.3.7 Frequency tabulation of TEAEs for action taken for protocol treatment was “discontinuation”
- 6.3.3.8 Frequency tabulation of TEAEs by severity for action taken for protocol treatment was “discontinuation”
- 6.3.3.9 Frequency tabulation of serious TEAEs
- 6.3.3.10 Frequency tabulation of serious TEAEs for which the causal relationship with protocol treatment was “related”
- 6.3.3.11 Frequency tabulation of serious TEAEs for which the causal relationship with panitumumab treatment was “related”
- 6.3.3.12 Frequency tabulation of non-serious TEAEs with $> 5\%$ incidence
- 6.3.3.13 Frequency tabulation of non-serious TEAEs with $> 5\%$ for which the causal relationship with protocol treatment was “related”
- 6.3.3.14 Frequency tabulation of non-serious TEAEs with $> 5\%$ for which the causal relationship with panitumumab was “related”
- 6.3.3.15 Frequency tabulation of TEAEs with \geq Grade 3
- 6.3.3.16 Frequency tabulation of TEAEs of Grade ≥ 3 for which the causal relationship with protocol treatment was “related”
- 6.3.3.17 Frequency tabulation of TEAEs of Grade ≥ 3 for which the causal relationship with panitumumab was “related”
- 6.3.3.18 The incidence rate of TEAEs of Grade ≥ 3
- 6.3.3.19 The incidence rate of TEAEs of Grade ≥ 3 for which the causal relationship with protocol treatment was “related”
- 6.3.3.20 The incidence rate of TEAEs of Grade ≥ 3 for which the causal relationship with panitumumab was “related”

The following analyses will be performed on the “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria” and the “DLT evaluation set.”

The worst grade in each subject will be calculated. The incidence rate of TEAEs of Grade ≥ 3 and the 95% confidence intervals using Agresti-Coull methods will be calculated. Similarly, incidence rate and the 95% confidence interval of TEAEs will be calculated in the number of TEAE incidence with \geq Grade 3 as the numerator, and the TEAE collecting periods as the denominator. The 95%

confidence intervals will be calculated using the following formula:

$$95\% \text{ confidence interval of incidence rate} = \text{incidence rate} \pm 1.96 \sqrt{\frac{\text{incidence rate}}{\text{TEAE collecting period}}}$$

Skin toxicity will be analyzed similarly as described above (6.3.3.1 to 6.3.3.20)

7. Statistical analysis of the phase II part of the study

7.1 Analysis set

In the phase II part of the study, statistical analysis will be performed on a “full analysis set” and “safety analysis set.” The “full analysis set” will be the main efficacy analysis set, and is defined as “subjects enrolled in phase I and II who received at least one dose of protocol treatment (RD) and satisfied all of the enrollment criteria.” RD is the recommended dose that is confirmed in the phase I part. The “safety analysis set” is defined as “subjects enrolled in phase I and II who received at least one dose of either panitumumab or TAS-102.” Additionally, the set of all subjects who are enrolled in this study is defined as “all enrolled subjects.”

The statistics representative and analysis personnel should finalize a statistical analysis plan before data fixation based on confirmation of the definition of analysis sets and appropriateness of analytical handling rules of the subject data in the analysis sets, and additional handling rules for the issues that are not determined at planning before data fixation.

7.2 Evaluation of analysis set

7.2.1 Eligibility and analysis set

A flow chart showing the breakdown of “all enrolled subjects,” “full analysis set,” and “safety analysis set,” and reasons for patients not being included in the analysis set will be tabulated and shown with a flow chart.

Reason for exclusion of safety analysis set:

- Never received panitumumab or TAS-102

Reason for exclusion of the full analysis set

- Not meeting enrollment criteria
- Never received protocol treatment (RD)

7.2.2 Analysis of demographic and other baseline characteristics

7.2.2.1 Demographic and other baseline characteristics

The following analyses will be performed on “all enrolled subjects,” the “full analysis set,” and

the “safety analysis set”:

(1) Discrete data

A frequency distribution will be tabulated for discrete data, and the percentage (%) will be indicated with the analysis set as a denominator. Tabulation items are as follows:

- Age (≥ 20 to < 30 years, ≥ 30 to < 40 years, ≥ 40 to < 50 years, ≥ 50 to < 60 years, ≥ 60 to < 70 years, ≥ 70 to < 75 years; ≥ 20 to < 65 years, ≥ 65 to < 75 years), sex, information on primary organ tumor (solitary, multiple), primary tumor location [colon (cecum, ascending colon, transverse colon, descending colon, sigmoid colon), rectum (rectosigmoid, rectum)], [right side, left side], information on metastasis (number of organs with metastasis) (0, 1, ≥ 2), organs with metastasis (liver, lung, peritoneum, lymph node, bone, adrenal gland, skin, and others), ECOG Performance status (P.S.) [before treatment on Day 1 of Course 1 (0, 1)], resection of primary tumor (yes, no), adjuvant chemotherapy (yes, no), number of previous treatments (1, 2, 3), complications (absence, presence).

(2) Continuous data

Summary statistics (number of cases, the mean, standard deviation, minimum, maximum, quartiles) will be calculated for continuous data.

- Age (years), height (cm), body weight (kg) (at enrollment), BMI (kg/m^2) (at enrollment), period from the start date of first-line treatment to the date of enrollment.

7.2.2.2 Breakdown of complications

The frequency distribution of complications in “all enrolled subjects,” “full analysis set,” and “safety analysis set” will be tabulated, and the percentage (%) will be indicated with the analysis set as the denominator. Complications will be coded using MedDRA and summarized by SOC and PTs.

7.2.3 Medication status

7.2.3.1 Completion of administration

The summary statistics (number of cases, mean, median, standard deviation, minimum, maximum, quartiles) of the cumulative dose and relative dose intensity (RDI) up to 6 months after the start of protocol treatment (168 days) or until the completion date of the course over the period of 6 months (168 days) will be calculated by drug for the “full analysis set” and “safety analysis set.” The RDI will be calculated using the following formulae:

$$\text{Total RDI (\%)} = (\text{all actual dose/all planned dose}) \times (168/\text{actual number of days of all courses}) \times 100$$

7.2.3.2 Reason for discontinuation of protocol treatment

Reasons for discontinuation of patients who withdraw up to 6 months (168 days) and during the entire study period in the “full analysis set” and “safety analysis set” will be tabulated, and the percentage (%) will be indicated with the respective analysis set as the denominator.

Reasons for discontinuation of protocol treatment:

- Lack of efficacy (progression)
- Adverse event
- Voluntary discontinuation
- Death during protocol treatment
- Significant deviation from the protocol
- Lost to follow-up
- Discontinuation of the entire study
- Pregnancy
- Others

7.2.3.3 Dose reduction status

The frequency and percentage (%) of the subjects with dose reduction from the initial dose of the treatment period up to 6 months after the start of protocol treatment (168 days), or until the completion date of the course over the period of 6 months (168 days), and over the entire study period will be tabulated for each drug for the “full analysis set” and “safety analysis set.” Drug withdrawal or treatment discontinuation will not be regarded as dose reduction.

7.2.3.4 Follow-up status

The quartiles of follow-up period will be calculated in the “full analysis set” and “safety analysis set.” The follow-up period is the period from the day of enrollment until the day of completion of follow-up. The reverse Kaplan-Meier method will be used to calculate the quartiles of the follow-up period.¹⁾ The final date of follow-up is the date before the date of death for the case of death, and on the final day on which survival is confirmed for surviving subjects

7.2.4 Efficacy analysis

7.2.4.1 Primary endpoint and analysis method

[Primary endpoint]

Progression-free survival (PFS rate) at 6 months after enrollment

The PFS rate 6 months after enrollment, the primary endpoint, is the gross proportion of surviving subjects without documented progression up to 6 months after enrollment (date of enrollment + 24 weeks \pm 2 weeks), counting from the day of enrollment. Subjects with no imaging data on

progression at 6 months after enrollment and subjects lost to follow-up will be included in the denominator, but will not be handled as progression-free.

Definition of progression:

Progression will include both progressive disease (PD) based on diagnostic imaging assessed according to RECIST ver. 1.1 and primary disease progression that cannot be confirmed by diagnostic imaging (clinical progression). When progression is documented by diagnostic imaging, the day on which the diagnostic imaging is performed will be the progression date. For clinical progression, the day of the clinical determination will be the progression date. In a case in which, for example, tumor diameter has become extremely small, if the status is determined to be “not definite progression” clinically, although the assessment is PD according to the response criteria, the assessment of PD according to the response criteria will take precedence and the status will be considered progression. (In this case, the clinical determination on continuing protocol treatment will take precedence.) Even if the assessment is not PD according to the response criteria, if there is definite clinically documented progression, the clinical determination will take precedence and the status will be considered progression. For surviving subjects without documented progression, the period will be cut off on the final day when a progression-free status is confirmed (final day of progression-free survival confirmation). Confirmation of progression-free status by imaging test or sample test is not mandatory, and clinical confirmation by outpatient medical examination, etc., will be allowed. Contact by telephone only will not be allowed. Events and the cut-off will also be handled the same way in subjects who have discontinued protocol treatment for reasons such as toxicity and refusal of treatment, even if another (follow-up) therapy is added. Thus, the time of treatment discontinuation or the day of follow-up treatment initiation will not be the cut-off.

[Main analysis]

The following analysis will be performed on the “full analysis set.”

PFS rate at 6 months is calculated by counting of subjects with progression, without progression, and unconfirmed at 6 months. Based on the observed PFS rate at 6 months from the day of enrollment, binomial test will be conducted on the null hypothesis “value will be determined invalid at PFS rate $\leq 29\%$.” Significant level will be 2.5% (one-sided) in the main analysis. For interval estimation, accurate 90% confidence interval (two-sided) based on binomial distribution will be used.

7.2.4.2 Secondary endpoints and analysis method

[Secondary endpoints]

1) Progression-free survival (PFS)

PFS is the period from the day of enrollment until the day of documented PD (radiological decision or clinical decision) or the day of death due to any cause, whichever comes earlier.

