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

Protocol Approve Date: 29-Sep-2017

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If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

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

PROTOCOL

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

APOLLON study

A phase I/II study for the safety and efficacy of **P**anitumumab in c**o**mbination with TAS-102 for patients with *RAS* wild-type metastatic co**l**orecta**l** cancer refract**o**ry to sta**n**dard chemotherapy

Sponsor	Takeda Pharmaceutical Company Limited
Protocol number	Panitumumab-1501
Version	Second Edition
Product name	Panitumumab
Creation date	September 29, 2017

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1.0 CLINICAL STUDY PRINCIPLES AND CLINICAL STUDY MANAGEMENT INFORMATION

1.1 Clinical Study Principals

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- Ethical Guideline for Clinical Research (the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, December 22, 2014).
- International Conference on Harmonisation E6 Good Clinical Practice (hereinafter referred to as "GCP") (including ICH-GCP).
- All applicable laws and regulations, including, without limitation, data privacy laws, conflict of interest guidelines.

1.2 Clinical Study Administrative Structure

This study will be conducted under the following administrative structure.

Clinical research steering committee

Research steering committee chairman:

PPD

Research steering committee members:

PPD

Data Monitoring Committee (hereinafter referred to as DMC)

DMC chairman:

PPD

DMC members:

PPD

Statistics Representative:

PPD

Also, terms used in this protocol will be defined as follows:

Study site:

A corporation an administrative organization or a sole proprietor conducting the study, except for sites performing only a part of the study related activities on consignment such as sample/ information storage and statistic processing.

Joint research institution:

An institution jointly conducting the study based on the protocol, and will include institutions that will additionally obtain sample/ information from study subjects and providing them to other study sites.

Study staff:

Investigators and other staff personnel conducting the study (including activities performed in institutions that collect and provide samples/ information), except for personnel who only provides existing samples/information besides study site or partially engage in the study related activity on consignment.

Investigator:

A personnel taking part in conducting the study and presides over the study related activities within the belonging study site.

Study site director:

Director of a corporation, an administrative organization or a sole proprietor conducting the study

Study subjects:

A person who is applicable to either of the following:

1. A person who is being studied (including a person who has been requested to be studied)
2. A person who has given existing samples/information to be used in the study

1.3 Contacts for protocol inquiries

Study office: PPD

E-mail: PPD

Tel: PPD

[Reception hours]

PPD

1.4 Contacts for enrollment procedure

Case enrollment center: PPD

• E-mail: PPD

[E-mail receipt confirmation]

PPD

• Tel: PPD

[Reception hours]

PPD

1.5 Sponsor

Takeda Pharmaceutical Company Limited,

Strategic Medical Research Planning, Global Medical Affairs Department, Japan Oncology Business Unit

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2.0 STUDY SUMMARY

Sponsor:	**Test product:**
Takeda Pharmaceutical Company Limited	Panitumumab

Study title:

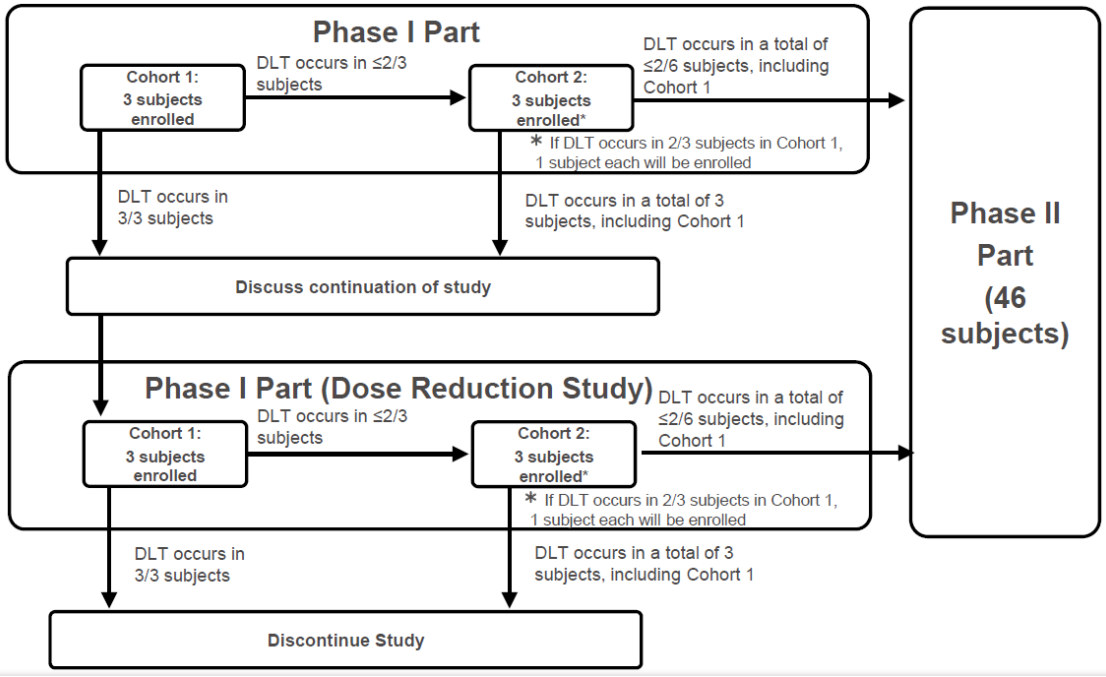
A phase I/II study for the safety and efficacy of Panitumumab in combination with TAS-102 for patients with *RAS* (*KRAS*, *NRAS*) wild-type unresectable, advanced/recurrent colorectal cancer

APOLLON study (**A** phase I/II study for the safety and efficacy of **P**anitumumab in c**o**mbination with TAS-102 for patients with RAS wild-type metastatic co**l**orecta**l** cancer refract**o**ry to sta**n**dard chemotherapy)

Protocol number: Panitumumab-1501

Clinical study design:

This phase I/II study is a multi-center, open-label single-arm study that consists of a phase I part (dose de-escalation) which will assess the tolerability, safety and Recommended Dose (hereinafter referred to as RD) of Panitumumab in combination with TAS-102 as primary objective, and a phase II part which will assess the efficacy and safety of Panitumumab in combination with TAS-102 as primary objective in patients with RAS wild-type unresectable, advanced/recurrent colorectal cancer. In the phase I part, the subjects will be included sequentially into Cohort 1 and 2, 3 subjects each with the same dosage and administration. In the phase II part, 46 subjects will be included additionally for RD confirmed in the phase I part.



In the phase I part, each cohort will be conducted with 3 subjects, the sponsor will assess tolerability of the dosage and administration based on the incidence of Dose Limiting Toxicity (hereinafter referred to as DLT) during the assessment period and determine whether or not to move on to the next cohort (opinion from the Data Monitoring Committee [hereinafter referred to as DMC] will be confirmed appropriately upon determination). Therefore, in Cohort 1, if occurrence of DLT is ≤ 2 subjects out of 3, the dosage and administration will be determined tolerable and will move on to Cohort 2. However, if DLT is observed in 2 subjects during DLT assessment period in Cohort 1, subjects will be included one at a time in Cohort 2 in consideration for safety to assess DLT. Similarly 3 subjects will be included in Cohort 2 and DLT will be assessed in a total of 6 subjects of Cohort 1 and 2 at most. If DLT is observed in 3 subjects included in Cohort 1, or DLT is observed in 3 subjects from a total of 6 subjects of Cohort 1 and 2, the sponsor will promptly request to postpone new enrollment of subjects to each site and after consultation with the Research Steering Committee and DMC on the continuation of the study, will determine whether or not to continue the study. If study is to be continued, taking in account of the adverse event that occurred, either panitumumab or TAS-102 or both drugs will be reduced one step and re-conducting the phase I part similarly will be considered. If DLT is observed in 3 subjects after reducing 1 step of panitumumab or TAS-102 or both drugs, the study will be discontinued. If DLT is observed in ≤ 2 subjects from a total of 6 subjects of Cohort 1 and 2, the sponsor will comprehensively assess with the Research Steering Committee based on the safety data of the phase I part, and after confirming the opinion of DMC, will determine the transit to phase II part. In the phase II part, in addition to the 6 subjects who received RD dose in the phase I part, a target of 46 subjects are to be accumulated (a total of 52 subjects).
Objective: Phase I part Assess RD (Recommended Dose) of panitumumab in combination with TAS-102 in patients with RAS wild-type unresectable, advanced/recurrent colorectal cancer Phase II part Assess efficacy and safety of panitumumab in combination with TAS-102 in patients with RAS wild-type unresectable, advanced/recurrent colorectal cancer
Study population: patients with RAS wild-type unresectable, advanced/recurrent colorectal cancer refractory or intolerant to fluropyrimidines, oxaliplatin, irinotecan and angiogenesis inhibitors (bevacizumab, aflibercept, ramycirumab, etc.)
Planned number of subjects: A maximum of 58 subjects

Number of study sites:

Phase I part: approximately 5

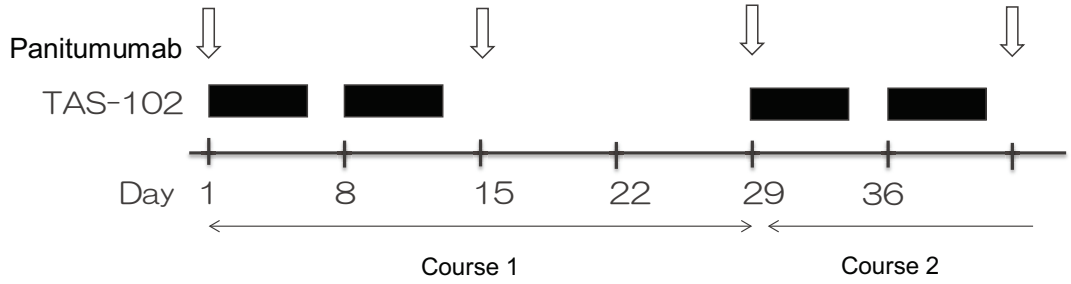
Phase II part: approximately 30

Method of administration:

Treatment for 4 weeks (28 days) as 1 course according to the dosage, schedule and route of administration as follows.

Panitumumab: 6 mg/kg/dose once each on Day 1 and Day 15 by IV administration (IV drip infusion)

TAS-102: 35 mg/m$^{2/}$dose given orally twice daily (after breakfast and after dinner) for 5 consecutive days followed by 2 days of washout and after this is repeated twice, 14 days washout will be implemented.



If either panitumumab or TAS-102 or both drugs are to be reduced for DLT occurrence in phase I part, dosage and administration will be as follows.

If panitumumab is to be reduced: 4.8 mg/kg/dose once each on Day 1 and Day 15 by IV administration (IV drip infusion)

If TAS-102 is to be reduced: 30 mg/m$^{2/}$dose given orally twice daily (after breakfast and after dinner) for 5 consecutive days followed by 2 days of washout and after this is repeated twice, 14 days washout will be implemented.

Dose limiting toxicity (DLT) definition

In this study, DLT will be assessed based on the adverse events observed in 6 subjects at maximum enrolled in phase I part. DLT will be defined as follows [definition and grade will be based on Common Terminology Criteria for Adverse Events (CTCAE) ver4.03]. Further, DLT will be assessed from Day 1 of course 1 of protocol treatment, and if DLT does not occur by Day 1 of course 2, it will be handled as no occurrence of DLT in the subject. Adverse events that can clearly be denied of causal relationship with the protocol treatment will not be assessed as DLT. If serious adverse event or unexpected adverse event occurs which causal relationship with the protocol treatment cannot be denied other than the following, it may be determined as to whether or not to handle it as DLT in consultation with the Investigator, the Research Steering Committee and the sponsor.

1. Persistent Grade 4 neutropenia for more than 7 days under maximum supportive therapy
2. Febrile neutropenia
3. Blood platelete decreased of Grade 3 requiring platelet transfusion or blood platelete decreased of Grade 4
4. If start of second course is delayed for more than 14 days due to adverse event related to protocol treatment
5. Grade 3 or higher non-hematologic toxicity that is clinically problematic however the following will not be applicable as DLT.

   -Grade 3 gastrointestinal symptoms that can be controlled with supportive care (appropriate use of antiemetics, antidiarrheals, etc.)

   -Grade 3 or higher electrolyte abnormalities that are not deemed clinically problematic

Duration of treatment (as a guide):	**Period of evaluation:**
6 months	12 months

Inclusion criteria at enrollment:

1. In the opinion of the investigator* or the subinvestigator, the patient is capable of understanding and complying with protocol requirements.

   *: A personnel taking part in conducting the study and presides over the study related activities within the belonging study site.
2. A patient who can sign and date a written, informed consent form prior to the study enrollment.
3. Patients aged ≥ 20 to < 75 years at the time of informed consent
4. Patients with unresectable adenocarcinoma originating in the large intestine (excluding carcinoma of the appendix and anal canal cancer)
5. Patients who have measurable lesion (refer to Appendix A) according to Response Evaluation

Criteria in Solid Tumors (hereinafter referred to as RECIST) ver 1.1

6. Patients with metastatic colorectal cancer refractory or intolerant* to chemotherapy including fluropyrimidines, oxaliplatin, irinotecan and angiogenesis inhibitors (bevacizumab, aflibercept, ramycirumab, etc.)

   *: Refractory or intolerant if applicable to any of the following

   1) If recurrence is observed during supportive chemotherapy before or after surgery or from imaging diagnosis within 6 months of completion.

   2) If imaging or clinical progression is observed during or within 3 months from the last administration of chemotherapy for advanced cancer

   3) When it is determined that resumption is not possible due to intolerable adverse event (serious allergic reaction, accumulative neuropathy, etc.)

7. Patients classified as *KRAS/NRAS* wild-type** by *KRAS*/*NRAS* testing*.

   *: *KRAS*/*NRAS* test will be performed using the in vitro diagnostic that has been approved for marketing.

   **: All codons listed below are required to be wild-type. If any codon is unmeasured or unmeasurable, it will not be defined as wild-type.

KRAS	EXON	2	3	4
	codon	12, 13	59, 61	117, 146
NRAS	EXON	2	3	4
	codon	12, 13	59, 61	117, 146

8. Patients who may receive oral administration

9. Patients who satisfy the following criteria for the major organ function in tests performed within two weeks (14 days) prior to enrollment.

   (1) Neutrophil count 1.5×10^3/L

   (2) Platelet count 10.0×10^4/L

   (3) Hemoglobin 8.0 g/dL

   (4) Total blood bilirubin 1.5 mg/dL

   (5) AST 100 IU/L (200 IU/L if liver metastases are present)

   (6) ALT 100 IU/L (200 IU/L if liver metastases are present)

   (7) Serum creatinine 1.5 mg/dL

10. Eastern Cooperative Oncology Group (hereinafter referred to as ECOG) performance status (P.S.) has been determined as 0-1.

11. Life expectancy of 3 months (90 days) after enrollment.

Exclusion criteria at enrollment:

1. Patients who have treatment history of anti-EGFR antibody drugs (cetuximab, panitumumab), regorafenib and TAS-102
2. Patients who have received radiotherapy and chemotherapy for primary disease as previous treatment and ≥ 2 weeks (14 days) have not passed since the last treatment at scheduled start day of treatment. However, excluding therapy received for pain relief of bone metastasis site
3. Patients with known brain metastasis or strongly suspected of brain metastasis
4. Patients with synchronous cancers or metachronous cancers with a disease-free period of 5 years (excluding colorectal cancer) However, excluding mucosal cancers cured or be possibly cured by regional resection (esophageal, stomach, and cervical cancer, non-melanoma skin cancer, bladder cancer, etc.)
5. Patients with body cavity fluid that requires treatment (pleural effusion, ascites, pericardial effusion, etc.)
6. Patients who do not want to use contraception to prevent pregnancy, and women who are pregnant or breast-feeding, or test positive for pregnancy
7. Patients who have received other study drugs and ≥ 4 weeks (28 days) have not passed since at scheduled start day of treatment.
8. Patients with disease requiring systemic steroids for treatment (excluding topical steroids)
9. Patients with history or obvious and extensive computerized tomography (CT) findings of interstitial pulmonary disease (interstitial pneumonia, pulmonary fibrosis, etc.)
10. Patients with serious concurrent medical condition (intestinal paralysis, gastrointestinal obstruction, intestinal obstruction, uncontrollable diarrhoea, diabetes mellitus being treated with continuous use of insulin or that is difficult to control, renal failure, hepatic failure, psychiatric disorder, cerebrovascular disorder, gastrointestinal ulceration requiring blood transfusion)
11. Patients with serious drug hypersensitivity (excluding allergic reaction to oxaliplatin)
12. Patients with local or systemic active infection requiring treatment, or fever indicating infection
13. Patients with heart failure or serious heart disease of class II by New York Heart Association (NYHA).
14. Patients with active hepatitis B
15. Patients with known HIV infection
16. Patients who have adverse event from previous treatment that has not recovered to at least Grade 1 (Grade 2 for peripheral sensory neuropathy) by CTCAE, Japanese edition JCOG version v4.03) (excluding hemoglobin content)
17. Patients with known BRAF mutation.
18. Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study (such as patients who may be coerced to give consent)

Primary endpoint for phase I part:

Primary endpoint:

Incidence of DLT in panitumumab treatment in combination with TAS-102

Endpoints for phase II part:

(Regarding efficacy and other endpoints, subjects who have received RD in the phase I part will also be included)

Primary endpoint:

Efficacy

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

Secondary endpoints:

Safety

Percentage of subjects with adverse events

Efficacy

Overall survival (OS)

Progression-free survival (PFS)

Response rate (RR)

Duration of response (DOR)

Disease control rate (DCR)

Time to treatment failure (TTF)

Additional endpoints:

Follow-up therapy and its rate

Statistical method:

In the phase I part, incidence of DLT will be assessed in DLT assessment study population.

The primary objective for phase II part is to explore the additional effect on PFS rate in panitumumab monotherapy when TAS-102 is used in combination with PFS rate at 6 months as primary endpoint.

PFS rate at 6 months is the crude rate of subjects who survived or were not determined as progressive at 6 months from the day of enrollment. 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 5% (one-sided) in main analysis. For interval estimation, accurate 90% confidence interval (two-sided) based on binomial distribution will be used.

PFS is the period from the day of enrollment until the day of documented progression or the day of death due to all causes whichever comes earlier. Kaplan-Meier method will be used to illustrate progression free curve and quantile point and its 95% confidence interval (two-sided) of PFS will be calculated.

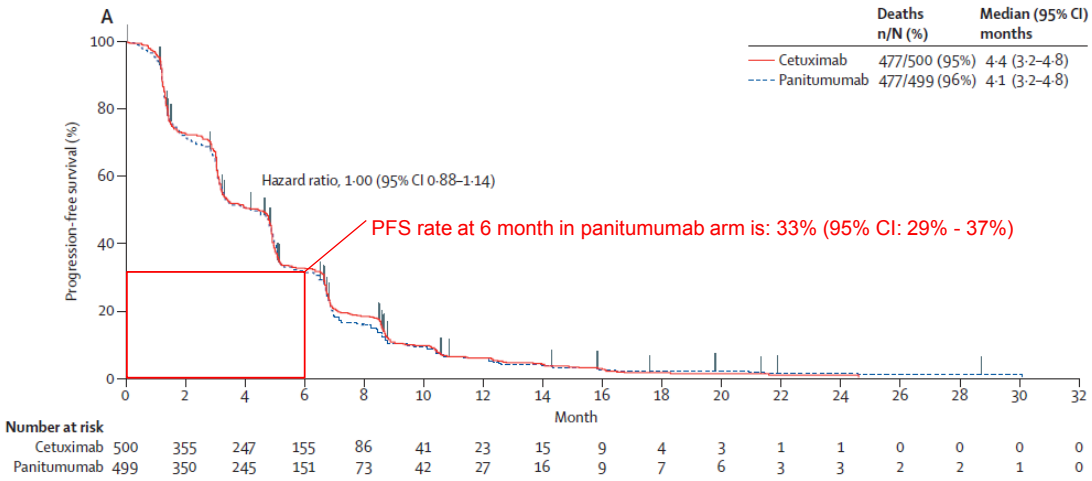
Rationale for planned number of subjects:

In the phase I part for the assessment of tolerability, 6 to 12 subjects were included according to the

"Guidelines for clinical evaluation methods of anti-cancer drugs" (PFSB/ELD notification No. 1101001, 01/Nov/2005).

Also, in the phase II part as efficacy will be assessed on PFS rate at 6 months as primary endpoint, according to the above guideline and precedent overseas clinical trial results, number of subjects were set as to confirm the expected PFS rate to overwhelm the PFS rate threshold.

In the panitumumab monotherapy vs. best supportive care (BSC) as third-line treatment control trial in patients with unresectable, advanced/recurrent colorectal cancer (trial 20020408), the PFS median, the primary endpoint, were 8.0 weeks for the panitumumab group and 7.3 weeks for the BSC group. In retrospectively conducted *KRAS* wild-type population and *KRAS*/*NRAS* wild-type population, PFS median were 12.3 weeks and 14.1 weeks respectively in the panitumumab group. On the other hand, in the panitumumab monotherapy vs. cetuximab monotherapy control study (ASPECCT study) in patients with *KRAS* wild-type unresectable, advanced/recurrent colorectal cancer that became resistant to fluoropyrimidine agents, OXA, and IRI, the secondary endpoint PFS were 4.1 months for panitumumab and 4.4 months for cetuximab and showed no difference (hazard ratio [HR], 1.00; two-sided 95% confidence interval [CI], 0.88–1.14). Further, PFS rate at 6 months was 33% (two-sided 95% CI, 29% to 37%) for the panitumumab group.



On the other hand, for TAS-102, in the domestic phase II study in previously treated subjects with unresectable, advanced/recurrent colorectal cancer refractory or intolerant to fluoropyrimidine agents, OXA, and IRI and has treatment history of 2 regimens of standard chemotherapy, the secondary endpoint PFS median assessed by the Investigator were 1.0 months in the placebo group but significantly prolonged to 2.7 months in the TAS-102 group (HR = 0.35, two-sided 95% CI 0.25 to 0.50, p<0.0001).

As increased anti-tumor effect can be expected by using TAS-102 in combination with panitumumab treatment which is the standard treatment for patients with unresectable, advanced/recurrent colorectal cancer, the PFS rate at 6 months in this study was assumed to be 48% and this was set as the expected

value for the panitumumab treatment in combination with TAS-102 therapy in patients with RAS wild-type unresectable, advanced/recurrent colorectal cancer. *Also, for the threshold where* further testing for panitumumab treatment in combination with TAS-102 may be considered not necessary, it was assumed to be 29% from the CI lower limit of the PFS rate at 6 months in the ASPECCT study.

For the main analysis, based on the observed PFS rate at 6 months from start of treatment, binomial test will be conducted on the null hypothesis "the true PFS rate at 6 months from start of treatment will be not more than the PFS threshold rate where value is determined invalid". With the PFS threshold rate at 29%, PFS expected rate at 48% at 6 months from start of treatment, and one-sided significant level at 5.0%, power at 80%, the necessary number of subjects will be 47. Taking into consideration of ineligible or discontinued subjects at approximately 10%, the target number of subjects was set to 52 (including subjects that received RD in the phase I part).

Study period:

Total study period: November 2015 to March 2018 (29 months)

Enrollment period: November 2015 to March 2017 (17 months)

Follow-up period: 12 months after completion of enrollment

3.0 LIST OF ABBREVIATIONS

List of Abbreviations	Unabbreviated expression
5-FU	fluorouracil
ALT	ALanine aminoTransferase
AST	ASpartate aminoTransferase
BSC	Best Supportive Care
COI	Conflict of Interest
CR	Complete Response
CRO	Contract Research Organization
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DMC	Data Monitoring Committee
DOR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
FTD	Trifluridine
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
HBs	Hepatitis B surface
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IRI	IRInotecan
JCOG	Japan Clinical Oncology Group
KRAS	Kirsten rat Sarcoma-2 virus
l-LV	Levofolinate calcium
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NRAS	Neuroblastoma Rat Sarcoma
NYHA	New York Heart Association
OS	Overall Survival
OXA	OXAliplatin

List of Abbreviations	Unabbreviated expression
Unequivocal PD	Progressive Disease
PFS	Progression-Free Survival
PR	Partial Response
P.S.	Serformance Status
RAS	RAt Sarcoma
RD	Recommended Dose
RECIST	Response Evaluation Criteria In Solid Tumors
RR	Response Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOP	Standard Operating Procedures
TPI	Tipiracil hydrochloride
TEAE	Treatment-Emergent Adverse Event
TTF	Time to Treatment Failure
VEGF	Vascular Endothelial Growth Factor

4.0 INTRODUCTION

4.1 Background

4.1.1 Etiology of colon cancer

According to "Cancer Statistics 2014," [1)] and "Site-specific Cancer Prevalence" in 2010 in Japan, colon cancer was the third most prevalent cancer in men (14.5%) and the second in women (15.1%). According to "Site-specific Cancer Deaths (2013)," in men, lung cancer was the leading cause of cancer death (accounting for 24.0% of cancer deaths), followed by gastric cancer (14.7%) and hepatic cancer (9.1%); colorectal cancer (colon cancer and rectal cancer combined) accounted for 11.9% of cancer deaths which exceeded the death rate of hepatic cancer, representing that colorectal cancer is the third leading cause of cancer death. In women, lung cancer (14.0%) was also the leading cause of cancer death, followed by gastric cancer (11.3%) and colon cancer (10.0%); deaths from colorectal cancer (colon cancer and rectal cancer combined) accounted for 14.9% of cancer deaths, representing that colorectal cancer is the first leading cause of cancer death.

4.1.2 Standard treatment for colon cancer

The "Guidelines for Treatment of Colorectal Cancer (2014)"[2)] classify the standard treatment of colorectal cancer according to staging as follows: endoscopic resection for Stage 0, in which the lesion is limited in the mucosa; Surgical resection for Stage I to III with postoperative adjuvant chemotherapy for Stage II which is at high risk or Stage III involving lymph nodes; and surgical resection for Stage IV and recurrent disease if liver or lung metastasis is resectable, and systemic chemotherapy if not.