For surviving subjects without documented progression, the period will be cut off on the final day on which progression-free status is confirmed (final day of progression-free survival confirmation). Events and the cut-off will also be handled the same way in subjects who have discontinued protocol treatment for reasons such as toxicity and refusal of treatment, even if another (follow-up) therapy is added. Thus, the time of treatment discontinuation or the day of follow-up treatment initiation will not be the cut-off.

[Analysis method]

Kaplan-Meier method will be used to illustrate survival curve until the onset of event in the “full analysis set,” and the point estimation value of survival rate and its 95% confidence interval (two-sided) will be calculated at the quartile of PFS and specified time points. The Log-Log conversion of Brookmeyer and Crowley will be used to calculate the 95% confidence intervals of the quartiles for PFS.

2) Overall survival (OS)

OS is the period from the day of enrollment until death by any cause. For surviving subjects, the period is terminated on the final day of survival confirmation or data cut-off date, whichever occurs earlier.

[Analysis method]

Kaplan-Meier method will be used to illustrate survival curve until the onset of event in the “full analysis set,” and the point estimation value of survival rate and its 95% confidence interval (two-sided) will be calculated at the quartile of OS and specified time points. The Log-Log conversion of Brookmeyer and Crowley will be used to calculate the 95% confidence intervals of the quartiles for OS.

3) Response rate (RR)

RR is the percentage of subjects whose best overall response after enrollment according to RECIST ver. 1.1 is either complete response or partial response. Overall response will be graded by favorability in the order of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE). Best overall response is the best response recorded throughout all courses.

[Analysis method]

RR of target lesion and its 95% confidence interval (two-sided) will be calculated in the “full analysis set.”

Further, the maximum tumor reduction rate will be calculated for each subject, and a waterfall plot will be created by arranging the maximum tumor reduction rate in ascending order. Lines of reference at -30% indicating PR and at + 20% indicating PD will be drawn.

$$\text{Reduction ratio of SoD} = \frac{\text{SoD at evaluation point} - \text{SoD before treatment}}{\text{SoD before treatment}} \times 100\%$$

4) Duration of response (DOR)

DOR is the period from the day when either CR or PR is first confirmed until the day of documented PD or the day of death due to any cause, whichever occurs earlier. For surviving subjects without documented PD, the period will be cut off on the final day of progression-free survival confirmation.

[Analysis method]

The Kaplan-Meier survival curve will show the subject status until the onset of event for the subjects who showed response among the “full analysis set,” and the point estimation value of survival rate and its 95% confidence interval (two-sided) will be calculated at the quartile of DOR and specified time points.

5) Disease control rate (DCR)

DCR is the percentage of subjects whose best overall response after enrollment according to RECIST ver. 1.1 is CR, PR, or SD.

[Analysis method]

DCR and its 95% confidence interval (two-sided) will be calculated in the “full analysis set.”

6) Time to treatment failure (TTF)

TTF is the period from the day of enrollment until the day of the decision to discontinue protocol treatment, the day of documented progression during protocol treatment (day of decision on clinical PD or radiological PD), or the day of death due to any cause, whichever

comes earlier. Subjects not included in the above criteria will be censored at the dose starting date in the final course.

[Analysis method]

Kaplan-Meier method will be used to illustrate survival curve until the onset of event in the “full analysis set,” and the point estimation value of survival rate and its 95% confidence interval (two-sided) will be calculated at the quartile of TTF and specified time points. The Log-Log conversion of Brookmeyer and Crowley will be used to calculate the 95% confidence intervals of the quartiles for TTF.

7.2.4.3 Subgroup analysis of efficacy

Subgroup analysis on the following items will be performed for each primary lesion location (right side, left side). The same analysis method will be used as in Sections 7.2.4.1 and 7.2.4.2.

7.2.4.3.1 PFS rate

7.2.4.3.2 PFS

7.2.4.3.3 OS

7.2.4.3.4 RR

7.2.4.3.5 DCR

7.2.4.4 Level of significance, confidence coefficient

Significance level: Main analysis only, 5% (one-sided); other analyses, 5% (two-sided)

Confidence coefficient: Main analysis only, 90% (two-sided); other analyses, 95% (two-sided)

7.2.5 Safety analysis

The following analyses regarding TEAEs will be performed on the “full analysis set” and “safety analysis set.”

TEAEs will be coded using MedDRA and summarized by SOC and PTs.

A subject with multiple events in the same SOC will be counted once for that SOC. A subject with multiple events with the same PT will be counted once for that PT.

7.2.5.1 Frequency tabulation of all TEAEs

7.2.5.2 Frequency tabulation of TEAEs for which the causal relationship with protocol treatment was “related”

7.2.5.3 Frequency tabulation of TEAEs for which the causal relationship with panitumumab was “related”

- 7.2.5.4 Frequency tabulation of all TEAEs by severity
- 7.2.5.5 Frequency tabulation of TEAEs by severity for which the causal relationship with protocol treatment was “related”
- 7.2.5.6 Frequency tabulation of TEAEs by severity for which the causal relationship with panitumumab was “related”
- 7.2.5.7 Frequency tabulation of TEAEs for action taken for protocol treatment was “discontinuation”
- 7.2.5.8 Frequency tabulation of TEAEs by severity for action taken for protocol treatment was “discontinuation”
- 7.2.5.9 Frequency tabulation of serious TEAEs
- 7.2.5.10 Frequency tabulation of serious TEAEs for which the causal relationship with protocol treatment was “related”
- 7.2.5.11 Frequency tabulation of serious TEAEs for which the causal relationship with panitumumab treatment was “related”
- 7.2.5.12 Frequency tabulation of non-serious TEAEs with > 5% incidence
- 7.2.5.13 Frequency tabulation of non-serious TEAEs with > 5% for which the causal relationship with protocol treatment was “related”
- 7.2.5.14 Frequency tabulation of non-serious TEAEs with > 5% for which the causal relationship with panitumumab was “related”
- 7.2.5.15 Frequency tabulation of TEAEs with \geq Grade 3
- 7.2.5.16 Frequency tabulation of TEAEs with \geq Grade 3 for which the causal relationship with protocol treatment was “related”
- 7.2.5.17 Frequency tabulation of TEAEs with \geq Grade 3 for which the causal relationship with panitumumab was “related”
- 7.2.5.18 The incidence rate of TEAEs with \geq Grade 3
- 7.2.5.19 The incidence rate of TEAEs with \geq Grade 3 for which the causal relationship with protocol treatment was “related”
- 7.2.5.20 The incidence rate of TEAEs with \geq Grade 3 for which the causal relationship with panitumumab was “related”

The following analyses will be performed on the “full analysis set” and “safety analysis set”:

The worst grade in each subject will be calculated. The incidence rate of TEAEs of Grade \geq 3 and the 95% confidence intervals using Agresti-Coull methods will be calculated. Similarly, incidence rate and the 95% confidence interval of TEAEs will be calculated in the number of TEAE incidence with \geq Grade 3 as the numerator, and the TEAE collecting periods as the denominator. The 95% confidence intervals will be calculated using the following formula:

$$\text{The 95\% confidence intervals of incidence rate} = \text{incidence rate} \pm 1.96 \sqrt{\frac{\text{incidence rate}}{\text{TEAE collecting period}}}$$

Skin toxicity will be analyzed similarly as described above (7.2.5.1 to 7.2.5.20)

7.2.6 Other safety analysis items

7.2.6.1 ECOG P.S.

The frequency distribution of ECOG P.S. in the “full analysis set” and “safety analysis set” will be tabulated for each course, and the percentage (%) will be indicated with the analysis set at Day 1 of each course (excluding withdrawal cases) as the denominator.

7.2.6.2 Laboratory tests

A shift table will be prepared by performing a cross tabulation (number of cases and the percentages) of the results of CTCAE grading based on laboratory values for each test item in the “full analysis set” and “safety analysis set,” using the worst grade at the start and after the start of treatment. The percentage (%) will be indicated with the respective analysis set as the denominator.

Test items:

Neutrophil count, platelet count, hemoglobin level, total bilirubin, ALT (GPT), AST (GOT), creatinine, Mg, albumin, Na, K, Ca

7.2.7 Table listing

The following tables will be created for the “enrolled subjects” in section 7.2.7.2 and for the “safety analysis set” in other sections

7.2.7.1 List of subjects who discontinued protocol treatment

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, date of discontinuation, reason for discontinuation, adverse event name (event name recorded by physician, LLT code, LLT (English, Japanese), PT code, PT English, Japanese), SOC code, SOC (English, Japanese), date of onset, severity, causal relationship of adverse event with protocol treatment, causal relationship with panitumumab, seriousness, discontinuation of protocol treatment, outcome, date of resolution

7.2.7.2 List of subjects/data excluded from analysis

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age

(years), start date of protocol treatment, reason for exclusion

7.2.7.3 List of fatal cases

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, date of death, reason for death, adverse event name (event name recorded by physician, LLT code, LLT (English, Japanese), PT code, PT (English, Japanese), SOC code, SOC (English, Japanese), date of onset, seriousness, causal relationship of adverse event with protocol treatment, causal relationship with panitumumab, seriousness, discontinuation of protocol treatment, outcome, date of resolution

7.2.7.4 List of treatments

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, primary lesion (information on primary organ, site, with/without resection, date of surgery), metastatic lesion (number of organs with metastases, site, with/without resection, date of surgery), performing a palliative colostomy (with/without, date of surgery), bypass surgery (with/without, date of surgery), radiation therapy (radical irradiation) (with/without, date of surgery, date of final dose), first-line treatment (start date, treatment details), second-line treatment (treatment details), third-line treatment (with/without, treatment details), preoperative/postoperative adjuvant chemotherapy (with/without, time period, oxaliplatin-containing regimen, date of final dose)

7.2.7.5 List of protocol treatment status

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, start date of TAS-102 by course, dose, number of doses, date of panitumumab administration, dose, presence or absence of discontinuation of protocol treatment, date of discontinuation, reason for discontinuation

7.2.7.6 List of complications

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, name of complication (name of complication recorded by physician, LLT code, LLT (English, Japanese), PT code, PT (English, Japanese), SOC code, SOC (English, Japanese)

7.2.7.7 Table of MedDRA-coded AEs

Display items:

Name of AE recorded by physician LLT code, LLT (English, Japanese), PT code, PT (English, Japanese), SOC code, SOC (English, Japanese)

7.2.7.8 List of TEAEs

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, adverse event name (event name recorded by physician, LLT code, LLT (English, Japanese), PT code, PT (English, Japanese), SOC code, SOC (English, Japanese), date of onset, severity, causal relationship with protocol treatment, causal relationship with panitumumab, seriousness, discontinuation of protocol treatment, outcome, date of resolution.

7.2.7.9 List of Deaths and other serious adverse events

Display items:

Same as “List of TEAEs”

7.2.7.10 List of skin toxicity

Display items:

Same as “List of TEAEs”

7.2.7.11 List of RECIST response evaluations

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, evaluation period, sum of target lesion diameter (before treatment, at evaluation), reduction rate of sum of target lesion diameter, results of response evaluation of target lesion, results of response evaluation of non-target lesion, development of new lesion, site of new lesion, results of overall response evaluation

$$\text{Reduction ratio of SoD} = \frac{\text{SoD at evaluation point} - \text{SoD before treatment}}{\text{SoD before treatment}} \times 100\%$$

7.2.7.12 List of determinations of PD

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age

(years), start date of protocol treatment, day of decision on clinical PD, day of decision on radiological PD, final day of imaging test, final day on which progression-free survival is confirmed, start date of follow-up treatment

7.2.7.13 List of survival survey results

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, survival survey results, last confirmed date of survival, date of death, reason of death (other details)

7.2.7.14 List of laboratory test values

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, laboratory test items, test date, measured values (SI), Unit (SI), site reference values (SI) (lower limit – upper limit)

Test items: Same as 7.2.6.2.

7.3 Criteria for interim analysis and premature discontinuation

No interim analyses are scheduled.

7.4 Sensitivity analysis

Sensitivity analysis of primary endpoint

For the PFS rate at 6 months (the primary endpoint), results will be calculated for the case in which the period is terminated at the point follow-up treatment is initiated, and the difference between major analysis results will be confirmed.

Kaplan-Meier method will be used to illustrate survival curve until the onset of event in the “full analysis set,” and the point estimation value of survival rate and its 95% confidence interval (two-sided) will be calculated at the quartile of PFS and specified time points. The Log-Log conversion of Brookmeyer and Crowley will be used to calculate the 95% confidence intervals of the quartiles for PFS.

In evaluating PFS, results will be calculated for the case of termination at the point follow-up treatment is initiated (start date of follow-up treatment), and the difference between that and the results for the case in which the period is cut off on the last confirmed date of progression-free status.

8. References

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

APOLLON study

(A phase I/II study for the safety and efficacy of Panitumumab in combination with TAS-102 for patients with *RAS* wild-type metastatic colorectal cancer refractory to standard chemotherapy)

(Protocol number: Panitumumab-1501)

Statistics Analysis Plan

Version 2.0



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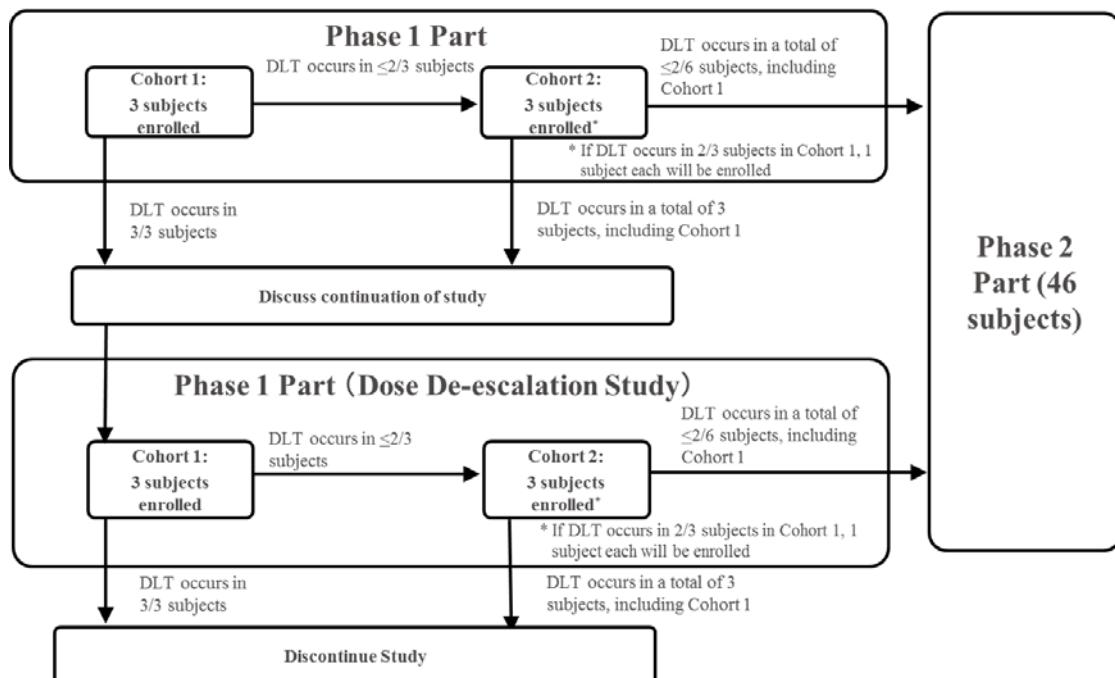
1. History of preparation and revision

Version	Date of approval	Author	Reason for revision
1.0	June 3, 2016	PPD [REDACTED]	Not applicable, because it is the first version
2.0	February 28, 2017	PPD [REDACTED]	(1) Addition of definition of protocol treatment and acceptable range (2) Addition of analysis plan for phase II part

2. Analysis Plan Objectives

This analysis plan specifies how the initial and final analyses of the clinical study are planned to be conducted in accordance with the “Clinical Study Protocol of A phase I/II study for the safety and efficacy of Panitumumab in combination with TAS-102 for patients with RAS wild-type metastatic colorectal cancer refractory to standard chemotherapy” (hereinafter, protocol).

The study design is shown below.



3. Time period for Analysis

Phase I part: Analysis will be performed after completion of enrollment for phase I part and after completion of Dose Limiting Toxicity (DLT) evaluation period for all enrolled subjects, and when DLT has been evaluated.

Phase II part: Analysis will be performed after completion of enrollment for phase II part and when evaluation has been performed in all the enrolled subjects at 6 months after the start of protocol treatment (initial analysis) and at completion of period for all observations (final analysis).

Protocol treatment

With protocol treatment, in principle, combination therapy with panitumumab and TAS-102 will be conducted, and even if any of the criteria for suspension or discontinuation of either drug is met, treatment with other drugs will be continued unless any of the criteria for discontinuation of protocol treatment is met (Section 8.7 of protocol). Protocol treatment in principle will be initiated within 14

days of entry.

4. Analysis data set

4.1 Handling of cases/data

(1) Handling of laboratory values/subjective and objective findings of adverse events

Adverse events recorded on the adverse event form will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred terms (PTs). Skin disorders will be regarded as events classified into “Skin and subcutaneous tissue disorders” of SOC or “Paronychia” by PT. The PTs classified as skin toxicity (Rash acneform, Paronychia, Dry skin, Pruritus) are defined in Table 4.1.

Table 4.1 Events classified as skin toxicity

Rash acneform	Acne, Dermatitis acneiform, Folliculitis, Rash, Dermatitis, Drug eruption, Rash pruritic, Eczema, Skin disorder, Rash generalized, Seborrhoeic dermatitis
Paronychia	Paronychia, Nail avulsion, Onychoclasis, Onychomadesis, Nail disorder, Ingrowing nail, Excessive granulation tissue, Pyogenic granuloma
Dry skin	Dry skin, Skin fissures, Xeroderma, Skin exfoliation, Skin chapped, Eczema asteatotic, Hyperkeratosis
Pruritus	Pruritus, General pruritus

(2) Handling of adverse event grade

If an AE is assessed multiple times in the same subject, the highest grade among all AE assessments shall be reported as the worst grade of the AE.

(3) Handling of missing/ejected data

Missing data will not be complemented unless the details of individual analysis items are specified. When rejecting data, the corresponding data will be indicated and the reason for rejection clarified in a table. However, handling of patients with no occurrence of events related to Progression-Free Survival (PFS), Overall Survival (OS), or Time to Treatment Failure (TTF) will be described in each section.

(4) Protocol treatment and acceptable range for tests

Performed items	Protocol specification	Allowance range
Protocol treatment	From the date of treatment of the previous course (Day 1) to after 4 weeks (Day 29)	Scheduled day \pm 3 days

4.2 Number of significant figures in analysis results

Percentages (%) expressing frequency distribution will be rounded to one decimal place unless the details of individual analysis items are specified.

Among summary statistics (number of cases, the mean, standard deviation, minimum, maximum, and inclusive quartiles), the mean, standard deviation, and quartiles will be rounded to one decimal place lower than the original data.

P-values will be indicated to 4 decimal places rounded from the 5th decimal. However, a p-value less than 0.0001 will be expressed as “p < 0.0001.” Hazard ratios and their 95% confidence intervals will be indicated to 2 decimal places rounded from the 3rd decimal.

5. Software used for analysis

The statistical software used for analysis will be CCI

6. Statistical analysis of the phase I part of the study

6.1 Analysis set

Two analysis sets will be created for the phase I part of the study: “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria” and the “DLT evaluation set.” The DLT evaluation set will be based on the following definition from the protocol, Section 8.9.2:

Subjects enrolled in the phase I part of the study will be included in the DLT evaluation set. Subjects will be excluded from the DLT evaluation if at least the designated dose of protocol treatment is not administered by the end of Course 1 (except when the protocol treatment is discontinued due to DLT), if there are major protocol deviations such as the use of contraindicated drugs, or if the subject is determined to be unsuitable for the DLT evaluation. The designated dose is 75% (15 doses) of the total number of doses (20 doses) of panitumumab (2 doses of 6 mg/kg) and TAS-102 (2 doses daily of 35 mg/m²) on Days 1-5 and Days 8-12.

6.2 Analysis of demographic and other baseline characteristics

The following analyses will be conducted in the “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria” and the “DLT evaluation set.”