The first-line treatment for unresectable, advanced/recurrent colorectal cancer that have been demonstrated to be useful in clinical studies and are currently covered by national health insurance in Japan are presented below. Also, cetuximab and panitumumab should be used for indications limited to Kirsten rat Sarcoma-2 virus wild-type (hereinafter referred to as *KRAS*).

1. FOLFOX therapy or bevacizumab or CapeOX (XELOX) therapy + bevacizumab[*1]
   FOLFOX therapy: combination chemotherapy with fluorouracil (hereinafter referred to as 5-FU), levofolinate calcium (hereinafter referred to as *l*-LV), and oxaliplatin (hereinafter referred to as OXA)
   CapeOX (XELOX) therapy: combination chemotherapy with capecitabine and OXA
2. FOLFIRI therapy + bevacizumab*[1]
   FOLFIRI therapy: combination chemotherapy with 5-FU, *l*-LV and irinotecan (hereinafter referred to as IRI)
3. FOLFOX therapy + cetuximab*[1, 2] or panitumumab*[1, 2]
4. FOLFIRI therapy + cetuximab*[1, 2] or panitumumab*[1, 2]

5. FOLFOXIRI therapy FOLFOXIRI therapy: combination chemotherapy with OXA, IRI, 5-FU and *l*-LV
6. FL*[3] or Capecitabine+ bevacizumab*[1] or UFT + *l*-LV
   UFT: combination preparation of tegafur and uracil

   *1: Combination with molecular-targeted drugs such as bevacizumab or anti-epidermal growth factor receptor (hereinafter referred to as EGFR) antibody is recommended, but if it is not an indication mono-chemotherapy will be conducted.

   *2: Indication only for *KRAS* wild-type

   *3: Infusional 5-FU + *l*-LV

FOLFOX-based therapy is more frequently selected as first-line treatment than FOLFIRI-based therapy, and bevacizumab is widely used for *KRAS* wild-type colorectal cancer as well. As a result, FOLFOX + bevacizumab combination therapy is the most common first-line treatment in Japan (in-house document).

It is recommended that in principle, a regimen not used in first-line treatment should be used for second-line treatment. More specifically, IRI-based regimens are recommended as a second-line treatment of patients who have received an OXA-based regimen as a first-line treatment, while OXA-based regimens are recommended for patients who have received an IRI-based regimen. This principle also applies to molecular-targeted drugs concomitantly used for second-line treatment. For *KRAS* wild-type colorectal cancer, bevacizumab is recommended as a second-line treatment of patients who have received an anti-EGFR antibody as a first-line treatment, while switching to an anti-EGFR antibody or continued use of bevacizumab is an option as a second-line treatment of patients who have received bevacizumab as a first-line treatment. Regimens that can be used for second-line treatment are as follows.

1. If subject becomes resistant to regimen including OXA
   1) FOLFIRI ± bevacizumab or IRI alone or IRI + S-1 (IRIS)
   2) FOLFIRI (or IRI alone) + cetuximab or panitumumab (*KRAS* wild-type)
2. If subject becomes resistant to regimen including IRI
   1) FOLFOX or CapeOX (XELOX) ± bevacizumab
3. If patient becomes resistant to regimen including fluropyrimidines, OXA, IRI
   1) IRI + cetuximab or panitumumab (*KRAS* wild-type)
   2) Cetuximab or panitumumab monotherapy (*KRAS* wild-type)

For third-line treatment and onwards, IRI + cetuximab or panitumumab combination therapy (*KRAS* wild-type) and cetuximab or panitumumab monotherapy (*KRAS* wild-type), and regorafenib monotherapy, TAS-102 monotherapy or symptomatic therapies are currently recommended.

4.1.3 Efficacy and safety of panitumumab in patients with unresectable, advanced/recurrent colorectal cancer

4.1.3.1 Panitumumab

EGFR is a member of the ErbB family of transmembrane receptor tyrosine kinases constantly expressed in epithelial-derived tissues, has been shown to be overexpressed in various types of solid tumors. Colorectal cancer is characterized by high EGFR expression, and the EGFR signaling pathway has been shown to play in the pathogenesis and progression of tumors. Binding of epidermal growth factor (hereinafter referred to as EGF), the major ligand of EGFR, to EGFR is considered to induce auto-phosphorylation of EGFR and activation of various signaling pathways, resulting in induction of cellular proliferation, inhibition of apoptosis, and increased production of inflammatory cytokines and angiogenesis factors. Panitumumab is a human IgG2 monoclonal antibody that binds to EGFR with specificity and high affinity, and inhibits the proliferation of tumor cells by competitively inhibiting the binding of the ligand to EGFR[3)].

4.1.3.2 Clinical study results for panitumumab in the U.S. and Europe

As a clinical trial of panitumumab monotherapy for colorectal cancer, a phase III study was conducted to compare best supportive care (hereinafter referred to as BSC) vs. BSC + panitumumab therapy in patients with unresectable, recurrent/advanced, EGFR-positive colorectal cancer that became resistant to fluoropyrimidine agents, OXA, and IRI (BSC group, 232 patients; BSC + panitumumab group, 231 patients)[4)]. The median of the primary endpoint of progression free survival (hereinafter referred to as PFS) with BSC alone at 7.3 weeks, whereas with BSC + panitumumab therapy at 8weeks, significantly longer than that of BSC, showed the efficacy of panitumumab therapy (hazard ratio [HR], 0.54; two-sided 95% confidence interval [CI], 0.44 to 0.66, $p< 0.0001$). The secondary endpoint of OS was not significantly different between the two groups (HR, 1.00, two-sided 95% CI 0.82 to 1.22, $p = 0.81$), however, this may be primarily due to the fact that 173 subjects (75%) in the BSC group received follow-up therapy with panitumumab. Also, a phase III randomized control study comparing cetuximab monotherapy and panitumumab monotherapy in patients with *KRAS* wild-type unresectable, recurrent/advanced colorectal cancer (anti-EGFR antibody untreated) after they became resistant to fluoropyrimidine agents, OXA, and IRI has been reported (ASPECCT study).[17)] In this study, the median of OS which is the primary endpoint was 10.4 months for the panitumumab group (499 subjects) compared to 10.0 months for cetuximab group (500 subjects) and this indicated that panitumumab is non-inferior to cetuximab (HR = 0.97, two-sided 95% CI 0.84 to 1.11) PFS which is the secondary endpoint were 4.1 months for panitumumab group and 4.4 months for cetuximab group and showed no difference (HR = 1.00, two-sided 95% CI 0.88 to 1.14).

With regard to clinical study of combination of chemotherapy and panitumumab, a phase III clinical study (PRIME Study) has been reported, in which FOLFOX4 monotherapy vs. FOLFOX4 therapy + panitumumab (given at a dose of 6 mg/kg every 2 weeks) as a first-line treatment was compared in a total of 1,183 patients (593 in monotherapy group, 590 in panitumumab group)[5]. The primary endpoint of median PFS in *KRAS* wild-type patients was 9.6 months and significantly longer in the FOLFOX4 + panitumumab group as compared with 8.0 months in the FOLFOX4 alone group (HR, 0.80; two-sided 95% CI, 0.66 to 0.97; p = 0.02). Of Grade 3/4 adverse events, panitumumab-related adverse events such as dermatologic toxicities, diarrhoea, and hypomagnesaemia occurred more frequently in the FOLFOX4 + panitumumab group, but there were no major differences in the incidence of other adverse events between the two groups. Grade 3 infusion reaction occurred in 2 patients (Table 4.a).

Table 4.a Grade 3/4 adverse events reported in *KRAS* wild-type patients in the PRIME study

Adverse event	FOLFOX4 + panitumumab (n = 322)		FOLFOX4 alone (n = 327)	
	n	%	n	%
Any adverse drug reaction	270	84	227	69
Leukopenia	136	42	134	41
Skin disorder	116	36	7	2
Diarrhoea	59	18	29	9
Nerve disorder	52	16	51	16
Hypokalaemia	32	10	15	5
Malaise	30	9	10	3
Stomatitis	28	9	2	< 1
Hypomagnesaemia	20	8	1	< 1
Paronychia	11	3	0	0
Pulmonary embolism	9	3	5	2
Febrile neutropenia	8	2	7	2
infusion reaction	2	< 1	-	-

With regard to second-line treatment, a phase III clinical study (Study 20050181) has been conducted, in which FOLFIRI monotherapy vs. FOLFIRI therapy + panitumumab (given at a dose of 6 mg/kg every 2 weeks) was compared[6]. The primary endpoints were PFS and OS in *KRAS* wild-type patients. In *KRAS* wild-type patients, PFS was 5.9 months and significantly longer in the FOLFIRI + panitumumab group than 3.9 months in the FOLFIRI alone group (HR = 0.73, two-sided 95% CI 0.59 to 0.90, p = 0.004). On the other hand, the OS median were 12.5 months in the FOLFIRI alone group and 14.5 months in the FOLFIRI + panitumumab group (HR = 0.85, two-sided 95% CI 0.70 to 1.04, p=0.12) and showed no significant difference. The response rate

(hereinafter referred to as RR) was 35% and higher in the FOLFIRI + panitumumab group as compared with 10% in the FOLFIRI alone group. Of Grade 3/4 adverse events, the incidence of dermatologic toxicities was higher and the incidences of diarrhoea and hypomagnesaemia tended to be higher in the FOLFIRI + panitumumab group; however, there were no major differences in the incidence of toxicities including hematologic toxicities between the two groups, and the incidence of infusion reaction was not more than 1%.

Both the PRIME Study[5)] and Study 20050181[6)] described above, in which the presence/absence of *KRAS* was prospectively studied, showed that combination therapy containing panitumumab was not effective in *KRAS*-mutant patients, suggesting that *KRAS* mutation is predictive of poor response to anti-EGFR antibody therapy.

4.1.3.3 Clinical study results for panitumumab in Japan

In a Japanese phase I clinical study of panitumumab, panitumumab was administered at the same dosing regimens with which the drug was confirmed to be safe and effective in overseas studies; i.e., a dose of 2.5 mg/kg once weekly, 6 mg/kg once every 2 weeks, and 9 mg/kg once every 3 weeks. Each of these dosing regimens was evaluated in 6 patients, and tolerance was ratified in overseas clinical trial.

In a Japanese phase II clinical study of panitumumab monotherapy, [7)] 52 patients with previously treated, unresectable colorectal cancer were enrolled. In this study, the 6 mg/kg biweekly regimen of panitumumab, which was the recommended dosing regimen in the overseas phase III clinical study, was well tolerated, and the incidence of adverse events was similar to that observed in the U.S. and Europe (Table 4.b). In addition, 7 patients (13.5%) had partial response (hereinafter referred to as PR), and this Japanese study yielded an RR of 13.5% (two-sided 95% CI: 5.6 to 25.8),a time to treatment failure of 11.4 weeks (two-sided 95% CI: 8.4 to 15.0), a PFS of 8.0 weeks (two-sided 95% CI: 7.4 to 11.4), and an OS of 9.3 months (two-sided 95% CI: 7.1 to 12.8), similar to those observed in clinical studies in the U.S and Europe.

On the basis of the above results, panitumumab was approved in April 2010 for the treatment of unresectable, advanced/recurrent colorectal cancer in Japan as well.

Table 4.b Common adverse events (≥ 20%) noted in a Japanese phase II clinical study of Panitumumab monotherapy

Adverse event	Panitumumab Monotherapy (n = 52)			
	Any Grade		Grade 3 or higher	
	n	%	n	%
Any adverse drug reaction	51	98	6	12
Skin disorder	51	98	3	6

Adverse event	Panitumumab Monotherapy (n = 52)			
	Any Grade		Grade 3 or higher	
	n	%	n	%
Acne	42	81	1	2
Dry skin	32	62	0	
Skin rash	24	46	1	2
Pruritus	17	33	0	
Paronychia	17	33	1	2
Hypomagnesaemia	17	33	0	0
Malaise	13	25	0	0
Stomatitis	12	23	0	0
Anorexia	11	21	1	2

4.1.3.4 Specified drug use surveillance results (all patients surveillance) in Japan

In the post- marketing surveillance conducted for a fixed period where all the patients treated were registered, [8)] the median of treatment period (first day of treatment to the final day of treatment) for the 3,085 patients who were subject to safety evaluation was 113 days (range: 1 to 559 days), incidence of adverse reaction was 84.1% (25.8% ≥ Grade 3), of which the panitumumab monotherapy group with 1,254 patients was 80.1% (19.7% ≥ Grade 3), panitumumab + chemotherapy combination group with 1,831 patients was 86.9% (30.0% ≥ Grade 3). The occurrence status of intensively investigated adverse reaction items are listed in Table 4.c.

Table 4.c Common adverse events in specified drug use surveillance in Japan

All patient surveillance	Panitumumab monotherapy group (n=1,254)				Panitumumab + chemotherapy combination group (n=1,831)			
	Any Grade		Grade 3 or higher		Any Grade		Grade 3 or higher	
Intensively investigated item	n	%	n	%	n	%	n	%
Skin & subcutaneous tissue disorders (SOC)	918	73.2	118	9.4	1446	79.0	274	15.0
Paronychia	272	21.7	33	2.6	459	25.1	99	5.4
Interstitial lung disease*	16	1.3	-	-	23	1.3	-	-
Infusion reaction	17	1.4	1	0.1	30	1.6	5	0.3
Hypomagnesaemia	257	20.5	61	4.9	263	14.4	62	3.4
Hypocalcaemia	59	4.7	16	1.3	77	4.2	26	1.4
Cardiac disorders (SOC)	2	0.2	0	0.0	5	0.3	1	0.1

SOC: System Organ Class

*: Interstitial pneumonia subcommittee criteria

4.1.4 Efficacy and safety of TAS-102 for unresectable, advanced/recurrent colorectal cancer

4.1.4.1 TAS-102

TAS-102 is a new nucleoside anticancer agent formulated with trifluridine (FTD) and tipiracil (TPI) prepared at a molar ratio of 1 : 0.5. FTD is an anticancer active ingredient of TAS-102 and TPI is an inhibitor specific to thymidine phosphorylase (TPase) which is a FTD decomposing enzyme.[9)] FTD will show anti-tumor effect when administered orally and taken in by DNA, while on the other hand, FTD will be metabolized promptly through first-pass effect of oral administration. Therefore, in order to have FTD taken in by DNA efficiently, it is necessary to inhibit TPase that engages in metabolizing FTD and it is necessary to administer FTD in combination with TPI. In the non-clinical study, in a nude mouse subcutaneously implanted with human tumor-derived cell line, as the FTD amount taken in DNA and tumor proliferation inhibitory effect had correlated it was presumed that tumor proliferation inhibitory effect of TAS-102 is based on FTD and tumor proliferation inhibitory effect shows effectiveness when FTD is taken in by DNA. Also, when FTD alone is orally given to monkies, FTD could hardly be observed in blood, whereas in combination with TPI that inhibits TPase which is a FTD decomposing enzyme, FTD blood concentration was maintained.

4.1.4.2 Clinical study results for TAS-102

In Japan, after the phase I study in patients with solid tumors (J001 study) had been conducted, a phase II control study (J003 study) with OS as primary endpoint and PFS, DCR, etc. as secondary endpoints and the objective of assessing the superiority of TAS-102 group over placebo group in patients (number of safety assessed subjects: TAS-102 group 113, placebo group 57, efficacy assessed: TAS-102 group 112, placebo group 57) that have received previous treatment of 2 regimens including fluoropyrimidine agents, OXA, and IRI and with refractory or intolerant, unresectable, advanced/recurrent colorectal cancer was conducted. [10)] TAS-102 was given 35 mg/m^2/dose orally twice daily for 5 consecutive days, followed by 2 days of washout and after this was repeated twice, 14 days washout was implemented. As a result, OS prolongation was observed in the TAS-102 group compared to the placebo group. In the TAS-102 group, the OS median was 9.0 months, and by independent diagnostic imaging organization PFS median was 2.0 months, DCR was 43.8% (49/112 subjects).Common adverse events (occurrence 10%) noted in Japanese clinical study in 119* subjects are shown in Table 4.d.

*: 6 subjects who were given the same dosage and regimen as the J003 study in the Japanese phase I study (J001 study) were added to the 113 subjects of the Japanese phase II study (J003 study)

Table 4.d Common adverse events (occurrence 10%) noted in Japanese clinical study

Adverse event	Any Grades (n = 119)		Grade 3 or higher (n = 119)	
	n	%	n	%
Hematocrit decreased	34	28.6	1	0.8
Haemoglobin decreased	76	63.9	22	18.5
Lymphocyte count decreased	40	33.6	13	10.9
Neutrophil count decreased	87	73.1	61	51.3
Platelet count decreased	49	41.2	5	4.2
Red blood cell count decreased	38	31.9	1	0.8
White blood cell count decreased	91	76.5	36	30.3
Diarrhoea	40	33.6	6	5.0
Nausea	75	63.0	3	2.5
Stomatitis	18	15.1	-	-
Vomiting	34	28.6	3	2.5
Fatigue	63	52.9	7	5.9
Blood albumin decreased	13	10.9	-	-
Blood bilirubin increased	23	19.3	1	0.8
Weight decreased	14	11.8	-	-
Protein urine present	14	11.8	-	-
Decreased appetite	66	55.5	3	2.5

On the other hand, a phase III global study (RECOURSE study) with OS as primary endpoint and PFS, DCR, etc. as secondary endpoints and the objective of assessing the superiority of TAS-102 over placebo in patients (number of safety assessed subjects: TAS-102 group 533, placebo group 265, efficacy assessed: TAS-102 group 534, placebo group 266) that have received previous chemotherapy of 2 regimens and with refractory or intolerant to fluoropyrimidine agents, IRI,OXA, bevacizumab and anti-EGF-R antibody agents (*KRAS* wild-type), unresectable, advanced/recurrent colorectal cancer, was conducted.[11)] As a result, OS significantly prolonged in the TAS-102 group compared to placebo group. In the TAS-102 group, the OS median was 7.1 months, and by independent diagnostic imaging organization PFS median was 2.0 months, DCR was 44% (221/502 subjects).

Common adverse events (occurrence 10%) noted in the phase III global clinical study in 533 subjects are shown in Table 4.e.

Table 4.e Common adverse events (occurrence 10%) noted in the phase III global clinical study

Adverse event	Any Grades (n = 533)		Grade 3 or higher (n = 533)	
	n	%	n	%
Aneamia	168	31.5	65	12.2
Neutropenias	153	28.7	107	20.1
Neutrophil count decreased	145	27.2	83	15.6
White blood cell count decreased	140	26.3	52	9.8
Platelet count decreased	77	14.4	13	2.4
Diarrhoea	126	23.6	12	2.3
Nausea	210	394	5	0.9
Asthenia	58	10.9	9	1.7
Fatigue	132	24.8	11	2.1
Decreased appetite	141	26.5	9	1.7

Regarding combination of TAS-102 and antibody drugs, a phase I/II study in combination with bevacizumab was conducted in Japan. [12)] Patients with colorectal cancer refractory/intolerant to anticancer agent therapies including 5-FU, OXA, IRI, and anti VEGF inhibitors (bevacizumab, etc.), anti EGFR antibody agents (in cases of RAS wild-type) and has no treatment history of regorafenib and TAS-102, and DLT was not observed in the phase I part (6 subjects), RD was determined at 35 mg/m^2 of TAS-102 given twice daily and 5 mg/day of bevacizumab. For efficacy, 21 subjects (total from phase I part and phase II part) were analyzed and PFS at week 16 was 42.9%. Also, from the assessment by the attending physician PFS median was 24.1 weeks, DCR was 72%. Neutropenia as drug related adverse event (Grade 3: 56%, Grade 4: 12%), leukopenia (Grade 3: 40%), febrile neutropenia (Grade 3: 16%) were many but no study related deaths. In 17 subjects (68%) start of treatment was delayed, in 6 subjects (24%) dose reduction of TAS-102 was necessary, many of the causes were neutrophenia. Therefore, tolerance and efficacy has been observed in combination therapy with TAS-102 and bevacizumab for unresectable, advanced/recurrent colorectal cancer after becoming refractory to standard treatment.

4.1.5 *RAS* (*KRAS*/*NRAS*) mutation and panitumumab in unresectable, advanced/recurrent colorectal cancer

In a phase III randomized control study (Study 20040408[4)]) of panitumumab monotherapy that investigated its efficacy as a third-line treatment in patients with unresectable, advanced/recurrent colorectal cancer after receiving standard treatment, the enrolled subjects were analyzed for the relationship of the presence or absence of mutations in the genes of *KRAS* exons 3 (codon 61) and 4 (codons 117, 146), *NRAS* exons 2 (codons 12, 13), 3 (codon 61) and 4 (codons 117, 146) in the

tumor using DNA sequencing by the Sanger method and WAVE-based SURVEYOR® Scan Kit. In patients with *KRAS* wild-type and *NRAS* wild-type colorectal cancer (hereinafter referred to as RAS wild-type), the PFS median was 14.1 weeks and significantly prolonged by 7.1 weeks in the panitumumab combination group as compared with 7.0 weeks in the BSC group (HR = 0.36, two sided 95% CI 0.25 to 0.52, p<0.001). On the other hand, in patients with RAS mutation (*KRAS* or *NRAS* mutation), the median PFS was 7.3 weeks in the BSC group as compared with 7.4 weeks in the panitumumab combination group and did not show significant difference. (HR = 0.97, two sided 95% CI 0.73 to 1.29). [13)]

Among the patients enrolled in the PRIME study, were analyzed for the relationship of the presence or absence of mutations in the genes of *KRAS* exons 2, 3, 4, *NRAS* exons 2, 3, 4, and BRAF exon 15 (codon 600) with PFS and OS. [5)] In patients with RAS wild-type, the OS median was 25.8 months and significantly prolonged by 5.6 month in the FOLFOX4 + panitumumab group as compared with 20.2 months in the FOLFOX4 alone group (HR = 0.77, two sided 95% CI 0.64 to 0.94, p = 0.009). On the other hand, in patients with RAS mutation, the OS median was 15.5 months and significantly shorter in the FOLFOX4 + panitumumab group as compared with 18.7 months in the FOLFOX4 alone group (HR = 1.21, two sided 95% CI 1.01 to 1.45, p = 0.04). [14)]

Also, in addition to the above studies, patients with *KRAS* (exons 3 and 4) and *NRAS* (exons 2, 3 and 4) mutations other than *KRAS* exon 2 showing ineffectiveness to anti-EGFR antibody drugs in several post hoc analysis has been reported, [15)]and for patients determined as having wild-types and currently measuring *KRAS* exon 2 only, it has been recognized that presence/absence of other RAS (*KRAS*/*NRAS*, hereinafter referred to as RAS) mutations should be added, and "Guidance for measuring RAS (*KRAS*/*NRAS*) mutations in colorectal cancer patients" [16)] has been published from Japanese Society of Medical Oncology.

4.2 Rationale for the proposed study

For the treatment of *KRAS* wild-type, unresectable, advanced/recurrent colorectal cancer it is recommended to use molecular target drugs of either anti-VEGF antibody agents or anti-EGFR antibody agents in combination with FOLFOX or FOLFIRI treatment. OXA combination treatment + anti-VEGF antibody agent for first-line treatment, and if IRI + anti-VEGF antibody agent is used in second-line treatment, anti-EGFR antibody agents alone based on the results from 20020408 study[4)] or ASPECCT study[17)], or IRI + anti-EGFR antibody agents based on results from BOND study[18)] or GERCOR study[19)], etc. for third-line treatment is used often.

Combination therapy with anti-EGFR antibody agents and chemotherapy has shown that it also has antitumor effect in patients that have become resistant to chemotherapy. In the BOND study in

which cetuximab alone group and cetuximab + IRI combination group were compared in patients with colorectal cancer that have become resistant to IRI, in spite of the fact that the patient group had already been IRI resistant, it has been reported that cetuximab + IRI combination group had superior antitumor effect and PFS (for RR, cetuximab + IRI combination group was 22.9% [two-sided 95% CI 17.5 to 29.1%], IRI group was 10.8% [two-sided 95% CI 5.7 to 18.1%], P=0.007; for PFS, cetuximab + IRI combination group was 4.1 months, IRI group was 1.5 months, P<0.001 by the log-rank test). [18] Also in the phase II GERCOR study[19] where panitumumab and IRI combination therapy was used in patients with colorectal cancer refractory to standard treatment, in spite of the fact that it included patients that had already become IRI resistant, anti-tumor effect was observed with combination use of panitumumab and IRI, and indicated that panitumumab and IRI combination therapy was a superior treatment than that of panitumumab monotherapy (PFS median in *KRAS* wild-type was 6.3 months, 95% CI 3.7 to 8.7).

As indicated in Section 4.1.4.2, regarding combination use of TAS-102 and antibody agents, tolerance and efficacy has been observed with TAS-102 and bevacizumab combination therapy in patients with unresectable, advanced/recurrent colorectal cancer after being refractory to standard treatment. For combination use of panitumumab and TAS-102, currently there is no clinical data that would confirm its efficacy, while in non-clinical studies in vitro tests show anti-tumor effect increases by combination use of FTD which is the active component of TAS-102 and panitumumab compared to using them alone in *KRAS* wild-type colorectal cancer cell strain (Figure 4.a, in-house data).