(1) Discrete data:

A frequency distribution for the discrete data will be computed indicating the percentage (%) with the analysis set as a denominator. Aggregation items are as follows:

- Age (≥ 20 to < 30 years, ≥ 30 to < 40 years, ≥ 40 to < 50 years, ≥ 50 to < 60 years, ≥ 60 to < 70 years, ≥ 70 to < 75 years; ≥ 20 to < 65 years, ≥ 65 to < 75 years), sex, information on primary organ tumor (solitary, multiple), primary tumor location [colon (cecum, ascending colon, transverse colon, descending colon, sigmoid colon), rectum (rectosigmoid, rectum)], information on metastasis (number of organs with metastasis) (0, 1, ≥ 2), organs with metastasis (liver, lung, peritoneum, lymph node, bone, adrenal gland, skin, and others), ECOG Performance status (P.S.) [before treatment on Day 1 of Course 1 (0, 1)], resection of primary tumor (yes, no), adjuvant chemotherapy (yes, no), number of previous treatments (1, 2, 3), complications (absence, presence)

(2) Continuous data:

Summary statistics (number of cases, mean, standard deviation, minimum, maximum, and inclusive quartiles) will be calculated for continuous data.

- Age (years), height (cm), body weight (kg) (at enrollment), BMI (kg/m²) (at enrollment).

6.3 Safety analysis

6.3.1 Incidence of DLT events with panitumumab + TAS-102 combination therapy

In accordance with the protocol, Section 8.9.3., the number of cases determined as DLTs among subjects in the DLT evaluation set will be shown and the percentage (%) will be indicated with the total number of cases in the DLT evaluation set as a denominator.

6.3.2 Listing of DLT events

A table listing events determined as DLTs in the DLT evaluation set will be prepared.

Display items:

Subject No., sex, age (years), BMI (kg/m²) (at enrollment), protocol treatment initiation date, DLT event name (event name recorded by physician, Lowest Level Terms [LLT] code, LLT Japanese, PT code, PT Japanese, SOC code, SOC Japanese), date of onset, severity, causal relationship of adverse event with protocol treatment, causal relationship with panitumumab, seriousness, discontinuation of protocol treatment, outcome, date of resolution

6.3.3 Frequency tabulation of adverse events

The following analyses regarding treatment-emergent adverse events (TEAEs) and skin toxicity will be performed on the “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria” and the “DLT evaluation set.”

TEAEs are adverse events that develop after initiation of protocol treatment.

Skin toxicity are events meeting the definitions of TEAEs in Table 4.1.

TEAEs will be coded using MedDRA and summarized by SOC and PTs.

A subject with multiple events in the same SOC will be counted once for that SOC. A subject with multiple events with the same PT will be counted once for that PT.

6.3.3.1 Frequency tabulation of all TEAEs

6.3.3.2 Frequency tabulation of TEAEs for which the causal relationship with protocol treatment was “related”

6.3.3.3 Frequency tabulation of TEAEs for which the causal relationship with panitumumab was “related”

6.3.3.4 Frequency tabulation of all TEAEs by severity

6.3.3.5 Frequency tabulation of TEAEs by severity for which the causal relationship with protocol treatment was “related”

6.3.3.6 Frequency tabulation of TEAEs by severity for which the causal relationship with panitumumab was “related”

6.3.3.7 Frequency tabulation of TEAEs for action taken for protocol treatment was

“discontinuation”

6.3.3.8 Frequency tabulation of TEAEs by severity for action taken for protocol treatment was “discontinuation”

6.3.3.9 Frequency tabulation of serious TEAEs

6.3.3.10 Frequency tabulation of serious TEAEs for which the causal relationship with protocol treatment was “related”

6.3.3.11 Frequency tabulation of serious TEAEs for which the causal relationship with panitumumab treatment was “related”

6.3.3.12 Frequency tabulation of non-serious TEAEs with $\geq 5\%$ incidence

6.3.3.13 Frequency tabulation of TEAEs of Grade ≥ 3

6.3.3.14 Frequency tabulation of TEAEs of Grade ≥ 3 for which the causal relationship with protocol treatment was “related”

6.3.3.15 Frequency tabulation of TEAEs of Grade ≥ 3 for which the causal relationship with panitumumab was “related”

6.3.3.16 The incidence rate of TEAEs of Grade ≥ 3

6.3.3.17 The incidence rate of TEAEs of Grade ≥ 3 for which the causal relationship with protocol treatment was “related”

6.3.3.18 The incidence rate of TEAEs of Grade ≥ 3 for which the causal relationship with panitumumab was “related”

The following analyses will be performed on the “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria” and the “DLT evaluation set.”

The worst grade in each subject will be calculated. The incidence rate of TEAEs of Grade ≥ 3 and the 95% confidence intervals using Agresti-Coull methods will be calculated. Similarly, incidence rate and the 95% confidence interval of TEAEs will be calculated in the number of TEAE incidence with \geq Grade 3 as the numerator, and the TEAE collecting periods as the denominator. The 95% confidence intervals will be calculated using the following formula:

$$95\% \text{ confidence interval of incidence rate} = \text{incidence rate} \pm 1.96 \sqrt{\frac{\text{incidence rate}}{\text{TEAE collecting period}}}$$

7. Statistical analysis of the phase II part of the study

7.1 Analysis set

In the phase II part of the study, statistical analysis will be performed on a “full analysis set” and “safety analysis set.” The “full analysis set” will be the main efficacy analysis set, and is defined as “subjects enrolled in phase I and II who received at least one dose of protocol treatment (RD) and satisfied all of the enrollment criteria.” RD is the recommended dose that is confirmed in the phase I part. The “safety analysis set” is defined as “subjects enrolled in phase I and II who received at least one dose of either panitumumab or TAS102.” Additionally, the set of all subjects who are enrolled in this study is defined as “all enrolled subjects.”

The statistics representative and analysis personnel should finalize a statistical analysis plan before data fixation based on confirmation of the definition of analysis sets and appropriateness of analytical handling rules of the subject data in the analysis sets, and additional handling rules for the issues that are not determined at planning before data fixation.

7.2 Evaluation of analysis set

7.2.1 Eligibility and analysis set

A flow chart showing the breakdown of “all enrolled subjects,” “full analysis set,” and “safety analysis set,” and reasons for patients not being included in the analysis set will be tabulated and shown with a flow chart.

Reason for exclusion of safety analysis set:

- Never received panitumumab or TAS102

Reason for exclusion of the full analysis set

- Not meeting enrollment criteria
- Never received protocol treatment (RD)

7.2.2 Analysis of demographic and other baseline characteristics

7.2.2.1 Demographic and other baseline characteristics

The following analyses will be performed on “all enrolled subjects,” the “full analysis set,” and the “safety analysis set”:

(1) Discrete data

A frequency distribution will be tabulated for discrete data, and the percentage (%) will be indicated with the analysis set as a denominator. Tabulation items are as follows:

- Age (≥ 20 to < 30 years, ≥ 30 to < 40 years, ≥ 40 to < 50 years, ≥ 50 to < 60 years, ≥ 60 to < 70 years, ≥ 70 to < 75 years; ≥ 20 to < 65 years, ≥ 65 to < 75 years), sex, information on primary organ tumor (solitary, multiple), primary tumor location [colon (cecum, ascending colon, transverse colon, descending colon, sigmoid colon), rectum (rectosigmoid, rectum)], information on metastasis (number of organs with metastasis) (0, 1, ≥ 2), organs with metastasis (liver, lung, peritoneum, lymph node, bone, adrenal gland, skin, and others), ECOG Performance status (P.S.) [before treatment on Day 1 of Course 1 (0, 1)], resection of primary tumor (yes, no), adjuvant chemotherapy (yes, no), number of previous treatments (1, 2, 3), complications (absence, presence).

(2) Continuous data

Summary statistics (number of cases, the mean, standard deviation, minimum, maximum, quartiles) will be calculated for continuous data.

- Age (years), height (cm), body weight (kg) (at enrollment), BMI (kg/m^2) (at enrollment).

7.2.2.2 Breakdown of complications

The frequency distribution of complications in “all enrolled subjects,” “full analysis set,” and “safety analysis set” will be tabulated, and the percentage (%) will be indicated with the analysis set as the denominator. Complications will be coded using MedDRA and summarized by SOC and PTs.

7.2.3 Medication status

7.2.3.1 Completion of administration

The summary statistics (number of cases, mean, median, standard deviation, minimum, maximum, quartiles) of the cumulative dose and relative dose intensity (RDI) for each course up to Course 6 and over the period up to Course 6 will be calculated by drug for the “full analysis set” and “safety analysis set.” For the RDI up to Course 6, a time plot with a boxplot will be constructed. The RDI will be calculated using the following formulae:

$$\text{RDI (\%)} = (\text{actual dose}/\text{initial planned dose}) \times (28/\text{number of days until completion of specific actual course}) \times 100$$

$$\text{Total RDI (\%)} = (\text{all actual dose}/\text{all planned dose}) \times (168/\text{actual number of days of all courses}) \times 100$$

7.2.3.2 Reason for discontinuation of protocol treatment

Reasons for discontinuation of patients who withdraw up to Course 6 and during the entire study period in the “full analysis set” and “safety analysis set” will be tabulated, and the percentage (%) will be indicated with the respective analysis set as the denominator.

Reasons for discontinuation of protocol treatment:

- Lack of efficacy (progression)
- Adverse event
- Voluntary discontinuation
- Death during protocol treatment
- Significant deviation from the protocol
- Lost to follow-up
- Discontinuation of the entire study
- Pregnancy
- Others

7.2.3.3 Dose reduction status

The frequency and percentage (%) of the subjects with dose reduction from the initial dose up to Course 6 and over the entire study period will be tabulated for each drug for the “full analysis set” and “safety analysis set.” Similarly, the frequency and percentage (%) will be tabulated for each specified course (6 courses).