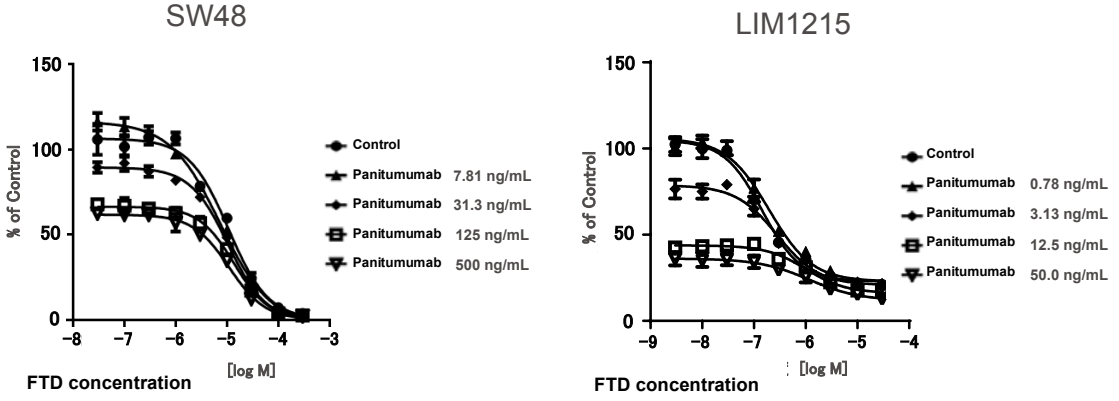


Figure 4.a Anti-tumor effect from combination use of FTD and panitumumab in *KRAS* wild-type colorectal cancer cell strain (SW48 and LIM1215, both are *KRAS*/BRAF wild type)

In a colorectal cancer cell strain trans planted mouse model, it was indicated that a higher anti-tumor effect may be obtained with combination use of panitumumab and TAS-102 compared to preparing them alone, and also weight decrease, etc. or increase of other toxicities have not been observed. [20] Although the mechanism of action is not known for this combination use effect, from the in vitro test

using colorectal cancer cell strain, FTD which is an active component of TAS-102 activates the phosphorylation of EGFR and AKT or MAPK protein that is located downstream from EGFR, and also erlotinib which is a tyrosine kinases inhibitor showed synergy effect of inhabitation of cell proliferation by simultaneous action with FTD and also indicated that erlotinib down regulates phosphorylation of AKT or MAPK protein by FTD.[21)] From these reasons, it was considered that a higher effect may be expected from combination use of TAS-102 and panitumumab compared to using them alone.

As mentioned earlier, for third-line treatment for colorectal cancer with treatment history of FOLFOX therapy or FOLFIRI therapy, taking in account of the results, etc. of the 20020408 study[4)] in which treatment with panitumumab alone and BSC were compared, the ASPECCT study[17)] in which panitumumab monotherapy and cetuximab monotherapy were compared, the NCIC CTG CO.17 study[22)] in which treatment with cetuximab alone and BSC were compared, the BOND study[18)] in which treatment groups of cetuximab alone and cetuximab and IRI combination use were compared and the GERCOR study[19)] in which effect of combination use of IRI + panitumumab was assessed, treatment with either cetuximab or panitumumab alone or combination use of IRI + cetuximab or IRI + panitumumab are recommended by the "Guidelines for Treatment of Colorectal Cancer (2014)".[2)] Actually, for subjects who did not show serious adverse event in IRI among patients with treatment history with fluropyrimidines, IRI, OXA, it is expected that IRI + anti-EGFR antibody combination therapy will be a treatment option, although it has not been proven that IRI + anti-EGFR antibody combination therapy has longer survival period compared to cetuximab or panitumumab monotherapy. If panitumumab + TAS-102 combination therapy has higher effectiveness than anti-EGFR antibody monotherapy and similar effect as IRI + anti-EGFR antibody in the same patient group, there will be major benefits for the patient such as avoidance of adverse event in IRI.

Comparison of adverse events in treatments with TAS-102 alone and panitumumab alone is shown in the table below. Adverse events for TAS-102 are from Japanese phase II study and for panitumumab are from Specified drug use surveillance results (all patients surveillance) in Japan, incidence of ≥ 10% has been extracted and presented Table 4.f and Table 4.g. As adverse events in both drugs do not hardly overlap besides stomatitis, and adverse events besides stomatitis from TAS-102 were all ≤ Grade 2, both drugs are considered usable in combination fairly safely.

Table 4.f Comparison of rate of adverse events

in panitumumab alone among common adverse events (incident ≥ 10%) in treatments with TAS-102

Common adverse events in TAS-102 (incident ≥ 10%)	TAS-102 (n = 119)		Panitumumab alone (n = 1254)	
	n	%	n	%
Hematocrit decreased	34	28.6	-	-
Haemoglobin decreased	76	63.9	1	0.1
Lymphocyte count decreased	40	33.6	0	0
Neutrophil count decreased	87	73.1	0	0
Platelet count decreased	49	41.2	4	0.3
Red blood cell count decreased	38	31.9	-	-
White blood cell count decreased	91	76.5	5	0.4
Diarrhoea	40	33.6	24	1.9
Nausea	75	63.0	9	0.7
Stomatitis	18	15.1	123	9.8
Vomiting	34	28.6	4	0.3
Fatigue	63	52.9	9	0.7
Blood albumin decreased	13	10.9	0	0
Blood bilirubin increased	23	19.3	1	0.1
Weight decreased	14	11.8	1	0.1
Protein urine present	14	11.8	2	0.2
Decreased appetite	66	55.5	25	2.0

Table 4.g Comparison of rate of adverse events

in TAS-102 among common adverse events (incident ≥ 10%) in treatment with panitumumab alone

Common adverse events in panitumumab alone (incident ≥ 10%)	Panitumumab alone (n = 1254)		TAS-102 (n = 119)	
	n	%	n	%
Paronychia	272	21.7	1	0.8
Hypomagnesaemia	223	17.8	-	-
Dermatitis acneiform	619	49.4	-	-
Dry skin	265	21.1	1	0.8

From the above, this study was planned as it was determined that assessment of recommended dose, efficacy and safety of panitumumab in combination with TAS-102 was necessary in RAS wild-type, unresectable, advanced/recurrent colorectal cancer. For combination therapy, panitumumab and TAS-102 were used as alone treatment and combined. Therefore, panitumumab will be given at a dose of 6 mg/kg every 2 weeks, TAS-102 will be given 35 mg/m^2/dose for 5 consecutive days orally followed by 2 days of washout and after repeating this twice, 14 days of washout will be implemented and if safety is confirmed in the phase I part, the dosage and administration will be the

recommended dose for the combination therapy and the same dosage and administration will be adopted in the phase II part. If it is determined intolerable in the phase I part, continuation of study will be considered and dose reduction will be assessed when necessary.

5.0 OBJECTIVE AND ENDPOINTS OF THE STUDY

5.1 Objective

Phase I part

To assess the recommended dose (RD) of panitumumab in combination with TAS-102 in patients with RAS wild-type, unresectable, advanced/recurrent colorectal cancer.

Phase II part

To assess the efficacy and safety of panitumumab in combination with TAS-102 in RAS wild-type, unresectable, advanced/recurrent colorectal cancer.

5.2 Definition of endpoints

5.2.1 Definition of endpoints for phase I part

Primary endpoint:

Incidence of DLT in panitumumab treatment in combination with TAS-102

5.2.2 Definition of endpoints for phase II part

(Including subjects who received RD in phase I part)

Primary endpoint:

Efficacy

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

Secondary endpoints:

Safety

Percentage of subjects with adverse events

Efficacy

Overall survival (OS)

Progression-free survival (PFS)

Response rate (RR)

Duration of response (DOR)

Disease control rate (DCR)

Time to treatment failure (TTF)

Additional endpoints:

Follow-up therapy and its rate

5.3 Rationale for the endpoints

5.3.1 Primary endpoint

In the phase I part, incidence of DLT was set as primary endpoint to assess the tolerability and safety of panitumumab in combination with TAS-102 in patients with unresectable, advanced/recurrent colorectal cancer and determine RD.

In the phase II part, PFS rate at 6 months was set as primary endpoint as an important criteria in assessing the efficacy of combination use of TAS-102 with panitumumab monotherapy in patients with unresectable, advanced/recurrent colorectal cancer.

5.3.2 Secondary endpoints

The OS, PFS, RR, DOR, DCR, and TTF were selected as the secondary endpoint, because they reflect the anti-tumor efficacy. In addition, adverse events were selected as the secondary endpoint, because safety is also an important factor in treatment selection in phase II part.

6.0 CLINICAL STUDY DESIGN

6.1 Clinical study design

This phase I/II study is a multi-center, open-label single-arm study that consists of a phase I part (dose de-escalation) which will assess the tolerability and RD of Panitumumab in combination with TAS-102 as primary objective, and a phase II part which will assess the efficacy and safety of Panitumumab in combination with TAS-102 as primary objective in patients with RAS wild-type unresectable, advanced/recurrent colorectal cancer. In the phase I part, the subjects will be included sequentially into Cohort 1 and 2, 3 subjects each with the same dosage and administration. In the phase II part, 46 subjects will be included additionally for RD confirmed in the phase I part.

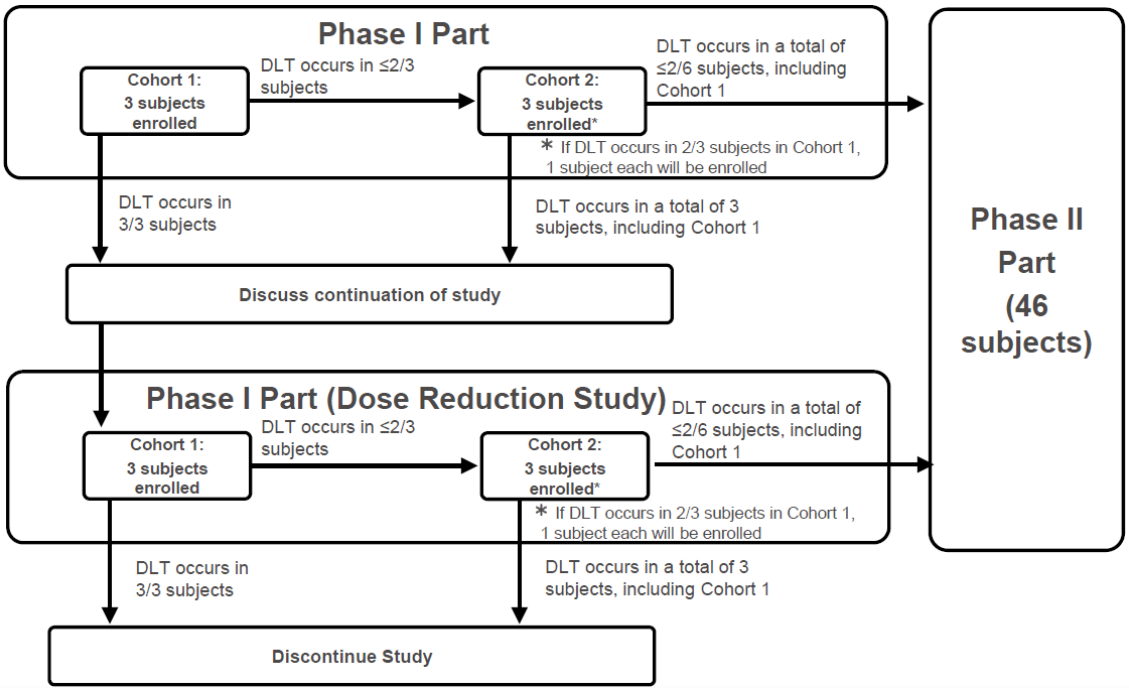


Figure 6.a Outline of study design

In the phase I part, each cohort will be conducted with 3 subjects, the sponsor will assess tolerability of the dosage and administration based on the incidence of Dose Limiting Toxicity (hereinafter referred to as DLT) during the assessment period and determine whether or not to move on to the next cohort (opinion from the Data Monitoring Committee [hereinafter referred to as DMC] will be confirmed appropriately upon determination). Therefore, in Cohort 1, if occurrence of DLT is ≤ 2 subjects out of 3, the dosage and administration will be determined tolerable and will move on to Cohort 2. However, if DLT is observed in 2 subjects during DLT assessment period in Cohort 1, subjects will be included one at a time in Cohort 2 in consideration for safety to assess DLT.

Similarly 3 subjects will be included in Cohort 2 and DLT will be assessed in a total of 6 subjects of Cohort 1 and 2 at most. If DLT is observed in 3 subjects included in Cohort 1, or DLT is observed in 3 subjects from a total of 6 subjects of Cohort 1 and 2, the sponsor will promptly request to postpone new enrollment of subjects to each site and after consultation with the Research Steering Committee and DMC on the continuation of the study, will determine whether or not to continue the study.

If study is to be continued, taking in account of the adverse event that occurred, either panitumumab or TAS-102 or both drugs will be reduced one step and re-conducting the phase I part similarly will be considered. If DLT is observed in 3 subjects after reducing 1 step of panitumumab or TAS-102 or both drugs, the study will be discontinued.

If DLT is observed in ≤ 2 subjects from a total of 6 subjects of Cohort 1 and 2, the sponsor will comprehensively assess with the Research Steering Committee based on the safety data of the phase I part, and after confirming the opinion of DMC, will determine the transit to phase II part.

In the phase II part, in addition to the 6 subjects who received RD dose in the phase I part, a target of 46 subjects are to be accumulated (a total of 52 subjects).

6.2 Rationale for study design

6.2.1 Study population

Survival period for unresectable, advanced/recurrent colorectal cancer patients is approximately two and a half years and still prognostic is poor. Although systemic chemotherapy is used for unresectable cases as first-line treatment, recovery is difficult and PFS after initial chemotherapy is about one year, second-line chemotherapy PFS is about half a year, and in most cases third-line, fourth-line treatment is necessary. Therefore, this became the object of this clinical research as development of appropriate treatment for unresectable cases that have become refractory/intolerant to existing chemotherapy is an important issue. The patients should also be RAS wild-type, because the above mentioned analysis results in the PRIME study[5)] suggest that panitumumab may be the most effective in these patients.

KRAS/*NRAS* test will be performed using the in vitro diagnostic that has been approved for marketing.

6.2.2 Treatment regimens and planned number of subjects

6.2.2.1 Reasons for selecting panitumumab + TAS-102 combination therapy as the treatment regimen

As described in Section 4.1.2, the following regimens using FOLFOX and FOLFIRI treatment and methods to use bevacizumab, panitumumab and cetuximab in combination, are shown in the Guidelines for Treatment of Colorectal Cancer (2014)[2)] as the first-line treatment and second-line treatment for patients with unresectable, advanced/recurrent colorectal cancer. In Japan, FOLFOX-based therapy is more frequently selected as first-line treatment for unresectable, advanced/recurrent colorectal cancer than FOLFIRI-based therapy, and bevacizumab is widely used for *KRAS* wild-type colorectal cancer as well. As a result, FOLFOX + bevacizumab combination therapy is the most common first-line treatment in Japan. Further, if it becomes refractory or intolerant to these first-line treatment, FOLFIRI+ bevacizumab is used widely as second-line treatment (in-house document). Furthermore, if it becomes refractory or intolerant to these second-line treatments, the following regimens are for third-line treatment and onwards.

1. Panitumumab monotherapy or cetuximab monotherapy
2. IRI + panitumumab combination therapy or IRI + cetuximab combination therapy
3. Regorafenib monotherapy
4. TAS-102 monotherapy
5. Symptomatic therapies

On the other hand, from the results of the randomized, double blinded, placebo controlled comparative study (Japanese phase II control study) in which unresectable, advanced/recurrent colorectal cancer that have received previous treatment of 2 regimens including fluoropyrimidine agents, OXA, and IRI and became refractory or intolerant was assessed, and it was reported that overall survival prolonged significantly compared to placebo administration and TAS-102 obtained approval in March 2014 for "unresectable, advanced/recurrent colorectal cancer (restricted to where standard treatment is difficult)" as indication. Also, from the results of the phase III global study (RECOURSE study[11)]) in which colorectal cancer patients had no change to standard therapy, it was reported that overall survival prolonged significantly compared to placebo and TAS-102 has become one of the options for third-line treatment as indication was changed and approved to "unresectable, advanced/recurrent colorectal cancer" in March 2015.

As mentioned in Section 4.2, anti-EGFR antibody agents and chemotherapy has shown that it also has anti-tumor effect in patients that have become resistant to chemotherapy. As for panitumumab and TAS-102 also, further anti-tumor effect can be expected from combination use. For combination

therapy to be assessed in this clinical research, panitumumab and TAS-102 were used as alone treatment and combined. Therefore, panitumumab will be given at a dose of 6 mg/kg every 2 weeks, TAS-102 will be given 35 mg/m^2/dose for 5 consecutive days orally followed by 2 days of washout and after repeating this twice, 14 days of washout will be implemented and if safety and tolerability is confirmed, the dosage and administration will be the RD for the combination therapy.

6.2.2.2 Rationale for planned number of subjects

In the phase I part for the assessment of tolerability and RD of panitumumab and TAS-102 combination therapy, 6 to 12 subjects were included according to the "Guidelines for clinical evaluation methods of anti-cancer drugs" (PFSB/ELD notification No. 1101001, 01/Nov/2005).

Also, in this study as efficacy will be assessed on PFS rate as primary endpoint, according to the above guideline and precedent overseas clinical trial results, number of subjects were set as to confirm the expected PFS rate to overwhelm the PFS rate threshold.

In the panitumumab monotherapy vs. BSC as third-line treatment control trial in patients with unresectable, advanced/recurrent colorectal cancer (20020408 study[4)]), the PFS median were 8.0 weeks for the panitumumab group and 7.3 weeks for the BSC group. In retrospectively conducted *KRAS* wild-type population and *KRAS*/*NRAS* wild-type population, PFS median were 12.3 weeks and 14.1 weeks respectively in the panitumumab group. On the other hand, in the panitumumab monotherapy vs. cetuximab monotherapy control study (ASPECCT study) in patients with *KRAS* wild-type unresectable, advanced/recurrent colorectal cancer that became resistant to fluoropyrimidine agents, OXA, and IRI[17)], the secondary endpoint PFS were 4.1 months for panitumumab and 4.4 months for cetuximab and showed no difference (hazard ratio [HR], 1.00; two-sided 95% confidence interval [CI], 0.88–1.14). Further, PFS rate at 6 months was 33% (two-sided 95% CI, 29% to 37%) for the panitumumab group.

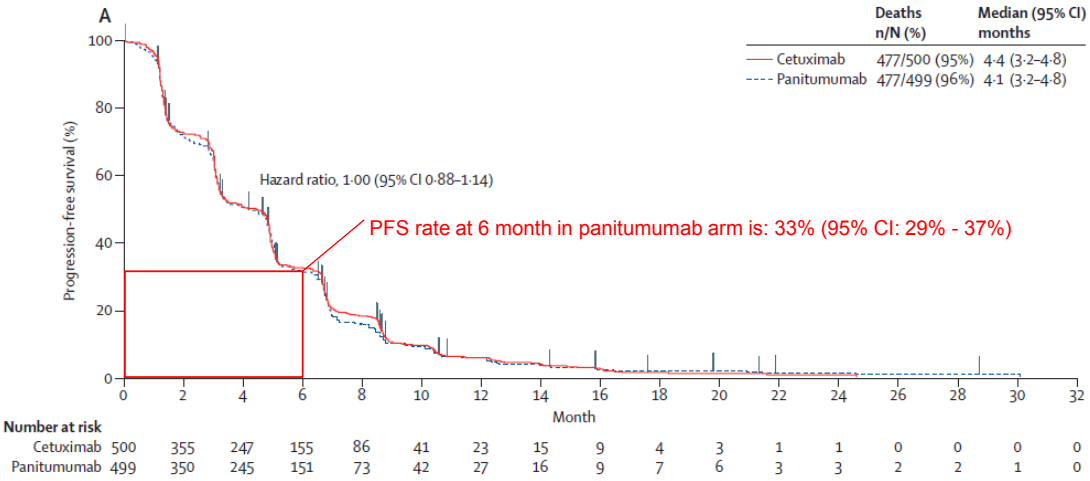


Figure 6.b ASPECCT study Progression-free survival

On the other hand, for TAS-102, in the domestic phase II study in previously treated subjects with metastatic, unresectable, colorectal cancer refractory or intolerant to fluoropyrimidine agents, OXA, and IRI, and has treatment history of 2 regimens of standard chemotherapy, the secondary endpoint PFS median assessed by the Investigator were 1.0 months in the placebo group but significantly prolonged to 2.7 months in the TAS-102 group (HR = 0.35, two-sided 95% CI 0.25–0.50, p<0.0001)

As increased anti-tumor effect can be expected by using TAS-102 in combination with panitumumab treatment which is the standard treatment for patients with unresectable, advanced/recurrent colorectal cancer, the PFS rate at 6 months in this study was assumed to be 48% and this was set as the expected value for the panitumumab treatment in combination with TAS-102 therapy in patients with RAS wild-type unresectable, advanced/recurrent colorectal cancer. *Also, for the threshold where* further development for panitumumab treatment in combination with TAS-102 may be considered not necessary, it was assumed to be 29% from the CI lower limit of the PFS rate at 6 months in the ASPECCT study. [17)]

For the main analysis, based on the observed PFS rate at 6 months from start of treatment, binomial test will be conducted on the null hypothesis "the true PFS rate at 6 months from start of treatment will be not more than the PFS threshold rate where value is determined invalid". With the PFS threshold rate at 29%, PFS expected rate at 48% at 6 months from start of treatment, and one-sided significant level at 5%, power at 80%, the necessary number of subjects will be 47. Taking into consideration of ineligible or discontinued subjects at approximately 10%, the target number of subjects was set to 52 (including subjects that received RD in the phase I part).

6.3 Discontinuation of entire clinical study or discontinuation of clinical study at a study site

6.3.1 Criteria for discontinuation of entire clinical study

The sponsor should immediately discontinue the study when at least one of the following criteria is applicable.

- When new information or other evaluation on the safety or efficacy of protocol treatment becomes available which shows a change in the known risk/benefit profile of the concerned compound, and risks/benefits are no longer tolerable for subject participation in the study.
- When suspension or discontinuation of the clinical study is notified by the DMC.
- Occurrence of serious violation of Ethical Guideline for Clinical Research or ICH-GCP which may endangers safety of subjects.

6.3.2 Criteria for discontinuation of clinical study at a study site

A study site may be notified to discontinue clinical study if the site (including the investigator) is found in significant violation of Ethical Guideline for Clinical Research, ICH-GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures of clinical study suspension and discontinuation of entire clinical study or study at a study site

In the event that the sponsor, the study site director or the investigator decides to suspend or discontinue the entire clinical study or clinical study at a study site, a study-specific procedure will be provided by the sponsor. The procedure will be followed by applicable study sites during the course of clinical study suspension or discontinuation.

6.4 Procedures for protocol amendment

When protocol amendment is required, the sponsor and the research steering committee chairman will assess and determine the propriety of the amendment.

The protocol will be amended when the following purposes are applicable, and when an amendment is made, the content will be notified to all study site investigators. Then, investigators should confirm the content of the amendment of the protocol and submit a letter of agreement to the sponsor to prove agreement for protocol amendment.

[When amendment of protocol is required]

1. Change or addition of objective
2. Change or addition of efficacy, safety evaluation method
3. Addition of test (frequency, items) or change in test method that may increase the burden of the subject
4. Dose alteration (including addition of treatment group)
5. Critical change or addition to inclusion/exclusion criteria
6. Change in planned number of subjects
7. Change of plan or description of content due to occurrence of serious adverse event, etc.
8. Following discussion between the sponsor and the research steering committee chairman, that it is determined to be applicable to critical change

Upon receiving the above notification, investigators of the study sites will be reviewed by the ethics review board again and must obtain approval from the study site director according to the regulations at each site when necessary.

7.0 SELECTION OF STUDY SUBJECTS AND ENROLLMENT

Prior to enrollment, it is necessary to confirm all inclusion/exclusion criteria including test results.

7.1 Inclusion criteria at enrollment

Patient's eligibility will be determined based on the following criteria.

1. In the opinion of the investigator* or the subinvestigator, the patient is capable of understanding and complying with protocol requirements.

   *: A personnel taking part in conducting the study and presides over the study related activities within the belonging study site.
2. Patients who signs and dates a written ICF prior to the initiation of any study procedures
3. Patients aged ≥ 20 to < 75 years at the time of informed consent
4. Patients with unresectable adenocarcinoma originating in the large intestine (excluding carcinoma of the appendix and anal canal cancer)
5. Patients who have measurable lesion (refer to Appendix A) according to Response Evaluation Criteria in Solid Tumors (hereinafter referred to as RECIST) ver 1.1
6. Patients with colorectal cancer refractory or intolerant* to chemotherapy including fluropyrimidines, oxaliplatin (OXA), irinotecan (IRI) and angiogenesis inhibitors (bevacizumab, aflibercept, ramycirumab, etc.)

   *: Refractory or intolerant if applicable to any of the following

   1) If recurrence is observed during supportive chemotherapy before or after surgery or from imaging diagnosis within 6 months of completion.

   2) If imaging or clinical progression is observed during or within 3 months from the last administration of chemotherapy for advanced cancer

   3) When it is determined that resumption is not possible due to intolerable adverse event toxicities (serious allergic reaction, accumulative neuropathy, etc.)
7. Patients classified as *KRAS/NRAS* wild-type** by *KRAS*/*NRAS* testing*.

   *: *KRAS*/*NRAS* test will be performed using the in vitro diagnostic that has been approved for marketing.

   **: All codons listed below are required to be wild-type. If any codon is unmeasured or unmeasurable, it will not be defined as wild-type.

KRAS	EXON	2	3	4
	codon	12, 13	59, 61	117, 146
NRAS	EXON	2	3	4
	codon	12, 13	59, 61	117, 146

8. Patients who may receive oral administration
9. Patients who satisfy the following criteria for the major organ function in tests performed within two weeks (14 days) prior to enrollment.
   (1) Neutrophil count 1.5×10^3/L
   (2) Platelet count 10.0×10^4/L
   (3) Hemoglobin 8.0 g/dL
   (4) Total blood bilirubin 1.5 mg/dL
   (5) AST 100 IU/L (200 IU/L if liver metastases are present)
   (6) ALT 100 IU/L (200 IU/L if liver metastases are present)
   (7) Serum creatinine 1.5 mg/dL
10. Eastern Cooperative Oncology Group (hereinafter referred to as ECOG) performance status (P.S.) has been determined as 0-1.
11. Life expectancy of 3 months (90 days) after enrollment.

7.2 Exclusion criteria at enrollment

A patient who meets any of the criteria below will not be included in this study.

1. Patients who have treatment history of anti-EGFR antibody drugs (cetuximab, panitumumab), regorafenib and TAS-102
2. Patients who have received radiotherapy and chemotherapy for primary disease as previous treatment and ≥ 2 weeks (14 days) have not passed since the last treatment at scheduled start day of treatment. However, excluding therapy received for pain relief of bone metastasis site
3. Patients with known brain metastasis or strongly suspected of brain metastasis
4. Patients with synchronous cancers or metachronous cancers with a disease-free period of 5 years (excluding colorectal cancer) excluding mucosal cancers cured or be possibly cured by regional resection (esophageal, stomach, and cervical cancer, non-melanoma skin cancer, bladder cancer, etc.)
5. Patients with body cavity fluid that requires treatment (pleural effusion, ascites, pericardial effusion, etc.)
6. Patients who do not want to use contraception to prevent pregnancy, and women who are pregnant or breast-feeding, or test positive for pregnancy
7. Patients who have received other study drugs and ≥ 4 weeks (28 days) have not passed since at scheduled start day of treatment.
8. Patients with disease requiring systemic steroids for treatment (excluding topical steroids)
9. Patients with history or obvious and extensive computerized tomography (hereinafter referred to as CT) findings of interstitial pulmonary disease (interstitial pneumonia, pulmonary fibrosis,

etc.)

10. Patients with serious concurrent medical condition (intestinal paralysis, gastrointestinal obstruction, intestinal obstruction, uncontrollable diarrhoea, diabetes mellitus being treated with continuous use of insulin or that is difficult to control, renal failure, hepatic failure, psychiatric disorder, cerebrovascular disorder, gastrointestinal ulceration requiring blood transfusion)
11. Patients with serious drug hypersensitivity (excluding allergic reaction to OXA)
12. Patients with local or systemic active infection requiring treatment, or fever indicating infection
13. Patients with heart failure or serious heart disease of class II by New York Heart Association (NYHA).
14. Patients with active hepatitis B
15. Patients with known HIV infection
16. Patients who have adverse event from previous treatment that has not recovered to at least Grade 1 (Grade 2 for peripheral sensory neuropathy) by Common Terminology Criteria for Adverse Events (hereinafter referred to as CTCAE, Japanese edition JCOG version v4.03) (excluding hemoglobin content)
17. Patients with known BRAF mutation.
18. Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study (such as patients who may be coerced to give consent)

7.3 Procedures for registration and protocol treatment

7.3.1 Procedures for registration and initiation of protocol treatment

The investigator or subinvestigator will register subjects according to the following procedure.

1. The investigator, subinvestigator or study collaborator should pre-register the subject who has been given written information on informed consent by entering the identification code and date of informed consent discussion into the Web case registration system. *

   PPD

   *: The study collaborator may enter data into the Web case registration system by instruction of the investigator or the subinvestigator.

2. After pre-registration, the investigator, subinvestigator or study collaborator should enter the necessary items into the Web case registration system (formal registration) for a subject who has given consent. After formal registration, eligibility of a prospective subject is judged by the Web case registration system and the registration will be completed.

3. The investigator, subinvestigator and study collaborator will check the registration result on the Web case registration system. The registration result will be sent via e-mail from the Web case registration system to the investigator, subinvestigator and study collaborator.

4. The investigator or the subinvestigator should start the protocol treatment within 2 weeks (14 days) of registration (including the same day of week as the day of enrollment). However, if protocol treatment cannot be initiated within 4 weeks of registration or predicted that the initiation of protocol will be after 4 weeks from registration, this must be reported to the study office before protocol treatment initiation. See Section 1.3 for study office contacts.

7.3.2 Contacts for enrollment procedure

Case enrollment center: PPD

• E-mail: PPD

[E-mail receipt confirmation]
PPD

• Tel: PPD

[Reception hours]
PPD

8.0 PROTOCOL TREATMENT

The protocol treatment, contraindicated drugs/therapies, and recommended supportive care/combination therapies in this study are explained in this section. The drugs used for this study should be ethical drugs used by the study site. See the latest package insert for details and handling of each drug.

8.1 Definition of protocol treatment

With protocol treatment in principle, combination therapy with panitumumab and TAS-102 stipulated in the "8.2 treatment regimen" will be conducted, and even if any of the criteria for suspension or discontinuation of each drug is met, treatment with other drugs will be continued unless any of the criteria for discontinuation of protocol treatment is met (such as in case of PD).

Protocol treatment in principle will be initiated within 14 days of entry.

8.2 Treatment regimen

The treatment regimen shown below should be administered (28 days [Day1-28] as one course) until any of the criteria specified in "8.7 Criteria for discontinuation of protocol treatment for each subject" is met. For administration of each drug, see "8.3 Recommended dose of protocol treatment", "8.4 Criteria for administration" and "8.5 Criteria for protocol treatment change".

Table 8a Treatment regimen of combination therapy with panitumumab + TAS-102

Drug	Dose	Method of administration	Date of administration
Panitumumab	6 mg/kg	IV drip infusion 60 min*	Day 1, 15
TAS-102	35 mg/m^2	Oral administration (twice daily**)	Day 1-5 Day 8-12

*: When the dose at one time exceeds 1,000 mg, intravenously administer it over 90 min or longer after dilution with JP physiological saline to make approximately 150 mL.

**: Within 1 hour of breakfast and dinner as reference. When TAS-102 is given at fasting state, elevation of Cmax of trifluridine (FTD) is observed, therefore fasting should be avoided.

***: Oral drug intake will start from Day 1 after dinner or the next morning and to oral drug intake on Day 6 after breakfast or after dinner will be the 5 day intake (however, in the phase I part, after dinner on Day 1 will be the start).

****: Oral drug intake will start from Day 8 after dinner or the next morning and to oral drug intake on Day 13 after breakfast or after dinner will be the 5 day intake (however, in the phase I part, after dinner in Day 8 will be the start).

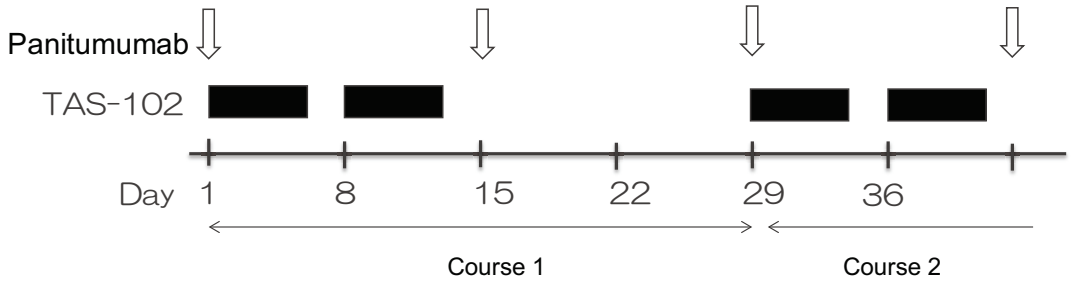


Figure 8.a Combination therapy with panitumumab and TAS-102

8.3 Recommended dose of protocol treatment

The dose will be calculated based on the body surface area (calculated using the DuBois & DuBois formula) and body weight at the time of study entry. Dose for panitumumab is round down in unit of 10 mg for reference, TAS-102 will be as Table 8.b and 8.c. At the time of entry, the data center will announce the reference dose and this should be recalculated and confirmed at the study site. The dose should be recalculated for 10% change in body weight, in principle, but at the discretion of the investigator or the subinvestigator. If more than 10% change in body weight is observed further after the recalculation the same method should be taken. However, TAS-102 dosage will be adjusted by course and adjustment from the middle of the course will not be conducted. Even if suspended during treatment period, drug will not be re-taken and drug will be taken according to stipulated treatment schedule (after 1 to 5 days, 8 to 12 days from initial administration of each course). Also, if subject missed any dose, remaining drug should not be taken.

Table 8.b TAS-102 dosage

TAS-102 dosage (twice daily)	**Body surface area (m^2)**	**One dose (mg)**	**Dose per day (mg)**	**One dosage**	
				15 mg tablet	20 mg tablet
35 mg/m^2 (70 mg/m^2/day)	< 1.07	35	70	1	1
	1.07 – 1.22	40	80	0	2
	1.23 – 1.37	45	90	3	0
	1.38 – 1.52	50	100	2	1
	1.53 – 1.68	55	110	1	2
	1.69 – 1.83	60	120	0	3
	1.84 – 1.98	65	130	3	1
	1.99 – 2.14	70	140	2	2
	2.15	75	150	1	3

Table 8.c TAS-102 dosage when dose is adjusted

TAS-102 dosage (twice daily)	Body surface area (m^2)	One dose (mg)	Dose per day (mg)	One dosage	
				15 mg tablet	20 mg tablet
Drug reduction (35 mg/m^2 to 30 mg/m^2)					
30 mg/m^2 (60 mg/m^2/day)	< 1.09	30	60	2	0
	1.09 – 1.24	35	70	1	1
	1.25 – 1.39	40	80	0	2
	1.40 – 1.54	45	90	3	0
	1.55 – 1.69	50	100	2	1
	1.70 – 1.94	55	110	1	2
	1.95 – 2.09	60	120	0	3
	2.10 – 2.28	65	130	3	1
	2.29	70	140	2	2
Drug reduction (30 mg/m^2 to 25 mg/m^2)					
25 mg/m^2 (50 mg/m^2/day)	< 1.10	25	50	2 (after dinner)	1 (after breakfast)
	1.10 – 1.29	30	60	2	0
	1.30 – 1.49	35	70	1	1
	1.50 – 1.69	40	80	0	2
	1.70 – 1.89	45	90	3	0
	1.90 – 2.09	50	100	2	1
	2.10 – 2.29	55	110	1	2
	2.30	60	120	0	3
Drug reduction (25 mg/m^2 to 20 mg/m^2)					
20 mg/m^2 (40 mg/m^2/day)	< 1.14	20	40	0	1
	1.14 – 1.34	25	50	2 (after dinner)	1 (after breakfast)
	1.35 – 1.59	30	60	2	0
	1.60 – 1.94	35	70	1	1
	1.95 – 2.09	40	80	0	2
	2.10 – 2.34	45	90	3	0
	2.35	50	100	2	1

*: If TAS-102 is to be given 50 mg/day, 20 mg will be given after breakfast, 30 mg after dinner.

8.4 Criteria for administration

In principle, the day (Day 29) that is 4 weeks after the starting day of treatment (Day 1) in the previous course will be Day 1 of the subsequent course (however, if the actual starting day is the next morning, the day before the starting day will be Day 1). Postponement or acceleration due to

holidays is allowed. See "Table 9.c Allowance range for protocol treatment and laboratory tests".

It should be confirmed that all of the criteria for initiation of protocol treatment (Table 8.d, Table 8.e) are satisfied on the starting day of treatment of each course. However, the latest data obtained from 2 days before treatment to the starting day of treatment may be used as test value.

Treatment will be postponed when any of the criteria for each drug is not met, and will be started after confirming that the symptom and laboratory data satisfy all of the criteria, and if only one drug satisfies the criteria for start of treatment then monotherapy with that drug may be allowed. However, at the starting point of the second course of the phase I part, both drugs are required to meet the treatment initiation criteria. If start of treatment with TAS-102 is postponed, the starting day thereafter (if the actual staring day is next morning, the day before) will be Day 1 of the course and that will be the schedule starting point, and if treatment with TAS-102 is determined to be discontinued and monotherapy with panitumumab is to be continued, the starting day of monotherapy with panitumumab will be defined as the start of course (Day 1), and the course will be defined as to give panitumumab on Day 1 and Day 15 between Day 1 and Day 28. However, while monotherapy with panitumumab is ongoing and treatment does not start beyond 42 days from scheduled start of treatment (starting day of treatment of previous course as Day 1, if treatment does not start by Day 57), protocol treatment will be discontinued. Postponement of start of treatment due to holidays is allowed.

Also, if start of treatment with panitumumab is postponed or discontinued, the starting day of treatment with TAS-102 (if the actual staring day is next morning, the day before) will be Day 1 of the course and that will be starting point for the schedule thereafter. However, while monotherapy with TAS-102 is ongoing and treatment does not start beyond 28 days from scheduled start of

treatment (starting day of treatment of previous course as Day 1, if treatment does not start by Day 57), protocol treatment will be discontinued. Postponement of start of treatment due to holidays is allowed.

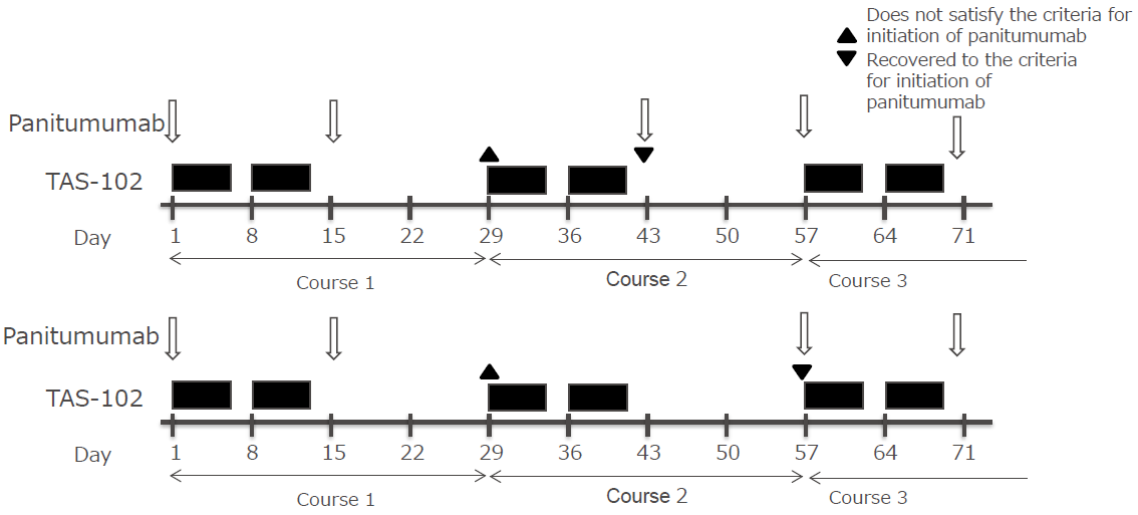


Table 8.d. Criteria for initiation of treatment with panitumumab

Item	Criteria for initiation
Skin symptom (e.g., rash acneiform, dry skin, paronychia)	≤ Grade 2
Hypomagnesaemia *	≤ Grade 2
Treatment may be postponed when suspension is needed at the discretion of the investigator or the subinvestigator due to adverse events not listed above.	

*: When accompanied by abnormal ECG findings requiring treatment such as significant QTc prolongation, discontinuation or suspension of panitumumab should be considered irrespective of the severity of hypomagnesaemia.

Table 8.e Criteria for initiation of treatment with TAS-102

Item	Criteria for initiation
Hemoglobin concentration	≥8.0 g/dL
Neutrophil count	≥ 1.5×10^3 μL
Platelet count	≥ 7.5×10^4/μL
Total bilirubin	≤ 1.5 mg/dL
AST	≤ 100 IU/L (≤ 200 IU/L with liver metastasis)
ALT	
Serum creatinine	≤ 1.5 mg/dL
Periphial sensory neuropathy	≤ Grade 2
Other non-hematological toxicity	(excluding alopecia, dygeusia, pigmentation, underlying disease related symptoms) ≤ Grade 1
Treatment may be postponed when suspension is needed at the discretion of the investigator or the subinvestigator due to adverse events not listed above.	

8.5 Criteria for protocol treatment change

8.5.1 Criteria for suspension/dose reduction of panitumumab

The criteria for suspension/dose reduction and doses of panitumumab are shown in Table 8.f and Table 8.g, respectively.

Table 8.f Criteria for suspension/dose reduction of panitumumab

Item	Grade	Dose adjustment for the next dose of panitumumab
Skin disorder	≥ 3	Dose reduction by **1** level after suspension However, treatment at a dose of **6 mg/kg** is allowed without dose reduction when it recovers to **Grade 2** or less within **6** weeks (**42** days).
Hypomagnesaemia *		
Pulmonary fibrosis (interstitial pneumonia)	≥ 2	Discontinue protocol treatment
Infusion reaction (reaction from injection) **, ***	≥ 3	Discontinuation (no resumption)
Dose reduction/suspension is allowed as necessary at the discretion of the investigator or the subinvestigator due to adverse events not listed above.		

*: When accompanied by abnormal ECG findings requiring treatment such as significant QTc prolongation, discontinuation or suspension of panitumumab should be considered irrespective of the severity of hypomagnesaemia.

**: Allergic reaction, anaphylactoid reaction, and chills, fever, and dyspnea occurring within 24 hours after the initial dose

***: If infusion reaction is observed, immediately discontinue administration. The course may be resumed at the discretion of the study site. In the event that Grade 1 or 2 infusion reaction occurs during infusion, careful administration will be allowed after appropriate supportive therapy has been given or infusion speed has been decreased by 50%, etc., upon administration of subsequent course.

Table 8.g Doses of panitumumab

Dose reduction level	Panitumumab
Initial dose	6 mg/kg
-1	4.8 mg/kg
-2	3.6 mg/kg
-3	Discontinuation (no resumption)

The administration of panitumumab may be postponed (skipped) and only TAS-102 therapy performed when the subject meets the panitumumab suspension criteria (in this case, the day of starting the next course (Day 1) will be the day of starting TAS-102 therapy). When the actual day of initiating administration starts on the morning of the next day, the day before starting administration will be Day 1. For the next dose of panitumumab, treatment will be resumed after it is confirmed that the subject does not meet the criteria for suspension of panitumumab, but if panitumumab cannot be administered for more than 28 days after the scheduled day of treatment initiation, panitumumab treatment will be discontinued.

8.5.2 Criteria for suspension/dose reduction of TAS-102

The criteria for suspension/dose reduction and doses of TAS-102 are shown in Tables 8.h-j.

Table 8.h Criteria for suspension of TAS-102

Item	Suspension criteria
Hemoglobin concentration	< 7.0 g/dL
Neutrophil count	< 1.0×10^3/Λ
Platelet count	< 5.0×10^4/Λ
Total bilirubin	> 2.0 mg/dL
AST	> 100 U/L (> 200 U/L with liver metastasis)
ALT	
Serum creatinine	> 1.5 mg/dL
Periphial sensory neuropathy	Grade 3 or higher
Other non-hematologic toxicity	Grade 3 or higher
Dose suspension is allowed as necessary at the discretion of the investigator or the subinvestigator due to adverse events not listed above.	

If adverse events meeting the criteria for dose reduction of TAS-102 shown in Table 8.i occur during the previous course (including the suspension period), dose will be reduced in course units, with a daily dose unit of reduction of 10 mg/m^2/day, when TAS-102 is resumed. However, the minimum dose will be 40 mg/ m^2/day (Table 8.j).

Table 8.i Criteria for dose reduction of TAS-102

Item	Criteria for dose reduction
Neutrophil count	< 0.5×10^3/Λ
Platelet count	< 5.0×10^4/Λ
Dose reduction is allowed as necessary at the discretion of the investigator or the subinvestigator due to adverse events not listed above.	

Table 8.j Doses of TAS-102

Dose reduction level	TAS-102
Initial dose	35 mg/m^2 (70 mg/m^2/day)
-1	30 mg/m^2 (60 mg/m^2/day)
-2	25 mg/m^2 (50 mg/m^2/day)
-3	20 mg/m^2 (40 mg/m^2/day)
-4	Discontinuation (no resumption)

When the subject meets the criteria for suspension of TAS-102, administration of TAS-102 will be suspended, and only panitumumab therapy will be administered. For the next dose of TAS-102,

TAS-102 treatment will be resumed after it is confirmed that the subject meets the criteria for initiation of TAS-102 treatment (however, when the subject satisfies the criteria for initiation of treatment from Day 13 to Day 28 of the suspension period, treatment will be resumed on Day 29). However, if TAS-102 cannot be administered for more than 28 days from the scheduled day of initiation of treatment, treatment with TAS-102 will be discontinued. (At this time, the day of initiating panitumumab monotherapy after it is determined that treatment with TAS-102 will be discontinued will be defined as the day for starting the course (Day 1), and the course will be defined as the administration of panitumumab between Day 1 and Day 28 on Days 1 and 15.)

8.6 Criteria for dose increase of protocol treatment

The dose should not be increased after dose reduction for any of the drugs.

8.7 Criteria for discontinuation of protocol treatment for each subject

The number of doses is not specified. However, protocol treatment should be discontinued when any of the criteria for discontinuation of protocol treatment listed below is met. The date of discontinuation of protocol treatment is defined as the date when the investigator or the subinvestigator decides on discontinuation of protocol treatment. The investigator or the subinvestigator should record the main reason for discontinuation of protocol treatment in the case report form (hereinafter referred to as CRF) according to the classification described below. For subjects discontinuing before enrollment, see 9.3 Records of subjects who discontinued before enrollment.

1. Lack of efficacy (exacerbation)
   When PD is evident in the clinical or imaging evaluation
2. Adverse event
   Discontinuation of treatment due to an adverse event in the opinion of the investigator or the subinvestigator, or according to the protocol treatment discontinuation criteria. However, death during protocol treatment will be classified in “4. Death during protocol treatment” and not in this item.
   Protocol treatment is postponed due to adverse event for 58 days or more after the day of starting the last course. However, postponement due to holidays is allowed.
3. Voluntary discontinuation
   A subject wishes to discontinue study participation. The reason for discontinuation should be recorded in CRF when it is clarified.

Note: Attempts should be made as best as possible to clarify the reason for voluntary discontinuation. (Discontinuation due to adverse event or lack of efficacy should not be classified as "voluntary discontinuation").

4. Death during protocol treatment
   Death before discontinuation of protocol treatment is decided. Date of death, reason of death (protocol treatment related, primary disease, others) should be described in the CRF.

5. Significant deviation from the protocol
   When study continuation may cause intolerable risk to the health of a subject because the subject was found not to satisfy the inclusion criteria specified in the protocol after enrollment or the protocol has not been observed.

6. Lost to follow-up
   When subject fails to make visits and cannot be contacted. The attempts that were made to contact the subject should be recorded in the source documents.

7. Discontinuation of the entire study
   For example, when the sponsor decides to discontinue the clinical study upon the recommendation of the DMC. See 6.3.1 Criteria for discontinuation of entire clinical study for details.

8. Pregnancy
   When a female subject is found to be pregnant.

   Note: Study participation should be immediately discontinued when pregnancy is known. See "9.2.13 Pregnancy" for procedures.

9. Others
   When the investigator or the subinvestigator decides that protocol treatment should be discontinued for other reasons. Details should be described in the CRF.

8.8 Procedures for Discontinuation or Withdrawal of a Subject

The investigator or the subinvestigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 8.7. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary reason for termination must be recorded in the CRF by the investigator or the subinvestigator. In addition, efforts should be made to perform all tests/observations/evaluation scheduled at the time of discontinuation.

8.9 DLT

In this study, DLT will be assessed based on the toxicity in 6 subjects at maximum enrolled in phase I part. The sponsor will confirm the opinion of the DMC in a suitable manner when evaluating DLT.

8.9.1 DLT Evaluation Period

The DLT evaluation period will be the period from Day 1 of Course 1 of protocol treatment to Day 1 of Course 2. However, it is mandatory that the treatment initiation criteria for both panitumumab and TAS-102 be satisfied in order to start Course 2 of protocol treatment. Furthermore, the DLT evaluation period will be the period until the test day at discontinuation of protocol treatment for subjects who could not start Course 2 of protocol treatment until Day 57 due to adverse events and discontinued the protocol treatment.

8.9.2 Subjects Included in the DLT Evaluation

Subjects enrolled in the phase I part of the study will be included in the DLT evaluation. 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/m^2) on Days 1-5 and Days 8-12.

8.9.3 DLT Criteria

DLT is defined as any adverse event for which a causal relationship with protocol treatment cannot be denied falling in the following categories. Adverse events will be graded according to the "Common Terminology Criteria for Adverse Events (CTCAE), ver. 4.03." Further, DLT will be assessed from Day 1 of course 1 of protocol treatment, and if DLT does not occur by Day 1 of course 2, it will be handled as no occurrence of DLT in the subject. Adverse events that can clearly be denied of causal relationship with the protocol treatment will not be considered DLT. If serious adverse event or unexpected adverse event occurs which causal relationship with the protocol treatment cannot be denied other than the following, it may be determined as to whether or not to handle it as DLT in consultation with the Investigator, the Research Steering Committee and the sponsor.

1. Persistent Grade 4 neutropenia for more than 7 days under maximum supportive therapy

2. Febrile neutropenia
3. Blood platelete decreased of Grade 3 requiring platelet transfusion or blood platelete decreased of Grade 4
4. If start of second course is delayed for more than 14 days due to adverse event related to protocol treatment
5. Grade 3 or higher non-hematologic toxicity that is clinically problematic however the following will not be applicable as DLT.

   - Grade 3 gastrointestinal symptoms that can be controlled with supportive care (appropriate use of antiemetics, antidiarrheals, etc.)

   - Grade 3 or higher electrolyte abnormalities that are not deemed clinically problematic

8.10 Replacement/Addition of Subjects

Should there be, during the DLT evaluation period in the phase I part of the study, a major deviation from the protocol affecting the DLT evaluation for a reason other than an adverse event classified as a DLT or if DLT cannot be evaluated appropriately, that subject can be excluded from the DLT evaluation and a new subject can be enrolled and added to that cohort.

8.11 Contraindicated drugs/therapies

The drugs and therapies shown below are contraindicated from informed consent until discontinuation of protocol treatment. The investigator or the subinvestigator should instruct the subjects not to use any drugs including over-the counter drugs other than the prescribed drugs without prior consultation.

- Chemotherapy for primary disease other than protocol treatment
- Hormone therapy for primary disease
- Immunotherapy for primary disease
  - Cellular immunotherapy
  - Vaccine therapy
  - Cytokine therapy
    Except for G-CSF
  - Biological Response Modifiers (BRM) therapy
  - Antibody therapy
  - Gene therapy
- Other antibody therapy (except for denosumab)
- Flucytosine (antifungal)

- Radiotherapy for primary disease
  Except for treatment for pain relief of bone metastasis site is allowed.
- Hyperthermia therapy for primary disease
- Study drug and unapproved drug

8.12 Recommended supportive care and combination medications

The supportive care and concomitant medications shown below are recommended during the study period (from obtaining consent until discontinuation of protocol treatment). The absence of supportive care or concomitant medications does not constitute a protocol deviation.