7.2.3.4 Follow-up status

The quartiles of follow-up period will be calculated in the “full analysis set” and “safety analysis set.” The follow-up period is the period from the day of enrollment until the day of completion of follow-up. The reverse Kaplan-Meier method will be used to calculate the quartiles of the follow-up period.¹⁾ The final date of follow-up is the date before the date of death for the case of death, and on the final day on which survival is confirmed for surviving subjects

7.2.4 Efficacy analysis

7.2.4.1 Primary endpoint and analysis method

[Primary endpoint]

Progression-free survival (PFS rate) at 6 months after enrollment

The PFS rate 6 months after enrollment, the primary endpoint, is the gross proportion of surviving subjects without documented progression up to 6 months after enrollment (date of enrollment + 24 weeks \pm 2 weeks), counting from the day of enrollment. Subjects with no imaging data on progression at 6 months after enrollment and subjects lost to follow-up will be included in the

denominator, but will not be handled as progression-free.

Definition of progression:

Progression will include both progressive disease (PD) based on diagnostic imaging assessed according to RECIST ver. 1.1 and primary disease progression that cannot be confirmed by diagnostic imaging (clinical progression). When progression is documented by diagnostic imaging, the day on which the diagnostic imaging is performed will be the progression date. For clinical progression, the day of the clinical determination will be the progression date. In a case in which, for example, tumor diameter has become extremely small, if the status is determined to be “not definite progression” clinically, although the assessment is PD according to the response criteria, the assessment of PD according to the response criteria will take precedence and the status will be considered progression. (In this case, the clinical determination on continuing protocol treatment will take precedence.) Even if the assessment is not PD according to the response criteria, if there is definite clinically documented progression, the clinical determination will take precedence and the status will be considered progression.

[Main analysis]

The following analysis will be performed on the “full analysis set.”

PFS rate at 6 months is calculated by counting of subjects with progression, without progression, and unconfirmed at 6 months. Based on the observed PFS rate at 6 months from the day of enrollment, binomial test will be conducted on the null hypothesis “value will be determined invalid at PFS rate $\leq 29\%$.” Significant level will be 2.5% (one-sided) in the main analysis. For interval estimation, accurate 90% confidence interval (two-sided) based on binomial distribution will be used.

7.2.4.2 Secondary endpoints and analysis method

[Secondary endpoints]

1) Progression-free survival (PFS)

PFS is the period from the day of enrollment until the day of documented PD (radiological decision or clinical decision) or the day of death due to any cause, whichever comes earlier.

For surviving subjects without documented progression, the period will be cut off on the final day on which progression-free status is confirmed (final day of progression-free survival confirmation). Events and the cut-off will also be handled the same way in subjects who have discontinued protocol treatment for reasons such as toxicity and refusal of treatment, even if another (follow-up) therapy is added. Thus, the time of treatment discontinuation or the day of

follow-up treatment initiation will not be the cut-off.

[Analysis method]

Kaplan-Meier method will be used to illustrate survival curve until the onset of event in the “full analysis set,” and the point estimation value of survival rate and its 95% confidence interval (two-sided) will be calculated at the quartile of PFS and specified time points. The Log-Log conversion of Brookmeyer and Crowley will be used to calculate the 95% confidence intervals of the quartiles for PFS.

2) Overall survival (OS)

OS is the period from the day of enrollment until death by any cause. For surviving subjects, the period is terminated on the final day of survival confirmation or data cut-off date, whichever occurs earlier.

[Analysis method]

Kaplan-Meier method will be used to illustrate survival curve until the onset of event in the “full analysis set,” and the point estimation value of survival rate and its 95% confidence interval (two-sided) will be calculated at the quartile of OS and specified time points. The Log-Log conversion of Brookmeyer and Crowley will be used to calculate the 95% confidence intervals of the quartiles for OS.

3) Response rate (RR)

RR is the percentage of subjects whose best overall response after enrollment according to RECIST ver. 1.1 is either complete response or partial response. Overall response will be graded by favorability in the order of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE). Best overall response is the best response recorded throughout all courses.

[Analysis method]

RR of target lesion and its 95% confidence interval (two-sided) will be calculated in the “full analysis set.”

Further, the maximum tumor reduction rate will be calculated for each subject, and a waterfall plot will be created by arranging the maximum tumor reduction rate in ascending order. Lines of reference at -30% indicating PR and at + 20% indicating PD will be drawn.

$$\text{Reduction ratio of SoD} = \frac{\text{SoD at evaluation point} - \text{SoD before treatment}}{\text{SoD before treatment}} \times 100\%$$

4) Duration of response (DOR)

DOR is the period from the day when either CR or PR is first confirmed until the day of documented PD or the day of death due to any cause, whichever occurs earlier. For surviving subjects without documented PD, the period will be cut off on the final day when specified diagnostic imaging reveals no PD (final day of progression-free survival confirmation). For surviving subjects without documented PD for whom curative resection is indicated during protocol treatment, the period will be cut off on the final day when specified preoperative diagnostic imaging reveals no PD (final day of progression-free survival confirmation).

[Analysis method]

The Kaplan-Meier survival curve will show the subject status until the onset of event for the subjects who showed response among the “full analysis set,” and the point estimation value of survival rate and its 95% confidence interval (two-sided) will be calculated at the quartile of DOR and specified time points.

5) Disease control rate (DCR)

DCR is the percentage of subjects whose best overall response after enrollment according to RECIST ver. 1.1 is CR, PR, or SD.

[Analysis method]

DCR and its 95% confidence interval (two-sided) will be calculated in the “full analysis set.”

6) Time to treatment failure (TTF)

TTF is the period from the day of enrollment until the day of the decision to discontinue protocol treatment, the day of documented progression during protocol treatment (day of decision on clinical PD or radiological PD), or the day of death due to any cause, whichever comes earlier. Subjects not included in the above criteria will be censored at the dose starting date in the final course.

[Analysis method]

Kaplan-Meier method will be used to illustrate survival curve until the onset of event in the “full analysis set,” and the point estimation value of survival rate and its 95% confidence interval (two-sided) will be calculated at the quartile of TTF and specified time points. The Log-Log conversion of Brookmeyer and Crowley will be used to calculate the 95% confidence intervals of the quartiles for TTF.

7.2.4.3 Level of significance, confidence coefficient

Significance level: Main analysis only, 5% (one-sided); other analyses, 5% (two-sided)

Confidence coefficient: Main analysis only, 90% (two-sided); other analyses, 95% (two-sided)

7.2.5 Safety analysis

The following analyses regarding TEAEs and skin toxicity will be performed on the “full analysis set” and “safety analysis set.”

TEAEs will be coded using MedDRA and summarized by SOC and PTs.

A subject with multiple events in the same SOC will be counted once for that SOC. A subject with multiple events with the same PT will be counted once for that PT.

7.2.5.1 Frequency tabulation of all TEAEs

7.2.5.2 Frequency tabulation of TEAEs for which the causal relationship with protocol treatment was “related”

7.2.5.3 Frequency tabulation of TEAEs for which the causal relationship with panitumumab was “related”

7.2.5.4 Frequency tabulation of all TEAEs by severity

7.2.5.5 Frequency tabulation of TEAEs by severity for which the causal relationship with protocol treatment was “related”

7.2.5.6 Frequency tabulation of TEAEs by severity for which the causal relationship with panitumumab was “related”

7.2.5.7 Frequency tabulation of TEAEs for action taken for protocol treatment was “discontinuation”

7.2.5.8 Frequency tabulation of TEAEs by severity for action taken for protocol treatment was “discontinuation”

7.2.5.9 Frequency tabulation of serious TEAEs

7.2.5.10 Frequency tabulation of serious TEAEs for which the causal relationship with protocol treatment was “related”

7.2.5.11 Frequency tabulation of serious TEAEs for which the causal relationship with panitumumab treatment was “related”

7.2.5.12 Frequency tabulation of non-serious TEAEs with $\geq 5\%$ incidence

7.2.5.13 Frequency tabulation of TEAEs of Grade ≥ 3

7.2.5.14 Frequency tabulation of TEAEs of Grade ≥ 3 for which the causal relationship with protocol treatment was “related”

7.2.5.15 Frequency tabulation of TEAEs of Grade ≥ 3 for which the causal relationship with panitumumab was “related”

7.2.5.16 The incidence rate of TEAEs of Grade ≥ 3

7.2.5.17 The incidence rate of TEAEs of Grade ≥ 3 for which the causal relationship with protocol treatment was “related”

7.2.5.18 The incidence rate of TEAEs of Grade ≥ 3 for which the causal relationship with panitumumab was “related”

Skin toxicity will be analyzed similarly as described above (7.2.5.1 to 7.2.5.30).

The following analyses will be performed on the “full analysis set” and “safety analysis set”:

The worst grade in each subject will be calculated. The incidence rate of TEAEs of Grade ≥ 3 and the 95% confidence intervals using Agresti-Coull methods will be calculated. Similarly, incidence rate and the 95% confidence interval of TEAEs will be calculated in the number of TEAE incidence with \geq Grade 3 as the numerator, and the TEAE collecting periods as the denominator. The 95% confidence intervals will be calculated using the following formula:

$$\text{The 95\% confidence intervals of incidence rate} = \text{incidence rate} \pm 1.96 \sqrt{\frac{\text{incidence rate}}{\text{TEAE collecting period}}}$$

7.2.6 Other safety analysis items

7.2.6.1 ECOG P.S.

The frequency distribution of ECOG P.S. in the “full analysis set” and “safety analysis set” will be tabulated for each course, and the percentage (%) will be indicated with the analysis set at Day 1 of that course (excluding withdrawal cases) as the denominator.

7.2.6.2 Laboratory tests

A shift table will be prepared by performing a cross tabulation (number of cases and the percentages) of the results of CTCAE grading based on laboratory values for each test item in the “full analysis set” and “safety analysis set,” using the worst grade at the start and after the start of treatment. The percentage (%) will be indicated with the respective analysis set as the denominator.