- Neutropenia
  Granulocyte colony stimulating factor (hereinafter referred to as G-CSF) should be administered The type of G-CSF products administered should depend on the insurance coverage.
- Nausea/vomiting
  Premedication including prophylactic administration of antiemetics is allowed. Premedication with 5-HT3 (serotonin) receptor antagonists, NK1 (neurokinin 1) receptor antagonists, steroids, and antihistamines may be carried out using the method employed at each study site.
- Diarrhoea
  Fluids and electrolyte balance will be followed adequately, and suitably supplemented, as necessary. If careful observation suggests that it is necessary, administration of an antidiarrheal such as loperamide hydrochloride may be considered.
- Allergic reaction
  Treatment with adrenal corticosteroids, antihistamines, etc. may be considered at the time of onset or for premedication at the start of the subsequent course. Careful administration of panitumumab by slowing the infusion speed may be considered.
- Pulmonary fibrosis (interstitial pneumonia)
  If it occurs, it should be treated according to the severity (e.g., steroid pulse therapy).
- Hepatitis B
  Refer to JSH Guidelines for the Management of Hepatitis B virus infection (http://www.jsh.or.jp/doc/guidelines/HBV_GL_ver2.201406.pdf**)** and take appropriate action and monitoring.
- Others
  Drugs for treatment of adverse events may be coadministered at the discretion of the investigator or the subinvestigator. Symptomatic therapies which have been continued from before the start of this study are allowed.

In addition, it is recommended that the supportive care shown below be performed at the discretion of the investigator or the subinvestigator when any of panitumumab-related adverse events listed below is observed. The absence of supportive care does not constitute a protocol deviation.

- Skin disorder
  - Tetracycline antibiotic (e.g. oral minocycline)

- External salicylic acid petrolatum (10%)
- External steroid therapy (example)
  - Face: hydrocortisone butyrate (0.1%)
  - Trunk: difluprednate (0.05%)
- Moisturizer (example): heparin analog lotion
- Sunscreen (example): not containing 4-aminobenzoic acid, SPF (Sun Protection Factor) 30, PA (Protection grade of UVA)++. Apply before going out to block ultraviolet rays (UVA and UVB).

Dermatopathy prevention with humectants, suntan lotion, antibiotic or external steroids may be carried out using the method employed at each study site, based on non-Japanese[29)] and Japanese reports[30)], etc.

- Electrolyte abnormality (e.g., hypomagnesaemia, hypocalcaemia)
  - ECG: ECG may be performed to determine whether there are abnormal ECG findings requiring treatment such as significant QTc prolongation. When any abnormal ECG findings requiring treatment are observed, suspension of panitumumab should be considered irrespective of the serum magnesium concentration.
  - Magnesium supplementation (example): intravenous infusion of magnesium sulfate (10 mmol) over 60 min

8.13 Recommended follow-up therapy

Approved drugs (e.g., regorafenib) should be used as appropriately as possible.

9.0 PROTOCOL, EVALUATION ITEMS AND PROCEDURES FOR OBSERVATIONS

9.1 Study calendar

The investigator or the subinvestigator should collect data according to "Table 9.a Study calendar (phase I part of the study)" in the phase I part of the study and "Table 9.b Study calendar (phase II part of the study)" in the phase II part of the study. The same investigator or the subinvestigator should perform tests/observations/evaluation of subjects in principle. For the allowance range of protocol treatment and various laboratory tests, see "Table 9.c Allowance range for protocol treatment and laboratory tests"

Table 9.a Study calendar (phase I part of the study)

Item	At enrollment	Protocol treatment period							Follow-up period#
		Course 1				Second and later courses		Discontinuation of protocol treatment †	
Reference day: Number of days counted from the first day of each course	-14, -1	1	8	15	22	1	15		
Informed consent obtained*1	●								
Patient Background	●								
RAS status*2	●								
Clinical findings*3	●	●	●	●	●	●	●	●	
Height*2	●								
Body weight*4	●*7	○	○	○	○	○	○		
ECOG P.S. *3	●*7	●	○	○	○	●	○	●	
Compliance*3		●	○	○		●	○		
Hematology*5	●*7	●	●	●	●	●	●	●	
Serum chemistry*5	●*7	●	●	●	●	●	●	●	
Immunology (HBs antigen)*6	●								
Tumor marker		●*8				<- ●*9->		●	
Imaging tests (thoracoabdominal-pelvic CT/MRI)	●*10					<- ●*9->		○*11	○
Follow-up treatment									●
Survival survey									●
Adverse events	−	<- ● ->							○

●: Mandatory, ○: Perform as necessary
†: Perform within 28days of discontinuation or earlier date than start of follow-up treatment, as well as possible.
#: Perform every 6 months as a guide with protocol discontinuation date as starting point.
*1: Consent must be obtained before enrollment. Further, consent should be obtained after RAS status has been identified.
*2: Values obtained after the diagnosis of colorectal cancer may be used.
*3: When the visit day is the treatment day, this will be done before administration.
*4: Measurement is not mandatory during protocol treatment period. Even if measured, it is unnecessary to record in the CRF.
*5: Testing will be performed from 2 days before to the day of the visit during each course.
*6: Test results from up to one year before obtaining consent may be used. It is unnecessary to record this in the CRF. However, follow JSH Guidelines for the Management of Hepatitis B virus infection for the measurement of HBs antibody, HBc antibody and HBV-DNA.
*7: If done within 14 days before enrollment, results from before obtaining informed consent may be used.

*8: If it has been performed within 28days before treatment day, the test for Course 1 may be omitted.
*9: Measure once every 8 weeks (56 days) with Day 1 of Course 1 as starting point. However, reduce the frequency to once every 12 weeks (84 days) when one year has passed since initiation of protocol treatment.
*10: Imaging test will be performed within 4 weeks (28 days) prior to enrollment (including the same day of week as the day of enrollment). The results of imaging diagnosis/test performed before obtaining consent may be used if it is performed within 4 weeks (28 days) prior to enrollment.
*11: This is only done when the subject is discontinued for a reason other than imaging results (PD).

Table 9.b Study calendar (phase II part of the study)

Item	At enrollment	Protocol treatment period						Follow-up period#
		Course 1			Second and later courses		Discontinuation of protocol treatment †	
Number of days counted from the first day of each course	-14, -1	1	15	22	1	15		
Informed consent obtained*1	●							
Patient Background	●							
RAS status*2	●							
Clinical findings*3	●	●	●	●	●	●	●	
Height*2	●							
Body weight*4	●*7	○	○	○	○	○		
ECOG P.S. *3	●*7	●	○	○	●	○	●	
Compliance*3		●	○		●	○		
Hematology*5	●*7	●	●	●	●	●	●	
Serum chemistry*5	●*7	●	●	●	●	●	●	
Immunology (HBs antigen)*6	●							
Tumor marker		●*8			<-●*9->		●	
Imaging tests (thoracoabdominal-pelvic CT/MRI)	●*10				<-●*9->		○*11	○
Follow-up treatment								●
Survival survey								●
Adverse events	−	<- ● ->						○

●: Mandatory, ○: Perform as necessary
†: Perform within 28days of discontinuation or earlier date than start of follow-up treatment, as well as possible.
#: Perform every 6 months as a guide with protocol discontinuation date as starting point.
*1: Consent must be obtained before enrollment. Further, consent should be obtained after RAS status has been identified.
*2: Values obtained after the diagnosis of colorectal cancer may be used.
*3: When the visit day is the treatment day, this will be done before administration.

*4: Measurement is not mandatory during protocol treatment period. Even if measured, it is unnecessary to record in the CRF.
*5: Testing will be performed from 2 days before to the day of the visit during each course.
*6: Test results from up to one year before obtaining consent may be used. It is unnecessary to record this in the CRF. However, follow JSH Guidelines for the Management of Hepatitis B virus infection for the measurement of HBs antibody, HBc antibody and HBV-DNA.
*7: If done within 14 days before enrollment, results from before obtaining informed consent may be used.
*8: If it has been performed within 28 days before treatment day, the test for Course 1 may be omitted.
*9: Measure once every 8 weeks (56 days) with Day 1 of Course 1 as starting point. However, reduce the frequency to once every 12 weeks (84 days) when one year has passed since initiation of protocol treatment.
*10: Imaging test will be performed within 4 weeks (28 days) prior to enrollment (including the same day of week as the day of enrollment). The results of imaging diagnosis/test performed before obtaining consent may be used if it is performed within 4 weeks (28 days) prior to enrollment.
*11: This is only done when discontinuation is for a reason other than imaging results (PD).

Table 9.c Allowance range for protocol treatment and laboratory tests

Performed items	Protocol specification	Allowance range
Clinical Laboratory test values (During protocol treatment)	Course 1: Day 1, 8, 15, 22 (phase I part of the study) or Day 1, 15, 22 (phase II part of the study) Course 2: Day 1, 15	From Day -2 before scheduled day (However, Mg is tested once per course.)
Protocol treatment	Day 1, 15, 29 (Day 29 is equal to Day 1 of next course)	Scheduled day ±3 days
Tumor markers and imaging tests (during protocol treatment)	Protocol treatment ≤ 1 year: 8 weeks (56 days)	Scheduled day ±1 week (7 days)
	Protocol treatment > 1 year: 12 weeks (84 days)	Scheduled day ±2 week (14 days)

9.2 Collection/test/observation items and procedures during the clinical study

The investigator or the subinvestigator will perform the following as scheduled in "9.1 Study calendar" or "Table 9.b Study calendar".

9.2.1 Informed consent procedure

Consent should be obtained from subject before initiation of study procedures.

A unique subject ID code to anonymize the subject will be assigned to each subject at the time of obtaining consent. The subject ID code will be used throughout the study period and not changed.

The method for obtaining consent is described in Section "15.3 Written information and subject's consent."

9.2.2 Enrollment and protocol treatment

For procedures and storage of enrollment and initiation of protocol treatment, see: "7.3 Procedures for Enrollment and Protocol Treatment."

9.2.3 Subject demographics

For demographic data of the subject, date of birth (or age at enrollment if date cannot be provided) and sex will be checked. Also, the following items concerning the primary disease of colorectal cancer will be examined.

(1) Information on primary organ

- Solitary/Multiple
- Primary tumor site (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectosigmoid, rectum)

(2) Information on metastasis

- Number of organs with metastasis (0, 1, ≥ 2)*

  *: Does not include primary tumor/regional lymph node, other lymph nodes in several sites will be counted as "1 organ". For example, even if it is observed in cervical lymph node and thoracic lymph node, it will be counted as 1 organ.

- Organs with metastasis (liver, lung, peritoneum, lymph node*, bone, adrenal gland, skin, and others**)

  *: Does not include regional lymph node, other lymph nodes in several sites will be counted as "1 organ". For example, even if it is observed in cervical lymph node and thoracic lymph node, it will be counted as 1 organ.

  **: Name of organ to be recorded in CRF

(3) History of treatment

- History of surgery in primary tumor site/palliative metastasis site and history of colostomy /bypass surgery
  - Subjects with history, the date of surgery
    However, endoscopic surgery, which is not considered a history of surgery, should not be entered into the CRF.
- History of radiotherapy (radical irradiation)
  - Subjects with history, the date of final dose
    However, irradiation for pain relief (palliative irradiation) in the bone metastasis site, which is not considered as radiotherapy, should not be entered into the CRF.
- Treatment history for subjects with unresectable lesions
  - Description of first-, second-, and third-line treatment (FOLFOX, FOLFOX + anti-angiogenic agent (e.g., bevacizumab); CapeOX, CapeOX + anti-angiogenic agent (e.g., bevacizumab); FOLFIRI, FOLFIRI + anti-angiogenic agent (e.g., bevacizumab); IRIS, IRIS + anti-angiogenic agent (e.g., bevacizumab); IRI, IRI + anti-angiogenic agent (e.g., bevacizumab); FOLFOXIRI, FOLFOXIRI + anti-angiogenic agent (e.g., bevacizumab); SOX, SOX + anti-angiogenic agent (e.g.,

bevacizumab); SOX, SOX + anti-angiogenic agent (e.g., bevacizumab); other), date of initiation of first-line treatment

- History of preoperative and/or postoperative adjuvant chemotherapy
  - Subjects with history, history of preoperative and/or postoperative adjuvant chemotherapy with OXA, date of final treatment

9.2.4 Concurrent medical condition

A concurrent medical condition is defined as any symptom or disease present at initiation of protocol treatment. Any notable concurrent medical condition will be entered into the CRF. Clinically problematic laboratory test data, ECG findings, and abnormal physical examination findings observed immediately before initiation of protocol treatment should be handled as a concurrent medical condition at the discretion of the investigator or the subinvestigator.

9.2.5 Clinical findings

Medical examination will be performed prior to protocol treatment. In particular, the following symptoms at the medical examination will be confirmed.

Allergic reaction, rash acneiform, cutaneous dryness, paronychia, infusion reaction (infusion related reaction), anorexia, diarrhoea, nausea, vomiting, oral mucositis, hypomagnesemia, blood neutrophil count decreased, febrile neutropenia, reduced blood platelet count, peripheral sensory neuropathy, thromboembolism, gastrointestinal perforation, interstitial pneumonia, fatigue.

The results of medical examinations after initiation of protocol treatment will be compared with the results of medical examinations before initiation of protocol treatment to evaluate the clinically problematic abnormalities.

See “10.0 Adverse event” for definition of adverse event.

9.2.6 Body weight, height

Body weight at enrollment should be measured within 2 weeks (14 days) before enrollment (including the same day of week as the day of enrollment) and recorded in the CRF. Height obtained after the diagnosis of colorectal cancer may be used.

9.2.7 Eastern Cooperative Oncology Group Performance Status (ECOG) Performance Status

ECOG Performance Status (P.S.) will be assessed according to Table 9.d. P.S. at enrollment will be determined within 2 weeks (14 days) prior to enrollment (including same day of the week as the day of enrollment). P.S. before initiation of each course will be determined before administration on treatment day. P.S. at discontinuation will be determined as much as possible within 4 weeks (28 days) after discontinuation or before the initiation of follow-up treatment whichever date is earlier.

Table 9.d Eastern Cooperative Oncology Group Performance Status (ECOG P.S.)

P.S.	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

9.2.8 Compliance

The investigator or the subinvestigator should record the compliance with protocol treatment in the CRF as follows:

- Doses and treatment days for panitumumab
- Doses, treatment initiation day, and number of doses of TAS-102

9.2.9 Clinical laboratory tests

In principle, laboratory tests should be conducted at each study site.

Laboratory tests at enrollment will be conducted within 2 weeks (14 days) prior to enrollment (including same day of the week as the day of enrollment).

Testing will be performed from 2 days before to the day of the visit during the protocol treatment period.

Tests at discontinuation will be conducted as much as possible within 4weeks (28 days) after discontinuation or before the initiation of follow-up treatment whichever date is earlier.

Test items and notes are listed in Table 9.e to Table 9.g.

The investigator and the subinvestigator should evaluate and store the reported laboratory test results.

For laboratory test standard values, common standard values (common standard range list, Japan Clinical Oncology Group, hereinafter referred to as JCOG) will be used.

Table 9.e Laboratory tests performed at the time of enrollment

Hematology	Serum chemistry	Immunology
Neutrophil count	Total bilirubin	HBs antigen *
Platelet count	ALT	
Hemoglobin content	AST	
	Creatinine	
	Mg	
	Albumin	
	Na	
	K	
	Ca	

*: Test results measured up to 1 year before obtaining consent may be used. However, follow JSH Guidelines for the Management of Hepatitis B virus infection for the measurement of HBs antibody, HBc antibody and HBV-DNA.

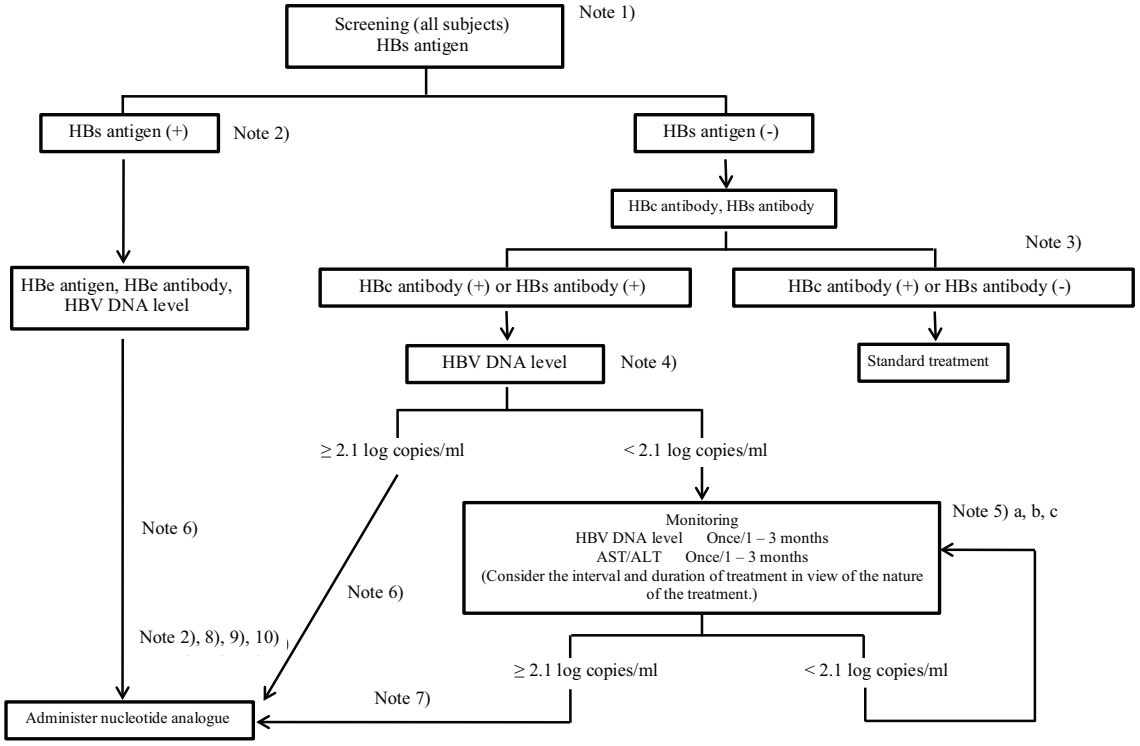


Figure 9.a JSH Guidelines for the Management of Hepatitis B virus infection

Supplementary note: During or after completion of potent chemotherapy for hematological malignancies, caution is required because hepatitis B occurs in a portion of HBs antigen-positive and -negative patients as a result of reactivation of the hepatitis B virus, and the disease becomes fulminant in portion of these patients. Action is also necessary with standard chemotherapy for hematological malignancies and solid tumors and

immunosuppressive therapy for autoimmune diseases such as rheumatological diseases in view of the risk of reactivation of HBV. The frequency of reactivation of HBV and the occurrence and progression to fulminant status of hepatitis with standard chemotherapy and immunosuppressive therapy is not known, and there is insufficient evidence related to guidelines. In addition, treatment with nucleotide analogues does not completely guarantee prevention of progression to a fulminant status.

Note 1) Screening will be conducted for HBV carriers and subjects with previous infections prior to immunosuppressive therapy or chemotherapy. First, HBs antigen will be measured to identify HBV carriers. In HBs antigen-negative subjects, HBc antibody and HBs antibody will be measured to identify subjects with previous infections. Highly sensitive techniques should be used to measure HBs antigen, HBc antibody, and HBs antibody. In subjects positive for HBs antibody only (HBs antigen-negative and HBc antibody-negative), HBV reactivation will be reported, and action should be taken according to guidelines, except when the subject is known to have been vaccinated.

Note 2) When a subject is HBs antigen-positive, consult with a hepatologist. A hepatologist should be consulted when administering nucleotide analogues to any subjects.

Note 3) Antibody titers may decrease when initially starting chemotherapy in subjects who are being retreated but have not been measured for HBc antibody and HBs antibody and subjects who have already been started on immunosuppressive therapy, and detailed examinations should be performed, e.g., measuring HBV DNA levels.

Note 4) Screening for HBV DNA will be performed by real time PCR in subjects with previous infections.

Note 5)

a. Caution is required with subjects receiving chemotherapy with rituximab, a steroid, and fludarabine and hematopoietic stem cell transplantation because they are at high risk of HBV reactivation from previously infected people. HBV DNA should be monitored once a month during and for a period of at least 12 months after completion of therapy. Subjects receiving hematopoietic stem cell transplantation require long-term monitoring after transplantation.
b. There is also a risk of HBV reactivation with combination therapy using standard chemotherapy and molecularly targeted drugs having an immunological effect, although the frequency of reactivation is low. As a general guideline, HBV DNA levels should be monitored every 1 to 3 months, but the frequency and time of monitoring should take the nature of the treatment into consideration. Action should be taken prudently in the case of hematological malignancies.
c. There is also a risk of HBV reactivation with immunosuppressive therapy using corticosteroids, immunosuppressives, and molecularly targeted drugs having an immunosuppressive or immunomodulating effect. With immunosuppressive therapy, HBV DNA levels should be monitored monthly for at least 6 months after staring or changing the therapy. After the first 6 months, the frequency and time of monitoring should take the nature of the treatment into consideration.

Note 6) Administration of nucleotide analogues should be started as early as possible before starting immunosuppressive therapy or chemotherapy. However, deaths from fulminant hepatitis during prophylactic nucleotide analogue therapy have been reported in HBs antigen-positive patients with a high viral load, and the viral load should therefore be reduced before starting immunosuppressive therapy or chemotherapy.

Note 7) Administration of nucleotide analogues should be started immediately when HBV DNA has reached 2.1 log copies/mL or higher during or after completion of immunosuppressive therapy or chemotherapy. During immunosuppressive therapy or chemotherapy, a hepatologist should be consulted about the action to be taken without immediately discontinuing the immunosuppressive agent or anti-neoplastic agent with an immunosuppressive action.

Note 8) The recommended nucleotide analogue is entecavir.

Note 9) Termination of nucleotide analogue treatment may be considered when the following conditions are satisfied. In subjects who are HBs antigen-positive at screening: when the criteria for terminating nucleotide analogue treatment in chronic hepatitis B are satisfied. In subjects who are HBc antibody-positive or HBs antibody-positive at screening: (1) Nucleotide analogue treatment should continue for at least 12 months after completing immunosuppressive therapy or chemotherapy. (2) Normalization of ALT (GPT) should be achieved during this period of continued treatment. (unless ALT is abnormal for a reason other than HBV). (3) Sustained negative HBV DNA should be maintained during this period of continued treatment.

Note 10) Subjects should be followed vigilantly, including HBV DNA monitoring, for at least 12 months after terminating nucleotide analogue treatment. The follow-up should be based on the Precautions for Use in the package insert of the nucleotide analogue used. Nucleotide analogue treatment should be resumed immediately when HBV DNA reaches 2.1 log copies/mL or higher in subjects being followed.

Table 9.f Clinical laboratory tests performed during the protocol treatment period

Hematology	Serum chemistry	Tumor markers
Neutrophil count *	Total bilirubin *	CEA**, †
Platelet count *	ALT*	
Hemoglobin content *	AST*	
	Creatinine *	
	Mg ***	
	Albumin *	
	Na*	
	K*	
	Ca*	

*: The test in Course 1 may be omitted when the pre-entry test had been performed within 2 days before treatment in Course 1. The test in Course 1 will be performed before administration in Course 1 when the pre-entry test had been performed more than 2 days before treatment in Course 1.

**: If it had been conducted within 28 days before treatment day, it may be omitted.

***: May be measured once during each course.

†: Measure every 8 weeks (56 days) with Day 1 of Course 1 as starting point. However, when 1 year has passed since initiation of protocol treatment, once every 12 weeks (84 days).

Table 9.g Laboratory tests performed at the time of discontinuation

Hematology	Serum chemistry	Tumor markers
Neutrophil count	Total bilirubin	CEA*
Platelet count	ALT	
Hemoglobin content	AST	
	Creatinine	
	Mg	
	Albumin	
	Na	
	K	
	Ca	

*: If ≥ 28days has not passed since the last measurement, the test can be omitted.

9.2.10 Imaging test (thoracoabdominal-pelvic CT/MRI)

Imaging test will be performed within 4 weeks (28 days) prior to enrollment (including the same day of week as the day of enrollment). The results of imaging diagnosis/test performed before obtaining consent may be used if it is performed within 4 weeks (28 days) prior to enrollment.

Furthermore, the data of measurable lesion should be evaluated with imaging test conducted within 2 weeks (14 days) prior to initiation of protocol treatment (including the same day of week as the day of enrollment) preferably. If another imaging test has been conducted newly after enrollment but before initial administration, this data should be recorded in CRF.

After initiation of protocol treatment, imaging test will be performed every 8 weeks (56 days) with protocol treatment initiation date (Day 1) of Course 1 as the starting point. However, when 1 year has passed since initiation of protocol treatment, imaging may be performed once every 12 weeks (84 days), counting from the point in time at which 1 year has passed. (For details, see "Table 9.a Study calendar (phase I part of the study)" or "Table 9.b Study calendar (phase II part of the study)."

Thoracoabdominal-pelvic CT (in principle, contrast CT; a slice width of 5 mm or less is recommended, but MRI is also acceptable) will be used for imaging test, and the modality and the date of imaging test will be entered into the CRF. If necessary, brain MRI / CT and a neck CT will be performed.

In principal, the same modality should be used for imaging test during protocol treatment throughout the study period.

The investigator or the subinvestigator should evaluate the test results according to the RECIST v1.1 (see Appendix A) and enter the determined results into the CRF.

Furthermore, for subjects withdrawn from the study for any reason other than imaging test results such as clinical PD, imaging test specified at the time of discontinuation should be performed within 4 weeks (28 days) including the day of decision (including the same day of week as the day of decision).

If the subject is not determined to have PD on imaging up to the time of withdrawal, the following information should be collected until the subject dies or the sponsor terminates the study, even after follow-up treatment has been started.

- Day of decision on clinical PD (only when the subject is not determined to have clinical PD by the time of discontinuation)
  - It will not be necessary to collect information if the subject is determined to have radiological PD before the subject is determined to have clinical PD.
- Day of decision on radiological PD
  - The day of decision on radiological PD will be collected, regardless of the state of clinical PD. The final imaging test date will be collected in subjects not determined to have radiological PD during the follow-up period as well.
- Date of last confirmed progression-free survival
  - The date of last confirmed progression-free survival will be collected in subjects not determined to have either clinical PD or radiological PD during the follow-up period as well.

However, when follow-up is not possible due to withdrawal of consent, loss to follow-up, etc., the date of the last visit will be entered in the CRF as the date of last confirmed progression-free survival.

9.2.11 Follow-up treatment

The following information will be collected when follow-up treatment is performed after discontinuation of protocol treatment. If several types of follow-up treatment are performed, information will only be collected on the follow-up treatment immediately following discontinuation of protocol treatment.

- Name of drugs used (regorafenib, other)
- Initiation date

9.2.12 Survival survey

After discontinuation of protocol treatment, every subject will be followed-up to confirm survival of subjects every 6 months in principle after discontinuation of protocol treatment. The following information on survival should be collected. The survey should be continued until the subject dies or the sponsor terminates the study.

- Survival survey date
- Date of death or last confirmed date of survival
  - If deceased, the reason of death (death from primary disease/others)

9.2.13 Pregnancy

When it becomes apparent that a female subject is pregnant, with consent from female subject, the investigator or the subinvestigator should notify the primary care physician (obstetrician and gynecologist, etc.) that the female subject was participating in a clinical study at the time she became pregnant and provide details of protocol treatment.

For every female subject reported to have become pregnant, the investigator or subinvestigator should follow-up to delivery including result of premature delivery with consent from the female subject and report to the sponsor using the specified follow-up form. Evaluation after delivery will also be conducted.

9.3 Records of subjects who discontinued before enrollment

Every subject who has signed the ICF and dropped-out before enrollment should be registered in the Web registration center and a CRF should be prepared.

The following items are to be entered in the CRF.

- Date of consent obtained

- Date of birth (the age at enrollment)
- Sex
- Eligibility
- Reason for discontinuation

For subjects who drop-out from the study before enrollment, the main reason for dropping-out should be entered into the CRF according to the following categories.

- Not satisfying at least one of the inclusion criteria or meeting any of the exclusion criteria
- Serious deviation from the protocol
- Lost to follow-up
- Voluntary discontinuation <specify the reason>
- Discontinuation of the entire study
- Others <specify the reason>

The subject ID code of a subject withdrawn from the study before enrollment should not be reused.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse events

Adverse events are any unfavorable medical events encountered in a subject treated with a drug. They are not limited to the events with clear causal relationship with treatment with the concerned drug.

In other words, adverse events are any unfavorable or unintended sign (including clinically problematic abnormalities of laboratory test data), symptoms or diseases that develop after administration of a drug irrespective of a causal relationship with the relevant drug.

10.1.2 Items to be considered concerning adverse events

Generally unfavorable findings are shown below:

- Newly diagnosed disease or unexpected aggravation of existing symptom (intermittent event of the existing symptom is not considered an adverse event)
- Requiring action or medical practice
- Requiring invasive diagnostic treatment
- Requiring discontinuation of protocol treatment (panitumumab + TAS-102 combination therapy) or of combination therapy or change in dose
- Considered unfavorable by the investigator or the subinvestigator

Diagnosis name and signs/symptoms:
Adverse events should be recorded by a diagnosis name. Accompanying signs (including abnormal laboratory values, abnormal ECG findings) and symptoms should not be recorded as adverse events. If an adverse event could not be expressed by a diagnosis name, sign or symptom will be the adverse event.

Laboratory test values and ECG findings:
Abnormal laboratory values and ECG findings are recorded as adverse events when the investigator or the subinvestigator judges the course to be clinically problematic (in other words, when certain action or medical practice is required, or the investigator or the subinvestigator judges the change to have exceeded the normal physiological variation range of the subject). Retest and/or continued monitoring of abnormality are not considered medical practice. Also, repeated or additional conduct

of non-invasive test for verification, evaluation and monitoring of abnormality are not considered medical practice.

However, when abnormal laboratory values and ECG findings are the accompanying symptoms of the disease diagnosed as an adverse event (e.g., increased creatinine due to renal dysfunction, etc.), the diagnosis name is handled as an adverse event.

Existing symptoms (diseases and/or symptoms that have been present from before initiation of protocol treatment): Diseases and/or symptoms that have been present from before initiation of protocol treatment should be recorded as concurrent medical conditions and not as adverse events. When a concurrent medical condition is aggravated, the aggravation will be determined as an adverse event and the investigator or the subinvestigator should record in CRF that the adverse event is an aggravation of the concurrent disease (e.g., "aggravation of hypertension", etc.).

When a subject has an existing symptom that is transient (e.g., asthma, epilepsy) and incidence of the symptom is increased, or the symptom becomes serious or severe, it should be recorded as an adverse event. When a subject has a chronic disease (e.g., cataract, rheumatoid arthritis) and the symptom is aggravated more than anticipated, it should be recorded as an adverse event. The investigator or the subinvestigator should record in a way that will make the reported adverse event name be recognized as a change from baseline (e.g., aggravation of XX).

Change of severity of adverse events:
When the severity of an adverse event has changed, the event should be recorded once at the highest degree of severity (grade based on the CTCAE [Japanese edition JCOG version 4.03]), and should be recorded in each protocol treatment course.

Previously planned surgery or treatment:
Surgery or treatment planned before initiation of protocol treatment is not considered an adverse event. However, when the existing symptom is aggravated to require emergency surgery or treatment, the condition or the event is considered an adverse event. A complication which resulted from previously planned surgery is reported as an adverse event.

Non-urgent surgery or treatment:
Non-urgent surgery or treatment that does not induce a change in the condition of a subject (cosmetic surgery, etc.) is not considered an adverse event. However it should be recorded in the source documents. Complications due to a non-urgent surgery should be reported as an adverse event.

Progressive Disease (PD):
PD should be considered lack of efficacy, not an adverse event. In addition, the single fact of PD does not necessarily constitute a serious adverse event. However, if a clinical or on imaging progression of pre-existing cancer (including new metastasis) is confirmed, it will be determined as a serious adverse event if the severity satisfies any of the criteria specified in Section 10.1.3.

Panitumumab overdose:
When overdose of panitumumab becomes apparent, it should be recorded in the CRF. If adverse event occurs with overdose, it should be recorded as an adverse event in the adverse event column of the CRF.

Furthermore, the overdose of panitumumab is defined as follows.

1) Received administration exceeding approved dosage (6 mg/kg) of panitumumab
2) Received next administration within 10 days of previous administration

10.1.3 Serious adverse events

Of all the unfavorable medical events that developed with administration of drugs (irrespective of dose), serious adverse event is an event that:

1. Results in death during protocol treatment* and all deaths irrespective of a causal relationship with protocol treatment.
   *: Period from initiation of protocol treatment up to 4 weeks (28 days) after discontinuation of protocol treatment or initiation of follow-up treatment.
2. Results in death after discontinuation** of protocol treatment for which a causal relationship with protocol treatment cannot be denied. However, death obviously due to the underlying disease is not applicable.
   **: from 29 days after discontinuation of protocol treatment or from initiation of follow-up treatment
3. Is life-threatening. The term “life-threatening” refers to an event in which the subject was at risk of death during onset of the adverse event; it does not refer to an event which hypothetically might have caused death if it were severer.
4. Requiring hospitalization or prolongation of hospitalization
   However, hospitalization or prolongation of hospitalization for the following reasons will not be handled as a serious adverse event.
   (1) Preplanned inpatient hospitalization or prolongation of existing hospitalization

(2) Inpatient hospitalization or prolongation of existing hospitalization unrelated to an adverse event

5. Results in persistent or significant disability/incapacity.

6. Leads to a congenital anomaly/birth defect.

7. Other medically significant condition: medically important event which causes a risk to a subject even if it is not immediately life-threatening, nor does it result in death or hospitalization, or requires an action or treatment to prevent the results shown in 1 to 6 above.

10.1.4 Special interest adverse event for sponsor

Adverse events listed in Table 10.a "Takeda Medically Significant AE List" will be handled as "special interest adverse event" for sponsor irrespective of severity determined by the investigator or the subinvestigator. Further, any adverse events listed in Table 10.a that has been determined as serious by the investigator or the subinvestigator will be handled as serious adverse event.

Table 10.a Takeda Medically Significant AE List

Acute respiratory failure/acute respiratory distress syndrome (ARDS)	Hepatic necrosis
Torsades de pointes/ ventricular fibrillation/ventricular tachycardia	Acute hepatic failure
Malignant hypertension	Anaphylactic shock
Convulsive seizure (including convulsion and epilepsy)	Acute renal failure
Agranulocytosis	Pulmonary hypertension
Aplastic anemia	Pulmonary fibrosis (including interstitial pneumonia)
Toxic epidermal necrolysis/ oculomucocutaneous syndrome (Stevens-Johnson syndrome)	Neuroleptic malignant syndrome/ malignant hyperpyrexia
	Spontaneous abortion/ stillbirth and fetal death
	Confirmed or suspected transmission of infection by a medicinal product
	Confirmed or suspected endotoxin shock

10.1.5 Severity of adverse events

The severity of adverse event is classified into 5 grades (Grade 1-5) as follows based on the Common Terminology Criteria for Adverse Events (hereafter referred to as CTCAE, Japanese edition JCOG version 4.03), of the National Cancer Institute, USA. Furthermore, the grade for adverse events not listed in CTCAE will be classified according to the following criteria.

Table 10.b CTCAE (Japanese edition JCOG version 4.03) Grade

Grade 1	Mild; asymptomatic or slightly symptomatic; only clinical or test findings; or requiring no treatment
Grade 2	Moderate; requiring the least treatment or local or non-invasive treatment; or interfering with age-appropriate activities of daily living except for self-care activities*
Grade 3	Severe or medically critical, but not immediately life-threatening; requiring hospitalization or prolongation of existing hospitalization; disabling/incapacitating; or interfering with self-care activities of daily living**
Grade 4	Life-threatening; or requiring emergent treatment
Grade 5	Death due to an adverse event

AE: Adverse Event, ";" stands for "or"
*: Activities of daily living except for self-care activities include meal preparation, shopping for daily necessities and clothings, phone call, and financial management.
**: Self-care activities of daily living include bathing, dressing, eating, toilet, and oral drug intake, and indicate that a person is not confined to bed.

10.1.6 Causality of adverse events

Causal relationship between protocol treatment (panitumumab + TAS-102 combination therapy) and adverse events, and causal relationship between panitumumab and adverse events (information on causal relationship with panitumumab will be collected only when causal relationship is "related" with protocol treatment) is classified and defined as described below. Information on causal relationship with adverse event is not collected for any drugs other than protocol treatment.

Related	An adverse event with apparent temporal relation (including clinical course after discontinuation). Possibly due to protocol treatment or panitumumab although other factors such as underlying disease, complications, concomitant drugs/treatment are also presumed.
Not related	An adverse event with no chronological correlationship with protocol treatment (chemotherapy, panitumumab, or bevacizumab). Very likely due to other factors such as underlying disease, complications, and concomitant drugs/treatment.

10.1.7 Date of onset of adverse events

The date of onset of adverse events will be determined according to the following criteria.

Adverse event, etc.	Date of onset
Signs, symptoms, and diseases (diagnoses)	The subject, investigator, or subinvestigator will record the date on which the sign or symptom of an adverse event is first noticed.
Asymptomatic diseases	The date on which diagnosis is confirmed by testing will be recorded. Even if testing reveals old findings or if the time of occurrence can generally be estimated, the date on which diagnosis is confirmed will be recorded.
Aggravation of concurrent medical conditions	The subject, investigator, or subinvestigator will record the date on which a disease or aggravation of a disease is first noticed.
Test results that became abnormal after initiation of protocol treatment	The test date on which abnormal test results determined to be clinically problematic were observed will be recorded.
Test results that are abnormal at initiation of protocol treatment and aggravated in later testing	The date on which the time profile of a laboratory value shows a clear increase or decrease, based on medical judgment, will be recorded.

10.1.8 Action taken for protocol treatment

As for action concerning protocol treatment, when protocol treatment is discontinued as an action against the concerned adverse event, it will be defined as “discontinuation”.

10.1.9 Outcome

Outcome of adverse events is classified as follows.

Category	Criteria for judgment
Recovered	• disappearance or recovery of symptoms and findings • laboratory values returned to normal or baseline
Improved	• severity was improved by one or more grades • symptoms or findings mostly disappeared • laboratory values improved but has not returned to normal or baseline • when the subject died from a cause other than the adverse event concerned while the event was resolving
Not recovered	• no change in symptoms, findings, or laboratory data • the symptoms, findings, or laboratory data on the final day of observable period aggravated compared with the date of onset • irreversible congenital anomaly • when a subject died where the concerned adverse event is not a direct cause of death and the concerned adverse event remained not recovered
Recovered with sequelae	• disability which disturbs daily life
Death	• direct relationship between death and the concerned adverse event • "Direct relationship" means that the concerned adverse event was the cause of death, or the concerned adverse event was clearly responsible for death. • Outcome of an adverse event which was not determined (judged, presumed) a direct cause of death observed in the same subject is not considered as death.
Unknown	• follow-up specified in the protocol after the date of onset was not possible due to change of hospitals or relocation, etc.

10.2 Procedures

10.2.1 Collection and reporting of adverse events

10.2.1.1 Period for collection of adverse events

Adverse events should be continuously collected from initiation of protocol treatment up to 4 weeks (28 days) after discontinuation of protocol treatment or initiation of follow-up treatment, whichever date is earlier. In addition, adverse event causal relationship cannot be ruled out of protocol treatment collected later 4 weeks (28 days) after discontinuation of protocol treatment or initiation of follow-up treatment.

10.2.1.2 Reporting of adverse events

At each visit of subject, the investigator or the subinvestigator should confirm whether the onset of subjective symptoms is present or not. Onset of any adverse event that developed after the previous visit should be checked by asking a question such as "how has your condition been since the last visit?" to a subject.

The investigator or the subinvestigator should follow up all subjects who developed adverse events irrespective of a causal relationship with protocol treatment until disappearance of symptoms or abnormal laboratory values, return of clinically problematic abnormal laboratory values to the value before administration of study drug, or if not, until observed changes can be sufficiently explained for other events (persistent/irreversible adverse event, etc.).

All adverse events should be entered into the CRF. The name of the adverse event, date of onset, severity, seriousness, causal relationship with protocol treatment (unrelated or related), further if event has causal relationship "related" to protocol treatment, causal relationship with panitumumab (unrelated or related) should be recorded. Also, for the last course, action taken and outcome concerning protocol treatment as well as date of resolution should be recorded.

Follow-up period of adverse events is until recovery of an adverse event, or the investigator or the subinvestigator judges that further follow-up would be unnecessary.

10.2.2 Collection and reporting of serious adverse events

When a serious adverse event develops during the period of collecting adverse events, it should be reported according to the following procedures.

When the investigator or the subinvestigator judges that a serious adverse event has occurred based on the reporting by a subject, etc., or results of various tests, imaging findings or definitive diagnosis, etc., it should be reported immediately to the director of the study site.

Also, the investigator or the subinvestigator should report to the sponsor (see attached sheet for contact information) within 72 hours of recognition of onset of event. Further, the investigator should submit a formal report within 10 calendar days to the sponsor.

Furthermore, the content below which is to be reported to the sponsor within 72 hours is mandatory, and other items should be reported as much as possible.

- Brief description of adverse event and the reason for why it was determined as serious
- Study title

- Subject ID code
- Name of study site
- Name of investigator or the subinvestigator
- Name of protocol treatment being conducted
- Determined causal relationship

10.2.3 Follow-up of serious adverse events

The investigator or the subinvestigator should follow-up all serious adverse events, etc., until recovery is confirmed, or the final outcome is determined.

When a change such as alteration of outcome was made to the report of a serious adverse event, the investigator or the subinvestigator should submit a report specifying details of the change to the director of study site and the sponsor. When requested by the sponsor or the study site committee such as the ethics review committee, related data of the study site (e.g., ECG, laboratory test values, summary of discharge report, result of autopsy, etc.) should be provided.

10.2.4 Reporting of additional information concerning adverse events

If the sponsor requests provision of additional information concerning adverse events for reporting to regulatory authorities, the investigator or the subinvestigator should confirm the necessary additional information and enter in the EDC system or submit a report within the period specified by the sponsor.

10.2.5 Dissemination of unknown serious adverse event to joint research institutions

If the director of the study site receives a report of an unexpected serious adverse event, for which a direct causal relationship with protocol treatment cannot be denied, from the investigator or subinvestigator, the director should ask the opinion of a study site committee such as the ethics review committee and add the items below to the report submitted by the investigator, and disseminate it to the monitoring committee and research institutions that are jointly conducting clinical study through the sponsor.

- Date of review, summery of review, result, necessary action, etc., related to the study site committee such as ethics review committee.

10.2.6 Reporting of serious adverse events, etc., to ethics review committee, etc., and regulatory authorities

If the director of the study site receives report of serious adverse event from the investigator, the director should ask opinion of the ethics review committee, etc., and disseminate the study sites that are conducting clinical study through the sponsor or the CRO (research secretariat office) consigned by the sponsor.

If the director of the study site receives report of unexpected serious adverse event, the director should add the items below to the report submitted by the investigator, and prepare unexpected serious adverse event report and report to the Minister of Health, Labour and Welfare, and disseminate the study sites that are conducting clinical study (report to the Minister of Health, Labour and Welfare, and dissemination to study sites through sponsor is also possible).

- Action taken for serious adverse event
  (discontinuation of new enrollment, revision of ICF, re-consent from other subjects, etc.)
- Date of review, summery of review, result, necessary action, etc., related to ethics review committee, etc.
- Dissemination to joint research institutions.

The sponsor should report according to regulations, unexpected serious adverse drug reactions and other serious adverse events that are subject to emergency reporting to regulatory authorities, the investigator and director of study site.

From the time point of first acknowledging the event or receiving additional information, the sponsor or the CRO (research secretariat office) consigned by the sponsor should comply with regulatory required time frame for reporting, and make emergency report concerning unexpected serious adverse drug reactions and expected serious adverse drug reactions to regulatory authorities. Also, the sponsor should in the same way make an emergency report of other critical safety information that may have a major effect on the study drug risk-benefit, continuation of study drug administration, and continuation of clinical study. The study site should submit copies of emergency report documents to the ethics review committee, etc.

11.0 COMMIITTEES ESTABLISHED FOR THIS STUDY

11.1 Research steering committee

The research steering committee will be established to effectively promote this study.

The research steering committee will consist of the sponsor, research steering committee chairman, research steering committee members and statistics representative, and the sponsor or its designee will act as the secretariat.

Details of management of the research steering committee will be specified in a separately prepared procedure manual. Research steering committee members are listed in Section 1.2.

11.2 Data monitoring committee

The Data Monitoring Committee (hereinafter referred to as DMC) will be established according to the ICH E6 (1.25), and the sponsor or its designee will serve as the secretariat of the DMC.

The purpose of the DMC is to evaluate safety report data (including DLT occurring during the DLT evaluation period of the phase I part of the study) independent of the research steering committee concerning the appropriateness of continuing the study, or changing, discontinuing, suspending, or other measures regarding the study, and to submit the results to the sponsor. The sponsor will determine whether to continue, discontinue, or change the study based on the results.

The sponsor will prepare the DMC procedures (DMC charter) specifying the details such as the objective, roles, and responsibilities of the DMC, and management procedure. DMC members are listed in Section 1.2.

12.0 DATA MANAGEMENT AND STORAGE OF RECORDS

Detailed procedure of data management is described in data management plan. Adverse events and concurrent conditions should be coded using MedDRA.

12.1 Case report form

The investigator or the subinvestigator should prepare the case report form (CRF) for all subjects who have given consent.

The sponsor or its designee should provide study sites with access authorization to the electronic data capture (hereinafter referred to as EDC). The sponsor should provide the investigator, subinvestigators, and study collaborators with training for utilization of EDC. The CRF will be used to report the information collected during the study period to the sponsor. The CRF will be prepared in Japanese. Data will be directly entered in preparing the CRF.

A change or correction of the CRF will be recorded as an audit trail that records the information before and after the change or correction, the person who made the change or correction, date of change or correction, and its reason.

The investigator or its designee should ensure the accuracy and completeness of the CRF, and provide an electronic signature on the relevant page of the case report form. The investigator bear full responsibility for the accuracy and reliability of all the data entered into the CRF.

The data below will be directly recorded into the CRF.

- Seriousness, severity and causal relationship of adverse event with protocol treatment and "panitumumab"

When the investigator or the subinvestigator makes a change or correction in the data entered into the CRF after fixation of clinical data base, a record (Data Clarification Form) of change or correction in the CRF provided by the sponsor should be used. The investigator should confirm that the record of change or correction in the CRF is accurate and complete, and sign or write name/ affix a seal, and date it.

The sponsor or its designee should confirm CRF has been prepared appropriately. The sponsor or its designee should have access to the medical records of study subjects and in-house records to ensure the accuracy of the CRF as necessary. The completed CRF is the property of the sponsor, and the investigator or the subinvestigator should not disclose the information to a third party without a written permission from the sponsor.

12.2 Time limit for data input into the EDC

The sponsor or its designee should request the investigator or the subinvestigator to promptly enter EDC during the period from enrollment of subject to the end of follow-up.

It is recommended that after consent has been obtained from subject, the EDC should be entered within the time frame described below, in principle. A failure to enter the data within the time frame does not constitute a deviation, but it is recommended that it should be entered as much as possible.

1. At enrollment: within 2 weeks (14 days) after enrollment (within 1 week (7 days) of course 1 of the phase I part of the study (the DLT evaluation period))
2. During protocol treatment: within 2 weeks (14 days) after the final day of each course (the starting day of the next course) (within 1 week (7 days) of course 1 of the phase I part of the study (the DLT evaluation period))
3. At discontinuation of protocol treatment: within 4 weeks (28 days) after the day of discontinuing protocol treatment (within 2 weeks (14 days) of course 1 of the phase I part of the study (the DLT evaluation period))
4. Imaging test results: within two weeks (14 days) after evaluation of efficacy
5. Follow-up period: within two weeks (14 days) after request for follow-up
6. Inquiry about data input items: within two weeks (14 days) from inquiry

12.3 Storage of records

The investigator or the director of study site should store the following materials including those specified in Section 14.1 and study specific documents to be used by the sponsor or its designee for investigation and audit. The materials include a list of subject screening, medical records, signed and dated original consent form, and a record of change and correction of the CRF (copy)/electronic copy of electronic CRF containing audit trail. Also, the investigator and the director of study site should store the essential documents until the date that passes five years after discontinuation or completion of the study. However, when the sponsor requires a longer storage period, the director of the study site will discuss the period and methods of storage with the sponsor.

Further, the investigator and the director of the study site will store the essential documents until the sponsor notifies that storage is no longer necessary.

13.0 STATISTICAL ANALYSIS METHODS

The statistics representative or his/her designee (a personnel belonging to an institution independent from sponsor, analysis personnel) will conduct analysis. Sponsor will not be involved in analysis.

13.1 Statistical and analytical plans

The statistics representative or analysis personnel should start preparing the statistical analysis plan (SAP) (first version) and establish the SAP (first version) before conducting the final analysis. The SAP (first version) should be finalized before data fixation. Detailed definition of endpoints and analysis methods should be specified in the SAP to deal with all the purposes of the study.

Data review should be performed before data fixation. Data review is performed to evaluate the accuracy and completeness of the study data, subject evaluability, and appropriateness of the planned analysis methods.

13.2 Statistical analysis of the phase I part of the study

13.2.1 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 definition subjects included in the DLT evaluation in Section 8.9.2.

13.2.2 Analysis of demographic and other baseline characteristics

The following analyses will be performed in "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."

Demographic factors will be tabulated for each subject. Frequency will be tabulated for discrete data, and summary statistics will be calculated for continuous data.

13.2.3 Safety analysis

13.2.3.1 Primary endpoint and analysis method

[Primary endpoint]
Incidence of DLT with panitumumab + TAS-102 combination therapy

[Analysis method]

The incidence of DLT will evaluated in the DLT evaluation set according to Section 6.1 Study Design (Figure 6.a Outline of study design). In addition, a table listing each DLT event that occurs will be prepared.

13.3 Statistical analysis of the phase II part of the study

13.3.1 Analysis sets

In the phase II part of the study, statistical analysis will be performed in a “full analysis set” and “safety analysis set”. The “full analysis set” is the main efficacy analysis set, and is defined as “subjects enrolled in phase I and 2 who received at least one dose of protocol treatment (RD) and satisfied all of the enrollment criteria”. RD is recommended dose which 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 panitumumab and/or TAS-102”. Additionally, all subjects who are enrolled in this study is defined as "all enrolled subjects".

The statistics representative and analysis personnel should finalize statistic alalysis plan before data fixation based on the confirmation of the definition of analysis sets and appropriateness of analytical handling rules of the subject data in the analysis sets and addition of handling rule for the sssues which are not determined at planning.

13.3.2 Analysis of demographic and other baseline characteristics

Perform the following analysis in the “all renrolled subjects set” and “full analysis set”.

In the analysis of the main subject demographic factors, frequency will be tabulated for discrete data, and summary statistics will be calculated for continuous data.

13.3.3 Efficacy analysis

13.3.3.1 Primary endpoint and analysis method

[Primary endpoint]
PFS rate 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. The criteria for determining progression are described in "13.3.3.2 Secondary Endpoints and Analytical Methods for Them".

[Main analysis]
The following analysis will be performed in the "full analysis set".

PFS rate at 6 months is calculated by counting of subjects each subjects with progression, not progression, or unconfirmed at 6 months. "At 6 months" in the main analysis is defined as 24 weeks (8 weeks x 3) with time window of 2 weeks before and after. 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 ≤ 29%". Significant level will be 2.5% (one-sided) in main analysis. For interval estimation, accurate 90% confidence interval (two-sided) based on binomial distribution will be used.

13.3.3.2 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 progression or the day of death due to all causes whichever comes earlier.

  Progression will include both PD based on diagnostic imaging assessed according to RECIST ver 1.1 (see Appendix A) and primary disease progression that cannot be confirmed by diagnostic imaging (clinical progression). When progression is documented by diagnostic imaging, the day that 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 where, 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 confirming progression-free survival). 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.