Test items:

Neutrophil count, platelet count, hemoglobin level, total bilirubin, ALT (GPT), AST (GOT), creatinine, Mg, albumin, Na, Ca

7.2.7 Table listing

The following tables will be created for the “safety analysis set”:

7.2.7.1 List of subjects who discontinued protocol treatment

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, date of discontinuation, reason for discontinuation, adverse event name (event name recorded by physician, LLT code, LLT Japanese, PT code, PT Japanese, SOC code, SOC Japanese), date of onset, severity, causal relationship of adverse event with protocol treatment, causal relationship with panitumumab, seriousness, discontinuation of protocol treatment, outcome, date of resolution

7.2.7.2 List of subjects/data excluded from analysis

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, reason for exclusion

7.2.7.3 List of fatal cases

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, date of death, reason for death, adverse event name (event name recorded by physician, LLT code, LLT Japanese, PT code, PT Japanese, SOC code, SOC Japanese), date of onset, seriousness, causal relationship of adverse event with protocol treatment, causal relationship with panitumumab, seriousness, discontinuation of protocol treatment, outcome, date of resolution

7.2.7.4 List of treatments

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, primary lesion (information on primary organ, site, with/without resection, date of surgery), metastatic lesion (number of organs with metastases, site, with/without resection, date of surgery), performing a palliative colostomy (with/without, date of surgery), bypass surgery (with/without, date of surgery), radiation therapy (radical irradiation) (with/without, date of surgery, date of final dose), first-line treatment (start date, treatment details), second-line treatment (treatment details), third-line treatment (with/without, treatment details), preoperative/postoperative adjuvant chemotherapy (with/without, time period, oxaliplatin-containing

regimen, date of final dose)

7.2.7.5 List of protocol treatment status

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, start date of TAS102 by course, dose, number of doses, date of panitumumab administration, dose, presence or absence of discontinuation of protocol treatment, date of discontinuation, reason for discontinuation

7.2.7.6 List of complications

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, name of complication (name of complication recorded by physician, LLT code, LLT Japanese, PT code, PT Japanese, SOC code, SOC Japanese)

7.2.7.7 Table of MedDRA-coded AEs

Display items:

Name of AE recorded by physician, LLT code, LLT Japanese, PT code, PT Japanese, SOC code, SOC Japanese

7.2.7.8 List of TEAEs

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, adverse event name (event name recorded by physician, LLT code, LLT Japanese, PT code, PT Japanese, SOC code, SOC Japanese), date of onset, severity, causal relationship with protocol treatment, causal relationship with panitumumab, seriousness, discontinuation of protocol treatment, outcome, date of resolution.

7.2.7.9 List of Deaths and other serious adverse events

Display items:

Same as "List of TEAEs"

7.2.7.10 List of skin toxicity

Display items:

Same as "List of TEAEs"

7.2.7.11 List of RECIST response evaluations

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, evaluation period, sum of target lesion diameter (before treatment, at evaluation), reduction rate of sum of target lesion diameter, results of response evaluation of target lesion, results of response evaluation of non-target lesion, development of new lesion, site of new lesion, results of overall response evaluation

$$\text{Reduction ratio of SoD} = \frac{\text{SoD at evaluation point} - \text{SoD before treatment}}{\text{SoD before treatment}} \times 100\%$$

7.2.7.12 List of determinations of PD

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, day of decision on clinical PD, day of decision on radiological PD, final day of imaging test, final day on which progression-free survival is confirmed, start date of follow-up treatment

7.2.7.13 List of survival survey results

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, survival survey results, last confirmed date of survival, date of death, reason of death (other details)

7.2.7.14 List of laboratory test values

Display items:

Subject No., enrollment phase, DLT evaluation set, full analysis set, safety analysis set, sex, age (years), start date of protocol treatment, laboratory test items, measured values, site reference values (lower limit – upper limit)

Test items: Same as 7.2.6.2.

7.3 Criteria for interim analysis and premature discontinuation

No interim analyses are scheduled.

7.4 Sensitivity analysis

Sensitivity analysis of primary endpoint

For the PFS rate at 6 months (the primary endpoint), results will be calculated for the case in which the period is terminated at the point follow-up treatment is initiated, and the difference between major analysis results will be confirmed.

Kaplan-Meier method will be used to illustrate survival curve until the onset of event in the “full analysis set,” and the point estimation value of survival rate and its 95% confidence interval (two-sided) will be calculated at the quartile of PFS and specified time points. The Log-Log conversion of Brookmeyer and Crowley will be used to calculate the 95% confidence intervals of the quartiles for PFS.

In evaluating PFS, results will be calculated for the case of termination at the point follow-up treatment is initiated (start date of follow-up treatment), and the difference between that and the results for the case in which the period is cut off on the last confirmed date of progression-free status.

8. References

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

APOLLON study

(A phase I/II study for the safety and efficacy of Panitumumab in combination with TAS-102 for patients with *RAS* wild-type metastatic colorectal cancer refractory to standard chemotherapy)

(Protocol number: Panitumumab-1501)

Statistics Analysis Plan

Version 1.0



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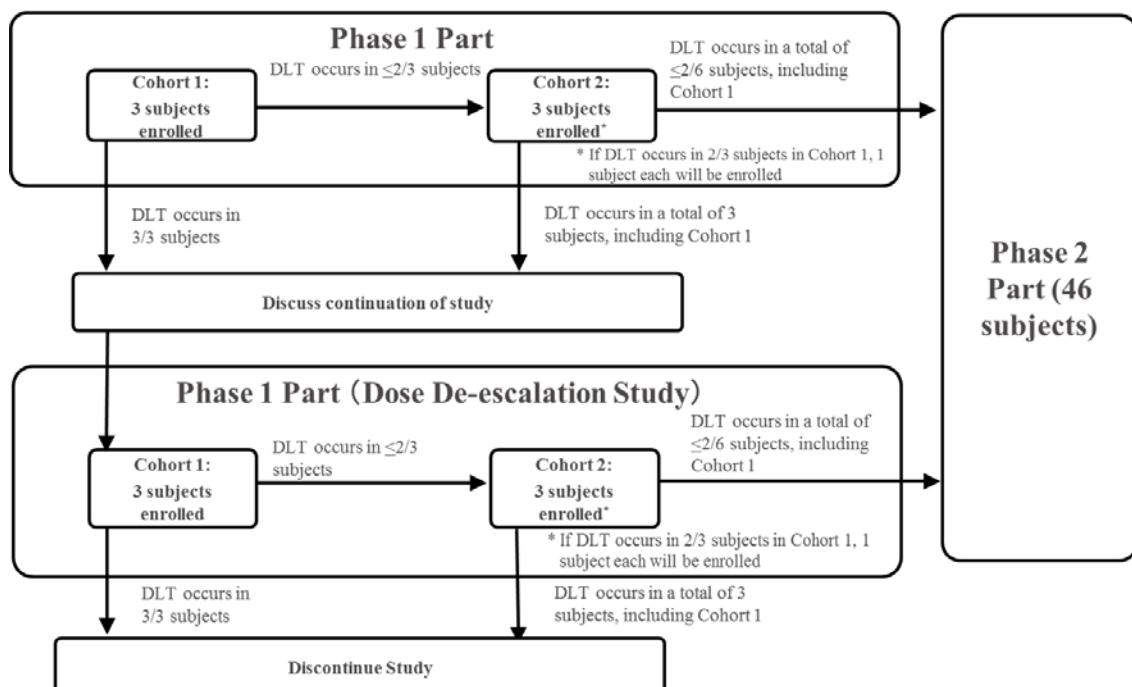
1. History of preparation and revision

Version	Date of approval	Author	Reason for revision
1.0	June 3, 2016	PPD	Not applicable, because it is the first version

2. Analysis Plan Objectives

This analysis plan specifies how the initial and final analyses of the clinical study are planned to be conducted in accordance with the “Clinical Study Protocol of A phase I/II study for the safety and efficacy of Panitumumab in combination with TAS-102 for patients with RAS wild-type metastatic colorectal cancer refractory to standard chemotherapy” (hereinafter, protocol).

The study design is shown below.



3. Time period for Analysis

Phase I part: Analysis will be performed after completion of enrollment for phase I part and after completion of Dose Limiting Toxicity (DLT) evaluation period for all enrolled subjects, and when DLT has been evaluated.

Phase II part: Analysis will be performed after completion of enrollment for phase II part and when evaluation has been performed in all the enrolled subjects at 6 months after the start of protocol treatment (initial analysis) and at completion of period for all observations (final analysis).

4. Analysis data set

4.1 Handling of cases/data

(1) Handling of laboratory values/subjective and objective findings of adverse events

Adverse events recorded on the adverse event form will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred terms

(PTs). Skin disorders will be regarded as events classified into “Skin and subcutaneous tissue disorders” of SOC or “Paronychia” by PT. The PTs classified as skin toxicity (Rash acneiform, Paronychia, Dry skin, Pruritus) are defined in Table 4.1.

Table 4.1 Events classified as skin toxicity

Rash acneiform	Acne, Dermatitis acneiform, Folliculitis, Rash, Dermatitis, Drug eruption, Rash pruritic, Eczema, Skin disorder, Rash generalized, Seborrhoeic dermatitis
Paronychia	Paronychia, Nail avulsion, Onychoclasia, Onychomadesis, Nail disorder, Ingrowing nail, Excessive granulation tissue, Pyogenic granuloma
Dry skin	Dry skin, Skin fissures, Xeroderma, Skin exfoliation, Skin chapped, Eczema asteatotic, Hyperkeratosis
Pruritus	Pruritus, General pruritus

(2) Handling of adverse event grade

If an AE is assessed multiple times in the same subject, the highest grade among all AE assessments shall be reported as the worst grade of the AE.

(3) Handling of missing/ejected data

Missing data will not be complemented unless the details of individual analysis items are specified. When rejecting data, the corresponding data will be indicated and the reason for rejection clarified in a table. However, handling of patients with no occurrence of events related to Progression-Free Survival (PFS), Overall Survival (OS), or Time to Treatment Failure (TTF) will be described in Section 7.2.4.3.

4.2 Number of significant figures in analysis results

Percentages (%) expressing frequency distribution will be rounded to one decimal place unless the details of individual analysis items are specified.

Among summary statistics, mean and standard deviation will be rounded to one decimal place lower than the original data.

P-values will be indicated to 4 decimal places rounded from the 5th decimal. However, a p-value less than 0.0001 will be expressed as “p < 0.0001.” Hazard ratios and their 95% confidence intervals will be indicated to 2 decimal places rounded from the 3rd decimal.