[Analysis method]

Show the Kaplan-Meier survival curve until the onset of event in the "full analysis set" and calculate the point estimation value of survival rate and its 95% confidence intervals (two-sided) at the quantile of PFS and specified time points. The Log-Log conversion of Brookmeyer and Crowley[23)] 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 all causes. For surviving subjects, the period is terminated on the final day of confirming survival 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 (see Appendix A) is either CR or PR. Overall response will be graded by favorability in the order of CR, PR, SD, PD, and NE. Best overall resonse is the best response recorded in the throughout of all courses.

  [Analysis method]

  RR of target lesion 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 progression or the day of death due to all causes, whichever occurs earlier. For surviving subjects without documented progression, the period will be cut off on the final day when specified diagnostic imaging reveals no PD (final day of confirming progression-free survival). For surviving subjects without documented progression 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 confirming progression-free survival).

[Analysis method]

Show the Kaplan-Meier survival curve until the onset of event for the subjects who showed response among the "full analysis set" and calculate the point estimation value of survival rate and its 95% confidence interval (two-sided) at the quantile 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 (see Appendix A) 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 all causes whichever comes earlier.. Subjects not included above criteria will be sonsored at the starting date of dose in the final course

  [Analysis method]

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

13.3.3.3 Data conversion method and handling of missing data

Details are separately determined in the SAP.

13.3.3.4 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)

13.3.4 Safety analysis

The following analysis will be performed in the "full analysis set" and "safety analysis set".

13.3.4.1 Treatment-Emergent Adverse Events

Treatment-Emergent Adverse Events (TEAE) are adverse events which develop after initiation of protocol treatment.

Perform the following analysis for TEAE. Code TEAE using MedDRA and summarize by Preferred Term (PT) and System Organ Class (SOC).

- Frequency tabulation of all TEAE
- Frequency tabulation of TEAE for which the causal relationship with protocol treatment was "related"
- Frequency tabulation of TEAE for which the causal relationship with panitumumab was "related"
- Frequency tabulation of all TEAE by severity
- Frequency tabulation of TEAE by severity for which the causal relationship with protocol treatment was "related"
- Frequency tabulation of TEAE by severity for which the causal relationship with panitumumab was "related"
- Frequency tabulation of TEAE for action taken for protocol treatment was "discontinuation"
- Frequency tabulation of TEAE by severity for action taken for protocol treatment was "discontinuation"
- Frequency tabulation of serious TEAE
- Frequency tabulation of serious TEAE for which the causal relationship with protocol treatment was "related"
- Frequency tabulation of serious TEAE for which the causal relationship with panitumumab treatment was "related"
- Frequency tabulation of non-serious TEAE with >5%.
- Frequency tabulation of non-serious TEAE with >5% for which the causal relationship with protocol treatment was "related".
- Frequency tabulation of non-serious TEAE with >5% for which the causal relationship with panitumumab was "related".
- Frequency tabulation of TEAE with ≥Grade 3.
- Frequency tabulation of TEAE with ≥Grade 3 for which the causal relationship with protocol treatment was "related".
- Frequency tabulation of TEAE with ≥Grade 3 for which the causal relationship with panitumumab was "related".
- The incidence rate of TEAE with ≥Grade 3
- The incidence rate of TEAE with ≥Grade 3 for which the causal relationship with protocol treatment was "related".
- The incidence rate of TEAE with ≥Grade 3 for which the causal relationship with panitumumab was "related".

Main skin toxicitywill be analyszed samely as described above (7.2.5.1～7.2.5.20)

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

The 95% confidence intervals is culculated by the fomula following;

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

13.4 Criteria for interim analysis and premature discontinuation

No interim analyses are scheduled.

13.5 Determination of the planned number of subjects

See "6.2.2.2 Rationale for planned number of subjects".

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring of study sites

The sponsor or its designee will perform periodic monitoring of study sites during the study to confirm that the study is carried out in accordance with all specifications in the protocol. Central monitoring and site visit monitoring, when necessary, will be performed in this study.

Details of procedures for monitoring will be determined in the separately prepared procedures.

14.1.1 Central monitoring

Central monitoring will be performed to check that the study is safely conducted in accordance with the protocol and that data are accurately collected, based on the data collected by EDC. Central monitoring will be conducted twice a year in principle, and periodic monitoring report will be prepared. Periodic monitoring report will be evaluated by research steering committee and feedback will be given to study sites when necessary.
Detailed procedures for central monitoring will be determined in the separately prepared procedures.

14.1.2 Site visit monitoring

Site visit monitoring is conducted to confirm that the study is carried out safely and in compliance with the protocol and the data are accurately collected by checking the data entered into the EDC against source documents. Source documents are the original documents, data and records. The investigator and the director of study site will ensure that the sponsor or its designee and the ethics review committee, etc., have access to the source documents.

The sponsor or its designee will access the records including the list of subject screening, medical records, signed and dated original consent forms to confirm that the study is appropriately conducted in compliance with the protocol. Also, confirm the consistency between CRF and the related source documents. The investigator and the subinvestigator and other personnel involved in the study will spare sufficient time to facilitate monitoring procedures during visits to the study site.

Prior to site visit monitoring, study sites will be randomly selected to perform Source Documents Verification (SDV) for the enrolled subjects.

The frequency and procedures of study site visit monitoring should follow separately prepared procedure manual.

14.1.3 Deviations from Ethical Guideline for Clinical Research, ICH-GCP, and Protocol

The investigator or the subinvestigator should record all deviations from Ethical Guideline for Clinical Research, ICH-GCP, and protocol.

The investigator or the subinvestigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from ethics review committee, etc. In the event of a deviation or change, the investigator should notify the sponsor and the director of the site of the deviation or change as well as its reason in a written form, and retain a copy of the written form. When necessary, the investigator may consult and agree with the sponsor on a protocol amendment. If the protocol is to be amended, the amendment proposal should be submitted to the director of the site as soon as possible and an approval should be obtained from site committee such as ethics review committee.

14.2 Quality assurance

The sponsor or its designee and site committee such as ethics review committee will perform audit at the study site when necessary. In such a case, the auditor designated by the sponsor should contact the study site in advance to determine the date of audit. The auditor may request a visit to other sites that will be used during the study. The investigator and the director of the study site should ensure that the auditor has access to study-related source documents.

15.0 ETHICAL CONDUCT OF CLINICAL STUDY

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, Ethical Guideline for Clinical Research and the ICH-GCP. Each investigator will conduct the study according to regulatory requirements and in accordance with Appendix B "Responsibilities of the Investigator".

15.1 Approval by the study site committee such as the ethics review committee

The study site committee such as the ethics review committee is constituted according to regulations.

The sponsor or its designee should obtain the document listing the name and title of each committee member.

The sponsor or its designee should provide related documents to the study site committee such as the ethics review committee for review and approval of the protocol. In addition to the protocol, a copy of informed consent form, written materials related to subject recruitment, advertisement, and other documents required by regulation, when necessary, should be submitted to the central committee or the study site committee such as the ethics review committee to obtain approval. The sponsor should notify the study site, the investigator and the subinvestigator after confirming the appropriateness of the regulatory documents of the study site. Protocol procedures such as obtaining consent should not be started until the study site, the investigator and the subinvestigator receive the notification.

The study site should comply with all the requirements specified by the study site committee such as the ethics review committee. The requirements include notifications to committees such as the ethics review committee, for instance, revision of the protocol, revision of the informed consent form, revision of materials related to subject recruitment, report on safety in accordance with the regulatory requirement, report on study implementation state at intervals determined by the study site committee such as the ethics review committee, and study completion report. The sponsor or its designee should obtain written approval from the study site committee such as the ethics review committee related to the above mentioned items and all related materials.

15.2 Conflict of interests

This study will be conducted with support from sponsor. Prior to conduct of the study, the investigator should appropriately manage according to the study site regulation, that this study has no conflict of interests (hereinafter referred to as COI). [24)~28)]

The study site should comply with all the requirements specified by the ethics review committee, etc. The requirements include the COI self-declaration, protocol, and informed consent form.

15.3 Written information and subject's consent

The informed consent form contains specific requirements of the Declaration of Helsinki, Ethical Guideline for Clinical Research and the ICH-GCP and all applicable laws and regulations. The informed consent form specifies the use of personal information and medical information of subjects in this study (both in and outside Japan: supply to a third party), and disclosure. Written explanation explains in detail the general idea and purpose of the study, and its possible risks and benefits. The informed consent form also clarifies the conditions for study participation and states the fact that subjects can discontinue study participation at any time without giving reasons and without loss of benefits in treatment. In principal, the items below are described.

1) Clinical study and informed consent form
2) Disease and condition
3) Method of treatment for disease
4) Name of study and explanation that approval has been obtained from the director of study site for conducting the study
5) Name of research steering committee chairman, study site, and investigator
6) Objective of study and meaning
7) Method of study (including purpose of use of samples/information collected from subject) and study duration
8) The estimated number of patients participating in the study
9) The reason for being selected as subject
10) Burden for the patient and foreseeable risk and benefits
11) Consent for participation
12) Even if consent for carrying out or continuing the study has been given, this can be withdrawn at any time
13) Explanation that the patient can disagree on or withdraw consent for carrying out or continuing the study without loss of benefits
14) Method of information disclosure
15) Explanation that upon request, the patient can obtain and have access to material concerning protocol and method of study, and on the method of obtainment and access within the scope where protection of personal information of other patients and the assurance of originality of the study is not hindered.
16) Handling of personal information (including method of anonymity)
17) Method of storage and destruction of sample/information

18) Status related to funding of study, etc., study site related conflict of interest and personal benefits upon study, etc., study staff related conflict of interest upon study
19) Intellectual property rights
20) Possibility that the data is used for future studies
21) Correspondence to inquiries from patients and persons concerned
22) Expenses
23) Items on other methods of treatment
24) Correspondence to health care provided after study has been conducted
25) Compensation for injuries related to the study and what they consist
26) Issues to be followed
27) Notification of new information and study discontinuation
28) Explanation that on the premises of patients privacy being preserved, monitoring personnel, audit personnel and ethic review committee will have access to sample/information of subjects in the study within the scope of necessity.
29) Explanation that informed consent cannot be obtained from anyone but the patient him or herself.

The investigator is responsible for preparation, content, and the site committee such as ethics review committee approval of the informed consent form. The informed consent form should be approved by the site committee such as ethics review committee before use.

The informed consent form should be written in a language easily understood by subjects. The investigator or the subinvestigator is responsible for providing detailed explanation of the informed consent form to subjects. Information should be provided orally and in writing as much as possible by the method deemed appropriate by the site committee such as ethics review committee.

The investigator or the subinvestigator should ensure that the subjects have (1) an opportunity to inquire about the study and (2) sufficient time to determine study participation. When a subject decides to participate in the study, the subject should sign or write name/affix seal, and date the consent form prior to study participation. The investigator and the subinvestigator should request the subject to sign or write name/affix seal using a legal name and not a popular name with black or blue ballpoint pen. The investigator or the subinvestigator should also sign or write name/affix seal, and date the consent form prior to subject participation. Further, if study collaborator has made complementary explanations, the collaborator should also sign or write name/affix seal, and date the consent form.

The investigator or the subinvestigator should store the original consent form which was signed or contains name/ affixed seal. The investigator or the subinvestigator should document in the subject's medical record the date when the subject signed or wrote name/ affixed seal on the consent form. A

copy of the consent form with signature or name typed with seal affixed should be provided to the subject.

The investigator or the subinvestigator should take the same procedures taken for obtaining the initial consent for newly obtaining consent from the concerned subject when the informed consent form is revised. The date of obtaining new consent should be recorded in the subject's medical record, and a copy of the revised consent form should be provided to the subject.

15.4 Subject confidentiality

The sponsor and its designee should comply with the principles of protection of the subject's right against invasion of privacy. The subject ID code in this study is used to connect the clinical study database and related study documents of the sponsor with the source data of subjects. The limited information of subjects such as sex, age, and date of birth may be used within the scope of all applicable laws and regulations for identification of subjects and confirmation of accuracy of subject ID code.

In compliance with Ethical Guideline for Clinical Research and the ICH-GCP, the sponsor should request the investigator for the access to the original laboratory test data, ECG, record of hospitalization/discharge during study period, and the original medical records such as autopsy report (source data or materials) by a monitor or the person designated by the sponsor, auditor designated by the sponsor, and the ethical committee, etc. The investigator or the subinvestigator should obtain approval from subject concerning access to the original medical records by a monitor when obtaining consent from a subject (see Section 15.3).

When providing a copy of source documents to the sponsor, the investigator or the subinvestigator should delete the information leading to identification of an individual (name and address of subject, other personal information not recorded in CRF of subject).

15.5 Contacts for inquiries from subjects and concerned people

The investigator should establish a contact service to respond to inquiries concerning this study from subjects or concerned people. Details of the contacts for inquiries will be described in the ICF.

15.6 Advantages and disadvantages to subjects

15.6.1 Advantage to subjects

This study is performed as part of normal medical practice, and no advantage is expected by participating in this study.

15.6.2 Disadvantage to subjects

This study is performed as part of normal medical practice, and no disadvantage is expected by participating in this study.

15.7 Attribution of study results and access rights

15.7.1 Attribution of study results

The study results and data obtained from this study belong to the sponsor. The intellectual property rights regarding the pharmaceutical products manufactured and/or distributed by Takeda Pharmaceutical Company Limited also belong to Takeda Pharmaceutical Company Limited. Data generated from this study may be made available for secondary use (e.g., meta-analysis) without any link to personally identifying information only with approval from the research steering committee chairman and the research steering committee.

15.7.2 Data access rights

Access rights for all data and information generated from this study will be given to personnel approved by the sponsor.

15.8 Reporting of results, Publication, disclosure, and clinical study registration policy

15.8.1 Reporting of results, publication and disclosure

The investigator should report to the director of the study site written summary of results of the study and provide the sponsor with all the results and data obtained from the study. Only the sponsor may disclose the study information to other investigators or subinvestigators during the study period except for a case required by laws and regulations. The sponsor will be responsible for publication of

the protocol and study-related results (including the public web site) except for other cases permitted in the study contract.

During study period and after the end of study, the sponsor or its designee should promptly summarize the results and present it to medical journals and academic conferences, etc.

The sponsor may publish the data and information obtained from the study (including the data and information provided by the investigator) based on the agreement with the research steering committee chairman.

The investigator or the subinvestigator should obtain the prior written approval from the sponsor when publishing the information obtained in this study at an academic conference, etc.

The sponsor should report to the director of the study site that final publication of the study result has been made.

15.8.2 Clinical study registration

Takeda Pharmaceutical Company Limited will ensure timely publication of the information of a clinical study and registration of all clinical researches in patients under way all over the world, prior to study initiation, with ClinicalTrials.gov, JAPIC, and UMIN to comply with the applicable laws/regulations and guidelines. The city and country where a study is performed, and the subject recruitment status should be registered as well as the contact information of Takeda Pharmaceutical Company Limited to enable general access.

15.8.3 Clinical trial results disclosure

Takeda Pharmaceutical Company Limited will post the results of a clinical study on ClinicalTrials.gov, JAPIC, and UMIN as specified by the applicable laws and/or regulations irrespective of results.

15.8.4 Method of storage and destruction of material/information concerning clinical study

The director of the study site should appropriately retain the material/information related to this study for at least to the date passing 5 years from the date of reporting of the ending of the study from the investigator or to the date passing 3 years from the date of reporting of final publication of the study result, whichever date is later.

15.9 Insurance and compensation for injury

The subjects participating in this study will be compensated for any injury resulting from participation in the study according to local regulations applicable to the study site. It should be noted that any treatment provided will be covered by health insurance, and no monetary compensation will be provided.

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Appendix A Evaluation according to RECIST ver 1.1

Evaluation will be conducted according to RECIST ver 1.1 as follows.

1. Definition of measurable lesion

   Lesion that fulfills any of the conditions below will be considered as a measurable lesion.

   (1) Lesions other than malignant lymph node (non-nodal lesion) that meet either of the below
      1) CT scan slice thickness no greater than 5 mm or MRI largest diameter at least10 mm
      2) CT scan slice thickness greater than 5 mm or MRI largest diameter is 2 folds or more the slice thickness

   (2) Malignant lymph node CT scan slice thickness 5 mm or less and short diameter at least 15 mm
   (Malignant lymph node with short diameter at least 10 mm and less than 15 mm will be a non-target lesion, lymph node with short diameter of less than 10 mm will not be considered as a lesion)

   Any other lesion besides the above will be considered as non-measurable lesions.

   Note that lesions below will be considered as non-measurable lesions irrespective of test method or size of lesion:

   - Bone lesions
   - Cystic lesions
   - Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy
   - Leptomeningeal disease lesion
   - Ascites, pleural effusion, pericardial effusion
   - Lymphangitic involvement of skin or lung
   - Abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques

2. Baseline documentation of target lesions

   From measurable lesions observed before initiation of protocol treatment, select 5 lesions highest in diameter (long diameter for non-nodal lesion and short diameter for malignant lymph node), 2 lesions at most for 1 organ and determine them as target lesions. Upon selection, organs with measurable lesions should be included evenly, and select in consideration of those that lend themselves to reproducible repeated measurements (lesions with large diameter but difficult to measure should be avoided).

   For chosen target lesion, in order from head to tail, record site, lesion diameters (long diameter for non-nodal target lesions, short axis for nodal target lesion) and a sum of diameters (hereinafter referred to as SoD) of all target lesions should be recorded.

3. Baseline documentation of non-target lesions

   Lesions not selected for target lesion should be recorded as present or absent non-target lesion irrespective of whether measurement is possible or not. Multiple non-target lesions in the same

organ can be recorded as 1 lesion (e.g. multiple enlarged pelvic lymph nodes, multiple liver metastases)

4. Tumor response criteria

   Evaluate target lesion and non-target lesion using the same method as at enrollment according to "9.2.10 Imaging test (thoracoabdominal-pelvic CT/MRI)", and record diameter of target lesion, presence or absence of non-target lesion or onset of new lesion.

5. Response criteria of target lesion

   - CR (Complete Response):

     Disappearance of all non-nodal target lesions and all lymph node target lesions short axis <10mm If nodal target lesion is selected at baseline, response criteria may be CR even though SoD is not 0 mm.

   - PR (Partial Response):

     At least a 30% decrease in the SoD of target lesions, taking as reference the baseline SoD.

   - PD (Progressive Disease):

     Taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), at least a 20% increase in the SoD of target lesions, and the sum must also demonstrate an absolute increase of at least 5 mm.

   - SD (Stable Disease):

     Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest SoD while on study.

   - Not all Evaluated:

     When test cannot be conducted for some reason, or cannot be determined as CR, PR, PD or SD.

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

$$\text{Increase ratio of SoD} = \frac{\text{SoD at evaluation} - \text{Smallest SoD}}{\text{Smallest SoD}} \times 100\%$$

* Diameter of target lesion is recorded with actual measurements (e.g., even if under 5 mm) as much as possible, but when target lesion is determined as "too small to measure", irrespective of CT slice thickness, if it is determined that tumor lesion no longer exists and the diameter will be recorded as 0 mm, whereas if it is determined to exist the diameter will be 5 mm.

* If reduction ratio meets the PR criteria and increase ratio meets the PD criteria at the same time, criteria will be determined as PD.
* If one lesion is divided during treatment, each diameter should be added to the SoD.
* If multiple lesions agglutinate and the border cannot be distinguished, the diameter of the agglutinated lesion should be added to the SoD.
* Whenever lesions are in contact, if the borders of the lesions are distinguishable, the diameter of each lesion should be added to the SoD.

6. Response criteria of non-target lesion
   - CR (Complete Response):

     Disappearance of all non-nodal non-target lesions and all lymph nodes short axis <10mm
   - Non-CR/non-PD:

     Persistence of one or more non-target lesion(s) including lymph nodes short axis ≥ 10 mm and/or maintenance of tumor marker either of which the level is above the common normal limits.
   - PD (Progressive Disease):

     "Unequivocal progression" of existing non-target lesions (including recurrence).

     When the patient has measurable lesion: In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. When response criteria for target lesion is SD or PR, an increase of non-target lesion that will overwhelm the tumor burden decrease will be determined as "unequivocal progression", and if not it will be Non-CR/non-PD.

     When the patient has only non-measurable lesion: a 20% increase diameter in a non-measurable lesion, an increase in tumor burden representing an additional 73% increase in 'volume' will be determined as "unequivocal progression".
   - Not all Evaluated:

     When test cannot be conducted for some reason, or cannot be determined as CR, Non-CR/non-PD, or PD.

7. Appearance of new lesions

   When a lesion that was not present at baseline has been observed after initiation of treatment, this will be determined as appearance of "new lesion". However, "new lesion" should not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. For example, necrosis of a liver lesion may be

reported as a "new" cystic lesion, which it is not. A newly identified lesion in a location by test that was not mandatory at baseline (evaluation before enrollment) is considered a new lesion

If a lesion disappears and reappears later, measurement will be continued. However, the response at the time of reappearance of the lesion will be different depending on other lesions. If lesion has reappeared after CR, it will be determined as PD at the time of reappearance. On the other hand, if it was PR or SD, when the once disappeared lesion reappears, in order to calculate the response, the diameter of the lesion will be added to the rest of the lesions. Thus, when there are a number of lesions still existing, if one lesion apparently "disappears" and reappears later, from that alone, it will not be determined as PD but if the SoD of all the lesions meet the PD criteria, it will be determined as PD. The reason for this is that there is an understanding that most of the lesions do not truly "disappear" and yet it cannot be extracted due to the limit to resolution of imaging modality.

If there is a possibility of new lesion but cannot be confirmed, it should not be determined as a new lesion but re-examination by imaging test should be conducted after clinically appropriate interval. If new lesion is confirmed by imaging test re-examination, the date of the imaging test that confirmed the new lesion will be the time point for appearance of new legion.

8. Overall Response

Overall Response will be determined with combination of target lesion response, non-target lesion response, appearance of new lesion according to Tables A.1 and A.2 below.

Table A.1 Overall response at each time point: When patient has target lesion (with or without non-target lesion)

Target lesion	Non-target lesion	New lesion	Overall response
CR	CR	Absent	CR
CR	Non-CR/non-PD	Absent	PR
CR	Not determined	Absent	PR
PR	Non-PD or defect in evaluation	Absent	PR
SD	Non-PD or defect in evaluation	Absent	SD
Defect in evaluation	Non-PD	Absent	NE
PD	Any	Present or absent	PD
Any	PD	Present or absent	PD
Any	Any	Yes	PD

9. Best Overall Response

   Response will be more favorable in the following order: CR>PR>SD>PD>NE. The most favorable overall response through the entire course will be the best overall response.

   When response could not be determined by imaging due to an obvious aggression of disease or death before the first response determination, it will be determined as PD. When response could not be determined by imaging due to discontinuation from toxicity or rejection by subject before the first response determination, it will be determined as NE.

Appendix B Responsibilities of the investigator

1. To appropriately conduct the study in accordance with the protocol, Ethical Guideline for Clinical Research and the ICH-GCP considering the human rights, safety, and wellbeing of human subjects.
2. When assigning a part of important duties related to this study to subinvestigators or study collaborators, prepare a list of subinvestigators or study collaborators, which will be submitted to the director of study site as necessary.
3. To prepare the informed consent form and revise it as necessary.
4. To check the contents of the study contract.
5. To provide sufficient information on the protocol, drug and duties of each personnel to subinvestigators and study collaborators, and give guidance and supervision.
6. To select subjects who satisfy the protocol, give explanation using written information, and obtain consent in writing.
7. To be responsible for all medical judgments related to the study.
8. Corresponding to request from the director of the study site, report the latest progress status at least once a year to the director of the study site.
9. To request COI committee of each study site to review and approve that there is no COI issues in conducting this study.
10. To ensure together with the director of study site that sufficient medical care is provided to subjects for all study-related clinically problematic adverse events throughout the period of subject's study participation and thereafter.
11. When a subject is treated at another medical institution or department, inform a physician of the medical institution or department in writing of the subject's study participation and study completion/discontinuation after obtaining the subject's consent, and prepare the record.
12. When emergency report of serious adverse events, etc. is required, immediately report it in writing to the director of the study site and the sponsor.
13. To prepare accurate and complete CRF and submit it to the sponsor with an electronic signature.
14. To inspect and check the contents of CRF prepared by subinvestigators, or transcribed by study collaborators from the source data, and submit it to the sponsor with an electronic signature.
15. To discuss a revision of the protocol, etc., when proposed by the sponsor.
16. To report the study completion in writing to the director of study site.

PROTOCOL

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

APOLLON study

A phase I/II study for the safety and efficacy of **P**anitumumab in c**o**mbination with TAS-102 for patients with *RAS* wild-type metastatic co**l**orecta**l** cancer refract**o**ry to sta**n**dard chemotherapy

Sponsor	Takeda Pharmaceutical Company Limited
Protocol number	Panitumumab-1501
Version	First Edition
Product name	Panitumumab
Creation date	October 27, 2015

CONFIDENTIAL

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1.0 CLINICAL STUDY PRINCIPLES AND CLINICAL STUDY MANAGEMENT INFORMATION

1.1 Clinical Study Principals

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- Ethical Guideline for Clinical Research (the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, December 22, 2014).
- International Conference on Harmonisation E6 Good Clinical Practice (hereinafter referred to as "GCP") (including ICH-GCP).
- All applicable laws and regulations, including, without limitation, data privacy laws, conflict of interest guidelines.

1.2 Clinical Study Administrative Structure

This study will be conducted under the following administrative structure.

Clinical research steering committee

Research steering committee chairman:

PPD

Research steering committee members:

PPD

Data Monitoring Committee (hereinafter referred to as DMC)

DMC chairman:

PPD

DMC members:

PPD

Statistics Representative:

PPD

Also, terms used in this protocol will be defined as follows:

Study site:

A corporation an administrative organization or a sole proprietor conducting the study, except for sites performing only a part of the study related activities on consignment such as sample/ information storage and statistic processing.

Joint research institution:

An institution jointly conducting the study based on the protocol, and will include institutions that will additionally obtain sample/ information from study subjects and providing them to other study sites.