5. Software used for analysis

The statistical software used for analysis will be CCI [REDACTED]

6. Statistical analysis of the phase I part of the study

6.1 Analysis set

Two analysis sets will be created for the phase I part of the study: “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria” and the “DLT evaluation set.” The DLT evaluation set will be based on the following definition from the protocol, Section 8.9.2:

Subjects enrolled in the phase I part of the study will be included in the DLT evaluation set. Subjects will be excluded from the DLT evaluation if at least the designated dose of protocol treatment is not administered by the end of Course 1 (except when the protocol treatment is discontinued due to DLT), if there are major protocol deviations such as the use of contraindicated drugs, or if the subject is determined to be unsuitable for the DLT evaluation. The designated dose is 75% (15 doses) of the total number of doses (20 doses) of panitumumab (2 doses of 6 mg/kg) and TAS-102 (2 doses daily of 35 mg/m²) on Days 1-5 and Days 8-12.

6.2 Analysis of demographic and other baseline characteristics

The following analyses will be conducted in the “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria” and the “DLT evaluation set.”

(1) Discrete data:

A frequency distribution for the discrete data will be computed indicating the percentage (%) with the analysis set as a denominator. Aggregation items are as follows:

- Age (≥ 20 to < 30 years, ≥ 30 to < 40 years, ≥ 40 to < 50 years, ≥ 50 to < 60 years, ≥ 60 to < 70 years, ≥ 70 to < 75 years; ≥ 20 to < 65 years, ≥ 65 to < 75 years), sex, information on primary organ tumor (solitary, multiple), primary tumor location (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectosigmoid, rectum), information on metastasis (number of organs with metastasis) (0, 1, ≥ 2), organs with metastasis (liver, lung, peritoneum, lymph node, bone, adrenal gland, skin, and others), ECOG Performance status (P.S.) (at enrollment) (0, 1, 2, 3, 4), complications (absence, presence)

(2) Continuous data:

Summary statistics (number of cases, mean, standard deviation, minimum, maximum, and inclusive quartiles) will be calculated for continuous data.

- Age (years), height (cm), body weight (kg) (at enrollment), BMI (kg/m²) (at enrollment).

6.3 Safety analysis

6.3.1 Incidence of DLT events with panitumumab + TAS-102 combination therapy

In accordance with the protocol, Section 8.9.3., the number of cases determined as DLTs among

subjects in the DLT evaluation set will be shown and the percentage (%) will be indicated with the total number of cases in the DLT evaluation set as a denominator.

6.3.2 Listing of DLT events

A table listing events determined as DLTs in the DLT evaluation set will be prepared.

Display items:

Subject No., sex, age (years), BMI (kg/m²) (at enrollment), protocol treatment initiation date, DLT event name (event name recorded by physician, Lowest Level Terms [LLT] code, LLT Japanese, PT code, PT Japanese, SOC code, SOC Japanese), date of onset, severity, causal relationship of adverse event with protocol treatment, causal relationship with panitumumab, seriousness, discontinuation of protocol treatment, outcome, date of resolution

6.3.3 Frequency tabulation of adverse events

The following analyses regarding treatment-emergent adverse events (TEAEs) and skin toxicity will be performed on the “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria” and the “DLT evaluation set.”

TEAEs are adverse events that develop after initiation of protocol treatment.

Skin toxicity are events meeting the definitions of TEAEs in Table 4.1.

TEAEs and skin toxicity will be coded using MedDRA and summarized by SOC and PTs.

A subject with multiple events in the same SOC will be counted once for that SOC. A subject with multiple events with the same PT will be counted once for that PT.

6.3.3.1 Frequency tabulation of all TEAEs

6.3.3.2 Frequency tabulation of TEAEs for which the causal relationship with protocol treatment was “related”

6.3.3.3 Frequency tabulation of TEAEs for which the causal relationship with panitumumab was “related”

6.3.3.4 Frequency tabulation of all TEAEs by severity

6.3.3.5 Frequency tabulation of TEAEs by severity for which the causal relationship with protocol treatment was “related”

6.3.3.6 Frequency tabulation of TEAEs by severity for which the causal relationship with panitumumab was “related”

6.3.3.7 Frequency tabulation of TEAEs for action taken for protocol treatment was “discontinuation”

6.3.3.8 Frequency tabulation of TEAEs by severity for action taken for protocol treatment was “discontinuation”

6.3.3.9 Frequency tabulation of serious TEAEs

6.3.3.10 Frequency tabulation of serious TEAEs for which the causal relationship with protocol treatment was “related”

6.3.3.11 Frequency tabulation of serious TEAEs for which the causal relationship with panitumumab treatment was “related”

6.3.3.12 Frequency tabulation of TEAEs of Grade ≥ 3

6.3.3.13 The incidence rate of TEAEs of Grade ≥ 3

The following analyses will be performed on the “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria” and the “DLT evaluation set.”

The worst grade in each subject will be calculated. The incidence rate of TEAEs of Grade ≥ 3 and the 95% confidence intervals using Agresti-Coull methods will be calculated. Similarly, incidence rate and the 95% confidence interval of TEAEs will be calculated in the number of TEAE incidence with \geq Grade 3 as the numerator, and the TEAE collecting periods as the denominator. The 95% confidence intervals will be calculated using the following formula:

$$95\% \text{ confidence interval of incidence rate} = \text{incidence rate} \pm 1.96 \sqrt{\frac{\text{incidence rate}}{\text{TEAE collecting period}}}$$

6.3.4 Table listing

The following items will be tabulated for the “set of enrolled subjects who received at least one dose of protocol treatment and satisfied all of the enrollment criteria”:

6.3.4.1 List of TEAEs

Display items:

Subject No., DLT evaluation set, sex, age (years), BMI (kg/m^2) (at enrollment), protocol treatment initiation date, DLT event name (event name recorded by physician, LLT code, LLT Japanese, PT code, PT Japanese, SOC code, SOC Japanese), date of onset, severity, causal relationship of adverse event with protocol treatment, causal relationship with panitumumab, seriousness, discontinuation of protocol treatment, outcome, date of resolution

6.3.4.2 List of protocol treatment status

Display items:

Subject No., DLT evaluation set, sex, age (years), BMI (kg/m^2) (at enrollment), start date of protocol treatment, start date of TAS102 by course, dose, number of doses, date of panitumumab administration, dose, presence or absence of discontinuation of protocol treatment, date of

discontinuation, reason for discontinuation

6.3.4.3 List of treatment history

Display items:

Subject No., DLT evaluation set, sex, age (years), BMI (kg/m²) (at enrollment), protocol treatment initiation date, primary lesion (information on primary organ, site, with/without resection, date of surgery), metastatic lesion (number of organs with metastases, site, with/without resection, date of surgery), performing a palliative colostomy (with/without, date of surgery), bypass surgery (with/without, date of surgery), radiation therapy (radical irradiation) (with/without, date of surgery, date of final dose), first-line treatment (start date, treatment details), second-line treatment (treatment details), third-line treatment (with/without, treatment details), preoperative/postoperative adjuvant chemotherapy (with/without, time period, oxaliplatin-containing regimen, date of final dose)

6.3.4.4 List of complications

Display items:

Subject No., DLT evaluation set, sex, age (years), BMI (kg/m²) (at enrollment), protocol treatment initiation date, name of complication (name of complication recorded by physician, LLT code, LLT Japanese, PT code, PT Japanese, SOC code, SOC Japanese)

6.3.4.5 List of laboratory values

Display items:

Subject No., DLT evaluation set, sex, age (years), BMI (kg/m²) (at enrollment), protocol treatment initiation date, test date, test item (category, item name), measured value, unit, baseline

7. Statistical analysis of the phase II part of the study

7.1 Analysis set

In the phase II part of the study, statistical analysis will be performed on a "full analysis set" and "safety analysis set." The "full analysis set" will be the main efficacy analysis set, and is defined as "subjects enrolled in phase I and II who received at least one dose of protocol treatment (RD) and satisfied all of the enrollment criteria." The "safety analysis set" is defined as "subjects enrolled in phase I and II who received at least one dose of protocol treatment (RD)." Additionally, the set of all subjects who are enrolled in this study is defined as "all enrolled subjects."

The statistics representative and analysis personnel should finalize a statistical analysis plan before data fixation based on confirmation of the definition of analysis sets and appropriateness of analytical handling rules of the subject data in the analysis sets, and additional handling rules for the issues that are not determined at planning before data fixation.

7.2 Evaluation of analysis set

7.2.1 Eligibility and analysis set

A flow chart showing the breakdown of “all enrolled subjects,” “full analysis set,” and “safety analysis set,” and tabulation of reasons for patients not being included in the analysis set will be prepared based on the CONSolidated Standards Of Reporting Trials (CONSORT).¹⁾

7.2.2 Analysis of demographic and other baseline characteristics

7.2.2.1 Demographic and other baseline characteristics

The following analyses of the main subject demographic factors will be performed on “all enrolled subjects,” the “full analysis set,” and the “safety analysis set”:

(1) Discrete data

A frequency distribution will be tabulated for discrete data, and the percentage (%) will be indicated with the analysis set as a denominator. Tabulation items are as follows:

- Age (≥ 20 to < 30 years, ≥ 30 to < 40 years, ≥ 40 to < 50 years, ≥ 50 to < 60 years, ≥ 60 to < 70 years, ≥ 70 to < 75 years; ≥ 20 to < 65 years, ≥ 65 to < 75 years), sex, information on primary organ [tumor (solitary, multiple), primary tumor location (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectosigmoid, rectum)], information on metastasis [(number of organs with metastasis) (0, 1, ≥ 2), organs with metastasis (liver, lung, peritoneum, lymph node, bone, adrenal gland, skin, and others)], ECOG Performance status (P.S.) (at enrollment) (0, 1, 2, 3, 4), complications (absence, presence).

(2) Continuous data

Summary statistics (number of cases, the mean, standard deviation, minimum, maximum, quartiles) will be calculated for continuous data.

- Age (years), height (cm), body weight (kg) (at enrollment), BMI (kg/m^2) (at enrollment).

7.2.2.2 Breakdown of complications

The frequency distribution of complications in “all enrolled subjects,” “full analysis set,” and “safety analysis set” will be tabulated, and the percentage (%) will be indicated with the analysis set as the denominator. Complications will be coded using MedDRA and summarized by SOC and PTs.

7.2.3 Medication status

7.2.3.1 Completion of administration

The total completion rate of administration in the “full analysis set” and “safety analysis set” will be calculated by course for protocol treatment and for each drug, frequency distribution will be

tabulated, and the percentage (%) will be indicated with the respective analysis set as the denominator.

The cumulative dose over the entire period and the period up to Course 6, and relative dose intensity (RDI) over the period up to Course 6, and summary statistics (number of cases, mean, median, standard deviation, minimum, maximum) will be calculated by drug. The RDI will be calculated using the following formulae:

$$\text{RDI (\%)} = (\text{actual dose}/\text{initial planned dose}) \times (28/\text{number of days until completion of specific actual course}) \times 100$$

$$\text{Total RDI (\%)} = (\text{all actual dose}/\text{all planned dose}) \times (168/\text{actual number of days of all courses}) \times 100$$

7.2.3.2 Reason for discontinuation of protocol treatment

Reasons for discontinuation in the “full analysis set” and “safety analysis set” will be tabulated for each course specified, and the percentage (%) will be indicated with the respective analysis set as the denominator. For subjects in whom the reason for discontinuation is “Other,” a list will be prepared summarizing reasons for discontinuation by status of completion of administration.

7.2.3.3 Dose reduction status

The frequency and percentage (%) of the subjects with dose reduction in the “full analysis set” and “safety analysis set” will be tabulated for each drug. Similarly, the frequency and percentage (%) will be tabulated for each specified course (6 courses), and the frequency distribution will be tabulated for each reason.

7.2.3.4 Follow-up status

The quartiles of follow-up period will be calculated in the “full analysis set” and “safety analysis set.” The follow-up period is the period from the day of enrollment until the day of completion of follow-up. The reverse Kaplan-Meier method will be used to calculate the quartiles of the follow-up period.²⁾

7.2.4 Efficacy analysis

7.2.4.1 Primary endpoint and analysis method

[Primary endpoint]

Progression-free survival (PFS rate) at 6 months after enrollment

The PFS rate 6 months after enrollment, the primary endpoint, is the gross proportion of surviving

subjects without documented progression up to 6 months after enrollment, counting from the day of enrollment. Subjects with no imaging data on progression at 6 months after enrollment and subjects lost to follow-up will be included in the denominator, but will not be handled as progression-free.

Definition of progression:

Progression will include both progressive disease (PD) based on diagnostic imaging assessed according to RECIST ver. 1.1 and primary disease progression that cannot be confirmed by diagnostic imaging (clinical progression). When progression is documented by diagnostic imaging, the day on which the diagnostic imaging is performed will be the progression date. For clinical progression, the day of the clinical determination will be the progression date. In a case in which, for example, tumor diameter has become extremely small, if the status is determined to be “not definite progression” clinically, although the assessment is PD according to the response criteria, the assessment of PD according to the response criteria will take precedence and the status will be considered progression. (In this case, the clinical determination on continuing protocol treatment will take precedence.) Even if the assessment is not PD according to the response criteria, if there is definite clinically documented progression, the clinical determination will take precedence and the status will be considered progression. For surviving subjects without documented progression, the period will be cut off on the final day on which progression-free status is confirmed (final day of progression-free survival confirmation). Confirmation of progression-free status by imaging test or sample test is not mandatory, and clinical confirmation by outpatient medical examination, etc., will be allowed (Contact by telephone only will not be allowed.). Events and the cut-off will also be handled the same way in subjects who have discontinued protocol treatment for reasons such as toxicity and refusal of treatment, even if another (follow-up) therapy is added. Thus, the time of treatment discontinuation or the day of follow-up treatment initiation will not be the cut-off.

[Main analysis]

The following analysis will be performed on the “full analysis set.”

PFS rate at 6 months is calculated by counting of subjects with progression, without progression, and unconfirmed at 6 months. Based on the observed PFS rate at 6 months from the day of enrollment, binomial test will be conducted on the null hypothesis “value will be determined invalid at PFS rate $\leq 29\%$.” Significant level will be 2.5% (one-sided) in the main analysis. For interval estimation, accurate 90% confidence interval (two-sided) based on binomial distribution will be used.

7.2.4.2 Secondary endpoints and analysis method

[Secondary endpoints]

- Progression-free survival (PFS)

PFS is the period from the day of enrollment until the day of documented PD or the day of death due to any cause, whichever comes earlier.

[Analysis method]

Kaplan-Meier method will be used to illustrate survival curve until the onset of event in the “full analysis set,” and quartile point and its 95% confidence interval (two-sided) of PFS will be calculated. The Log-Log conversion of Brookmeyer and Crowley will be used to calculate the 95% confidence intervals of the quartiles for PFS.

- Overall survival (OS)

OS is the period from the day of enrollment until death by any cause. For surviving subjects, the period is terminated on the final day of survival confirmation or data cut-off date, whichever occurs earlier.

[Analysis method]

The analysis will be performed in the same manner as for PFS in the “full analysis set.”

- Response rate (RR)

RR is the percentage of subjects whose best overall response after enrollment according to RECIST ver. 1.1 is either complete response or partial response. Overall response will be graded by favorability in the order of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE).

[Analysis method]

RR and its 95% confidence interval (two-sided) will be calculated in the “full analysis set.”

- Duration of response (DOR)

DOR is the period from the day when either CR or PR is first confirmed until the day of documented PD or the day of death due to any cause, whichever occurs earlier. For surviving subjects without documented PD, the period will be cut off on the final day when specified diagnostic imaging reveals no PD (final day of progression-free survival confirmation). For surviving subjects without documented PD for whom curative resection is indicated during

protocol treatment, the period will be cut off on the final day when specified preoperative diagnostic imaging reveals no PD (final day of progression-free survival confirmation).

[Analysis method]

The Kaplan-Meier survival curve will show the subject status until the onset of event for the subjects who showed response among the “full analysis set,” and the point estimation value of survival rate and its 95% confidence interval (two-sided) will be calculated at the quartile of survival period and specified time points.

- Disease control rate (DCR)

DCR is the percentage of subjects whose best overall response after enrollment according to RECIST ver. 1.1 is CR, PR, or SD. Overall response will be graded by favorability in the order of CR, PR, SD, PD, and NE

[Analysis method]

DCR and its 95% confidence interval (two-sided) will be calculated in the “full analysis set.”

- Time to treatment failure (TTF)

TTF is the period from the day of enrollment until the day of the decision to discontinue protocol treatment, the day of documented progression during protocol treatment, or the day of death due to any cause, whichever comes earlier.

[Analysis method]

The analysis of TTF will be performed in the same manner as for PFS in the “full analysis set.”

7.2.4.3 Data conversion method and handling of missing data

Subjects without occurrence of events listed in Section 7.2.4.2 will be treated as discontinued subjects in the analysis in the maintenance period for PFS, OS, and TIF.

The cut-off date will be the final day on which progression-free survival is confirmed, when the clinically progression-free status has been confirmed in the PFS analysis, the final day on which survival is confirmed in the OS analysis, and the start date of dosing in the final course in the TTF analysis.

7.2.4.4 Level of significance, confidence coefficient

Significance level: Main analysis only, 5% (one-sided); other analyses, 5% (two-sided)

Confidence coefficient: Main analysis only, 90% (two-sided); other analyses, 95% (two-sided)

7.2.5 Safety analysis

The following analyses regarding TEAEs and skin toxicity will be performed on the “full analysis set” and “safety analysis set.”

TEAEs and skin toxicity will be coded using MedDRA and summarized by SOC and PTs.

A subject with multiple events in the same SOC will be counted once for that SOC. A subject with multiple events with the same PT will be counted once for that PT.

7.2.5.1 Frequency tabulation of all TEAEs

7.2.5.2 Frequency tabulation of TEAEs for which the causal relationship with protocol treatment was “related”

7.2.5.3 Frequency tabulation of TEAEs for which the causal relationship with panitumumab was “related”

7.2.5.4 Frequency tabulation of all TEAEs by severity

7.2.5.5 Frequency tabulation of TEAEs by severity for which the causal relationship with protocol treatment was “related”

7.2.5.6 Frequency tabulation of TEAEs by severity for which the causal relationship with panitumumab was “related”

7.2.5.7 Frequency tabulation of TEAEs for action taken for protocol treatment was “discontinuation”

7.2.5.8 Frequency tabulation of TEAEs by severity for action taken for protocol treatment was “discontinuation”

7.2.5.9 Frequency tabulation of serious TEAEs

7.2.5.10 Frequency tabulation of serious TEAEs for which the causal relationship with protocol treatment was “related”

7.2.5.11 Frequency tabulation of serious TEAEs for which the causal relationship with panitumumab treatment was “related”

7.2.5.12 Frequency tabulation of TEAEs of Grade ≥ 3

7.2.5.13 The incidence rate of TEAEs of Grade ≥ 3

The following analyses will be performed on the “full analysis set” and “safety analysis set”:

The worst grade in each subject will be calculated. The incidence rate of TEAEs of Grade ≥ 3 and the 95% confidence intervals using Agresti-Coull methods will be calculated. Similarly, incidence rate and the 95% confidence interval of TEAEs will be calculated in the number of TEAE incidence with \geq Grade 3 as the numerator, and the TEAE collecting periods as the denominator. The 95%

confidence intervals will be calculated using the following formula:

$$\text{The 95\% confidence intervals of incidence rate} = \text{incidence rate} \pm 1.96 \sqrt{\frac{\text{incidence rate}}{\text{TEAE collecting period}}}$$

7.2.6 Table listing

7.3 Criteria for interim analysis and premature discontinuation

No interim analyses are scheduled.

7.4 Sensitivity analysis

7.4.1 Sensitivity analysis of primary endpoint

For the PFS rate at 6 months (the primary endpoint), results will be calculated for the case in which the period is terminated at the point follow-up treatment is initiated, and the difference between major analysis results will be confirmed.

7.4.2 Sensitivity analysis of secondary endpoints

In assessing PFS under the same conditions as in Section 7.4.1, the result will be calculated for cases in which there is a change in handling, to identify the differences between the results.

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.