Study staff:

Investigators and other staff personnel conducting the study (including activities performed in institutions that collect and provide samples/ information), except for personnel who only provides existing samples/information besides study site or partially engage in the study related activity on consignment.

Investigator:

A personnel taking part in conducting the study and presides over the study related activities within the belonging study site.

Study site director:

Director of a corporation, an administrative organization or a sole proprietor conducting the study

Study subjects:

A person who is applicable to either of the following:

1. A person who is being studied (including a person who has been requested to be studied)
2. A person who has given existing samples/information to be used in the study

1.3 Contacts for protocol inquiries

Study office: PPD

E-mail: PPD

Tel: PPD

[Reception hours]

PPD

1.4 Contacts for enrollment procedure

Case enrollment center: PPD

• E-mail: PPD

[E-mail receipt confirmation]

PPD

• Tel: PPD

[Reception hours]

PPD

1.5 Sponsor

Takeda Pharmaceutical Company Limited,

Strategic Medical Research Planning, Global Medical Affairs Department, Japan Oncology Business Unit

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2.0 STUDY SUMMARY

Sponsor:	**Test product:**
Takeda Pharmaceutical Company Limited	Panitumumab

Study title:

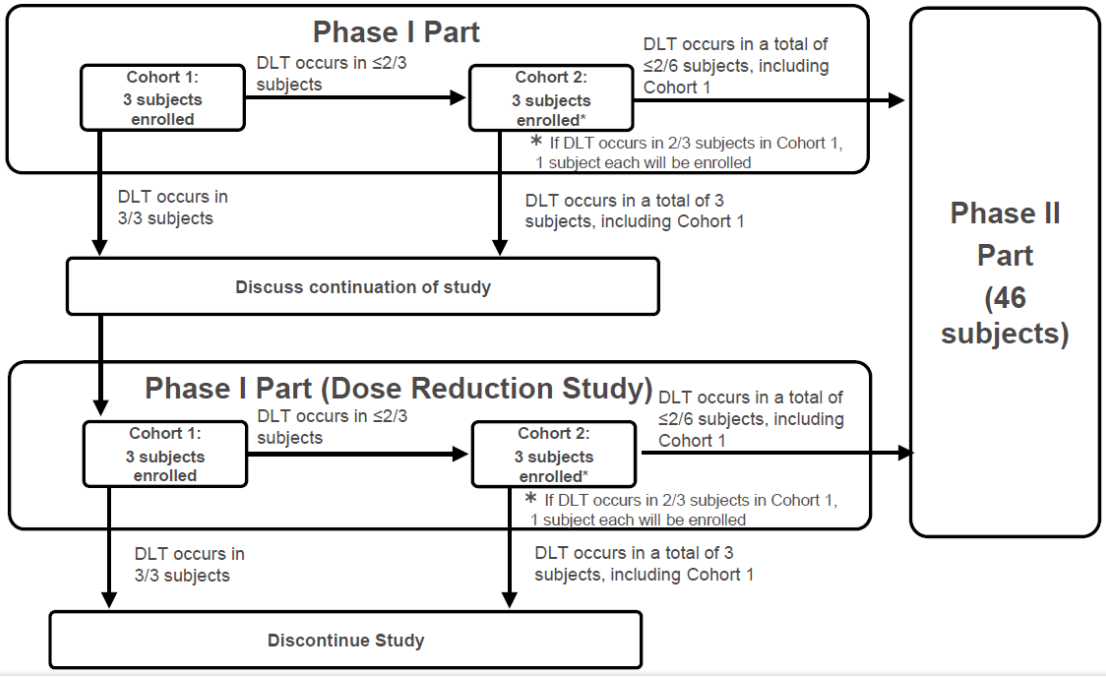
A phase I/II study for the safety and efficacy of Panitumumab in combination with TAS-102 for patients with *RAS* (*KRAS*, *NRAS*) wild-type unresectable, advanced/recurrent colorectal cancer

APOLLON study (**A** phase I/II study for the safety and efficacy of **P**anitumumab in c**o**mbination with TAS-102 for patients with RAS wild-type metastatic co**l**orecta**l** cancer refract**o**ry to sta**n**dard chemotherapy)

Protocol number: Panitumumab-1501

Clinical study design:

This phase I/II study is a multi-center, open-label single-arm study that consists of a phase I part (dose de-escalation) which will assess the tolerability, safety and Recommended Dose (hereinafter referred to as RD) of Panitumumab in combination with TAS-102 as primary objective, and a phase II part which will assess the efficacy and safety of Panitumumab in combination with TAS-102 as primary objective in patients with RAS wild-type unresectable, advanced/recurrent colorectal cancer. In the phase I part, the subjects will be included sequentially into Cohort 1 and 2, 3 subjects each with the same dosage and administration. In the phase II part, 46 subjects will be included additionally for RD confirmed in the phase I part.



In the phase I part, each cohort will be conducted with 3 subjects, the sponsor will assess tolerability of the dosage and administration based on the incidence of Dose Limiting Toxicity (hereinafter referred to as DLT) during the assessment period and determine whether or not to move on to the next cohort (opinion from the Data Monitoring Committee [hereinafter referred to as DMC] will be confirmed appropriately upon determination). Therefore, in Cohort 1, if occurrence of DLT is ≤ 2 subjects out of 3, the dosage and administration will be determined tolerable and will move on to Cohort 2. However, if DLT is observed in 2 subjects during DLT assessment period in Cohort 1, subjects will be included one at a time in Cohort 2 in consideration for safety to assess DLT. Similarly 3 subjects will be included in Cohort 2 and DLT will be assessed in a total of 6 subjects of Cohort 1 and 2 at most. If DLT is observed in 3 subjects included in Cohort 1, or DLT is observed in 3 subjects from a total of 6 subjects of Cohort 1 and 2, the sponsor will promptly request to postpone new enrollment of subjects to each site and after consultation with the Research Steering Committee and DMC on the continuation of the study, will determine whether or not to continue the study. If study is to be continued, taking in account of the adverse event that occurred, either panitumumab or TAS-102 or both drugs will be reduced one step and re-conducting the phase I part similarly will be considered. If DLT is observed in 3 subjects after reducing 1 step of panitumumab or TAS-102 or both drugs, the study will be discontinued. If DLT is observed in ≤ 2 subjects from a total of 6 subjects of Cohort 1 and 2, the sponsor will comprehensively assess with the Research Steering Committee based on the safety data of the phase I part, and after confirming the opinion of DMC, will determine the transit to phase II part. In the phase II part, in addition to the 6 subjects who received RD dose in the phase I part, a target of 46 subjects are to be accumulated (a total of 52 subjects).
Objective: Phase I part Assess RD (Recommended Dose) of panitumumab in combination with TAS-102 in patients with RAS wild-type unresectable, advanced/recurrent colorectal cancer Phase II part Assess efficacy and safety of panitumumab in combination with TAS-102 in patients with RAS wild-type unresectable, advanced/recurrent colorectal cancer
Study population: patients with RAS wild-type unresectable, advanced/recurrent colorectal cancer refractory or intolerant to fluropyrimidines, oxaliplatin, irinotecan and angiogenesis inhibitors (bevacizumab, aflibercept, ramycirumab, etc.)
Planned number of subjects: A maximum of 58 subjects

Number of study sites:

Phase I part: approximately 5

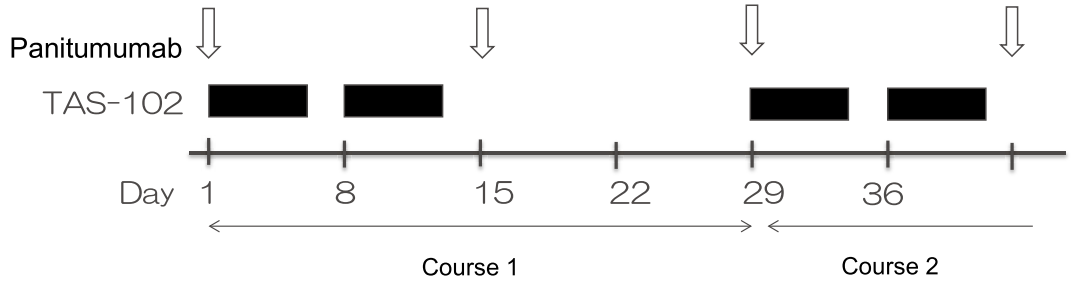
Phase II part: approximately 30

Method of administration:

Treatment for 4 weeks (28 days) as 1 course according to the dosage, schedule and route of administration as follows.

Panitumumab: 6 mg/kg/dose once each on Day 1 and Day 15 by IV administration (IV drip infusion)

TAS-102: 35 mg/m$^{2/}$dose given orally twice daily (after breakfast and after dinner) for 5 consecutive days followed by 2 days of washout and after this is repeated twice, 14 days washout will be implemented.



If either panitumumab or TAS-102 or both drugs are to be reduced for DLT occurrence in phase I part, dosage and administration will be as follows.

If panitumumab is to be reduced: 4.8 mg/kg/dose once each on Day 1 and Day 15 by IV administration (IV drip infusion)

If TAS-102 is to be reduced: 30 mg/m$^{2/}$dose given orally twice daily (after breakfast and after dinner) for 5 consecutive days followed by 2 days of washout and after this is repeated twice, 14 days washout will be implemented.

Dose limiting toxicity (DLT) definition

In this study, DLT will be assessed based on the adverse events observed in 6 subjects at maximum enrolled in phase I part. DLT will be defined as follows [definition and grade will be based on Common Terminology Criteria for Adverse Events (CTCAE) ver4.03]. Further, DLT will be assessed from Day 1 of course 1 of protocol treatment, and if DLT does not occur by Day 1 of course 2, it will be handled as no occurrence of DLT in the subject. Adverse events that can clearly be denied of causal relationship with the protocol treatment will not be assessed as DLT. If serious adverse event or unexpected adverse event occurs which causal relationship with the protocol treatment cannot be denied other than the following, it may be determined as to whether or not to handle it as DLT in consultation with the Investigator, the Research Steering Committee and the sponsor.

1. Persistent Grade 4 neutropenia for more than 7 days under maximum supportive therapy
2. Febrile neutropenia
3. Blood platelete decreased of Grade 3 requiring platelet transfusion or blood platelete decreased of Grade 4
4. If start of second course is delayed for more than 14 days due to adverse event related to protocol treatment
5. Grade 3 or higher non-hematologic toxicity that is clinically problematic however the following will not be applicable as DLT.

   -Grade 3 gastrointestinal symptoms that can be controlled with supportive care (appropriate use of antiemetics, antidiarrheals, etc.)

   -Grade 3 or higher electrolyte abnormalities that are not deemed clinically problematic

Duration of treatment (as a guide):	**Period of evaluation:**
6 months	12 months

Inclusion criteria at enrollment:

1. In the opinion of the investigator* or the subinvestigator, the patient is capable of understanding and complying with protocol requirements.

   *: A personnel taking part in conducting the study and presides over the study related activities within the belonging study site.
2. A patient who can sign and date a written, informed consent form prior to the study enrollment.
3. Patients aged ≥ 20 to < 75 years at the time of informed consent
4. Patients with unresectable adenocarcinoma originating in the large intestine (excluding carcinoma of the appendix and anal canal cancer)
5. Patients who have measurable lesion (refer to Appendix A) according to Response Evaluation

Criteria in Solid Tumors (hereinafter referred to as RECIST) ver 1.1

6. Patients with metastatic colorectal cancer refractory or intolerant* to chemotherapy including fluropyrimidines, oxaliplatin, irinotecan and angiogenesis inhibitors (bevacizumab, aflibercept, ramycirumab, etc.)

   *: Refractory or intolerant if applicable to any of the following

   1) If recurrence is observed during supportive chemotherapy before or after surgery or from imaging diagnosis within 6 months of completion.

   2) If imaging or clinical progression is observed during or within 3 months from the last administration of chemotherapy for advanced cancer

   3) When it is determined that resumption is not possible due to intolerable adverse event (serious allergic reaction, accumulative neuropathy, etc.)

7. Patients classified as *KRAS/NRAS* wild-type** by *KRAS*/*NRAS* testing*.

   *: *KRAS*/*NRAS* test will be performed using the in vitro diagnostic that has been approved for marketing.

   **: All codons listed below are required to be wild-type. If any codon is unmeasured or unmeasurable, it will not be defined as wild-type.

KRAS	EXON	2	3	4
	codon	12, 13	59, 61	117, 146
NRAS	EXON	2	3	4
	codon	12, 13	59, 61	117, 146

8. Patients who may receive oral administration

9. Patients who satisfy the following criteria for the major organ function in tests performed within two weeks (14 days) prior to enrollment.

   (1) Neutrophil count 1.5×10^3/L

   (2) Platelet count 10.0×10^4/L

   (3) Hemoglobin 8.0 g/dL

   (4) Total blood bilirubin 1.5 mg/dL

   (5) AST 100 IU/L (200 IU/L if liver metastases are present)

   (6) ALT 100 IU/L (200 IU/L if liver metastases are present)

   (7) Serum creatinine 1.5 mg/dL

10. Eastern Cooperative Oncology Group (hereinafter referred to as ECOG) performance status (P.S.) has been determined as 0-1.

11. Life expectancy of 3 months (90 days) after enrollment.

Exclusion criteria at enrollment:

1. Patients who have treatment history of anti-EGFR antibody drugs (cetuximab, panitumumab), regorafenib and TAS-102
2. Patients who have received radiotherapy and chemotherapy for primary disease as previous treatment and ≥ 2 weeks (14 days) have not passed since the last treatment at scheduled start day of treatment. However, excluding therapy received for pain relief of bone metastasis site
3. Patients with known brain metastasis or strongly suspected of brain metastasis
4. Patients with synchronous cancers or metachronous cancers with a disease-free period of 5 years (excluding colorectal cancer) However, excluding mucosal cancers cured or be possibly cured by regional resection (esophageal, stomach, and cervical cancer, non-melanoma skin cancer, bladder cancer, etc.)
5. Patients with body cavity fluid that requires treatment (pleural effusion, ascites, pericardial effusion, etc.)
6. Patients who do not want to use contraception to prevent pregnancy, and women who are pregnant or breast-feeding, or test positive for pregnancy
7. Patients who have received other study drugs and ≥ 4 weeks (28 days) have not passed since at scheduled start day of treatment.
8. Patients with disease requiring systemic steroids for treatment (excluding topical steroids)
9. Patients with history or obvious and extensive computerized tomography (CT) findings of interstitial pulmonary disease (interstitial pneumonia, pulmonary fibrosis, etc.)
10. Patients with serious concurrent medical condition (intestinal paralysis, gastrointestinal obstruction, intestinal obstruction, uncontrollable diarrhoea, diabetes mellitus being treated with continuous use of insulin or that is difficult to control, renal failure, hepatic failure, psychiatric disorder, cerebrovascular disorder, gastrointestinal ulceration requiring blood transfusion)
11. Patients with serious drug hypersensitivity (excluding allergic reaction to oxaliplatin)
12. Patients with local or systemic active infection requiring treatment, or fever indicating infection
13. Patients with heart failure or serious heart disease of class II by New York Heart Association (NYHA).
14. Patients with active hepatitis B
15. Patients with known HIV infection
16. Patients who have adverse event from previous treatment that has not recovered to at least Grade 1 (Grade 2 for peripheral sensory neuropathy) by CTCAE, Japanese edition JCOG version v4.03) (excluding hemoglobin content)
17. Patients with known BRAF mutation.
18. Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study (such as patients who may be coerced to give consent)

Primary endpoint for phase I part:

Primary endpoint:

Incidence of DLT in panitumumab treatment in combination with TAS-102

Endpoints for phase II part:

(Regarding efficacy and other endpoints, subjects who have received RD in the phase I part will also be included)

Primary endpoint:

Efficacy

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

Secondary endpoints:

Safety

Percentage of subjects with adverse events

Efficacy

Overall survival (OS)

Progression-free survival (PFS)

Response rate (RR)

Duration of response (DOR)

Disease control rate (DCR)

Time to treatment failure (TTF)

Additional endpoints:

Follow-up therapy and its rate

Statistical method:

In the phase I part, incidence of DLT will be assessed in DLT assessment study population.

The primary objective for phase II part is to explore the additional effect on PFS rate in panitumumab monotherapy when TAS-102 is used in combination with PFS rate at 6 months as primary endpoint.

PFS rate at 6 months is the crude rate of subjects who survived or were not determined as progressive at 6 months from the day of enrollment. Based on the observed PSF rate at 6 months from the day of enrollment, binomial test will be conducted on the null hypothesis "value will be determined invalid at PSF rate $\leq$ 29%". Significant level will be 2.5% (one-sided) in main analysis. For interval estimation, accurate 90% confidence interval (two-sided) based on binomial distribution will be used.

PFS is the period from the day of enrollment until the day of documented progression or the day of death due to all causes whichever comes earlier. Kaplan-Meier method will be used to illustrate progression free curve and quantile point and its 95% confidence interval (two-sided) of PFS will be calculated.

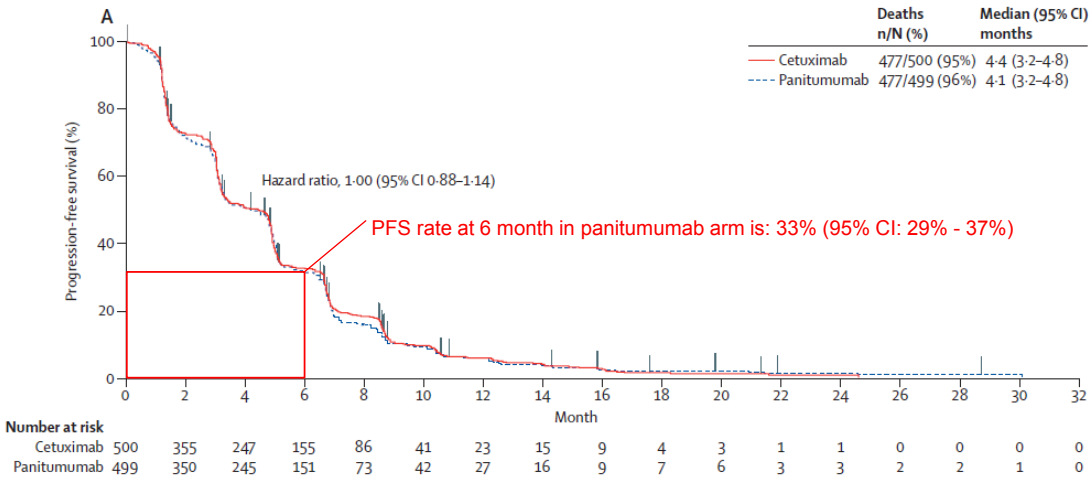
Rationale for planned number of subjects:

In the phase I part for the assessment of tolerability, 6 to 12 subjects were included according to the

"Guidelines for clinical evaluation methods of anti-cancer drugs" (PFSB/ELD notification No. 1101001, 01/Nov/2005).

Also, in the phase II part as efficacy will be assessed on PSF rate at 6 months as primary endpoint, according to the above guideline and precedent overseas clinical trial results, number of subjects were set as to confirm the expected PFS rate to overwhelm the PFS rate threshold.

In the panitumumab monotherapy vs. best supportive care (BSC) as third-line treatment control trial in patients with unresectable, advanced/recurrent colorectal cancer (trial 20020408), the PFS median, the primary endpoint, were 8.0 weeks for the panitumumab group and 7.3 weeks for the BSC group. In retrospectively conducted *KRAS* wild-type population and *KRAS*/*NRAS* wild-type population, PFS median were 12.3 weeks and 14.1 weeks respectively in the panitumumab group. On the other hand, in the panitumumab monotherapy vs. cetuximab monotherapy control study (ASPECCT study) in patients with *KRAS* wild-type unresectable, advanced/recurrent colorectal cancer that became resistant to fluoropyrimidine agents, OXA, and IRI, the secondary endpoint PFS were 4.1 months for panitumumab and 4.4 months for cetuximab and showed no difference (hazard ratio [HR], 1.00; two-sided 95% confidence interval [CI], 0.88–1.14). Further, PFS rate at 6 months was 33% (two-sided 95% CI, 29% to 37%) for the panitumumab group.



On the other hand, for TAS-102, in the domestic phase II study in previously treated subjects with unresectable, advanced/recurrent colorectal cancer refractory or intolerant to fluoropyrimidine agents, OXA, and IRI and has treatment history of 2 regimens of standard chemotherapy, the secondary endpoint PFS median assessed by the Investigator were 1.0 months in the placebo group but significantly prolonged to 2.7 months in the TAS-102 group (HR = 0.35, two-sided 95% CI 0.25 to 0.50, p<0.0001).

As increased anti-tumor effect can be expected by using TAS-102 in combination with panitumumab treatment which is the standard treatment for patients with unresectable, advanced/recurrent colorectal cancer, the PFS rate at 6 months in this study was assumed to be 48% and this was set as the expected

value for the panitumumab treatment in combination with TAS-102 therapy in patients with RAS wild-type unresectable, advanced/recurrent colorectal cancer. *Also, for the threshold where* further testing for panitumumab treatment in combination with TAS-102 may be considered not necessary, it was assumed to be 29% from the CI lower limit of the PFS rate at 6 months in the ASPECCT study.

For the main analysis, based on the observed PSF rate at 6 months from start of treatment, binomial test will be conducted on the null hypothesis "the true PSF rate at 6 months from start of treatment will be not more than the PFS threshold rate where value is determined invalid". With the PFS threshold rate at 29%, PFS expected rate at 48% at 6 months from start of treatment, and one-sided significant level at 5.0%, power at 80%, the necessary number of subjects will be 47. Taking into consideration of ineligible or discontinued subjects at approximately 10%, the target number of subjects was set to 52 (including subjects that received RD in the phase I part).

Study period:

Total study period: November 2015 to December 2017 (26 months)

Enrollment period: November 2015 to December 2016 (14 months)

Follow-up period: 12 months after completion of enrollment

3.0 LIST OF ABBREVIATIONS

List of Abbreviations	Unabbreviated expression
5-FU	fluorouracil
ALT	ALanine aminoTransferase
AST	ASpartate aminoTransferase
BSC	Best Supportive Care
COI	Conflict of Interest
CR	Complete Response
CRO	Contract Research Organization
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DMC	Data Monitoring Committee
DOR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
FTD	Trifluridine
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
HBs	Hepatitis B surface
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IRI	IRInotecan
JCOG	Japan Clinical Oncology Group
KRAS	Kirsten rat Sarcoma-2 virus
l-LV	Levofolinate calcium
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NRAS	Neuroblastoma Rat Sarcoma
NYHA	New York Heart Association
OS	Overall Survival
OXA	OXAliplatin

List of Abbreviations	Unabbreviated expression
Unequivocal PD	Progressive Disease
PFS	Progression-Free Survival
PR	Partial Response
P.S.	Serformance Status
RAS	RAt Sarcoma
RD	Recommended Dose
RECIST	Response Evaluation Criteria In Solid Tumors
RR	Response Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOP	Standard Operating Procedures
TPI	Tipiracil hydrochloride
TEAE	Treatment-Emergent Adverse Event
TTF	Time to Treatment Failure
VEGF	Vascular Endothelial Growth Factor

4.0 INTRODUCTION

4.1 Background

4.1.1 Etiology of colon cancer

According to "Cancer Statistics 2014," [1)] and "Site-specific Cancer Prevalence" in 2010 in Japan, colon cancer was the third most prevalent cancer in men (14.5%) and the second in women (15.1%). According to "Site-specific Cancer Deaths (2013)," in men, lung cancer was the leading cause of cancer death (accounting for 24.0% of cancer deaths), followed by gastric cancer (14.7%) and hepatic cancer (9.1%); colorectal cancer (colon cancer and rectal cancer combined) accounted for 11.9% of cancer deaths which exceeded the death rate of hepatic cancer, representing that colorectal cancer is the third leading cause of cancer death. In women, lung cancer (14.0%) was also the leading cause of cancer death, followed by gastric cancer (11.3%) and colon cancer (10.0%); deaths from colorectal cancer (colon cancer and rectal cancer combined) accounted for 14.9% of cancer deaths, representing that colorectal cancer is the first leading cause of cancer death.

4.1.2 Standard treatment for colon cancer

The "Guidelines for Treatment of Colorectal Cancer (2014)"[2)] classify the standard treatment of colorectal cancer according to staging as follows: endoscopic resection for Stage 0, in which the lesion is limited in the mucosa; Surgical resection for Stage I to III with postoperative adjuvant chemotherapy for Stage II which is at high risk or Stage III involving lymph nodes; and surgical resection for Stage IV and recurrent disease if liver or lung metastasis is resectable, and systemic chemotherapy if not.

The first-line treatment for unresectable, advanced/recurrent colorectal cancer that have been demonstrated to be useful in clinical studies and are currently covered by national health insurance in Japan are presented below. Also, cetuximab and panitumumab should be used for indications limited to Kirsten rat Sarcoma-2 virus wild-type (hereinafter referred to as *KRAS*).

1. FOLFOX therapy or bevacizumab or CapeOX (XELOX) therapy + bevacizumab[*1]
   FOLFOX therapy: combination chemotherapy with fluorouracil (hereinafter referred to as 5-FU), levofolinate calcium (hereinafter referred to as *l*-LV), and oxaliplatin (hereinafter referred to as OXA)
   CapeOX (XELOX) therapy: combination chemotherapy with capecitabine and OXA
2. FOLFIRI therapy + bevacizumab*[1]
   FOLFIRI therapy: combination chemotherapy with 5-FU, *l*-LV and irinotecan (hereinafter referred to as IRI)
3. FOLFOX therapy + cetuximab*[1, 2] or panitumumab*[1, 2]
4. FOLFIRI therapy + cetuximab*[1, 2] or panitumumab*[1, 2]

5. FOLFOXIRI therapy FOLFOXIRI therapy: combination chemotherapy with OXA, IRI, 5-FU and *l*-LV
6. FL*[3] or Capecitabine+ bevacizumab*[1] or UFT + *l*-LV
   UFT: combination preparation of tegafur and uracil

   *1: Combination with molecular-targeted drugs such as bevacizumab or anti-epidermal growth factor receptor (hereinafter referred to as EGFR) antibody is recommended, but if it is not an indication mono-chemotherapy will be conducted.

   *2: Indication only for *KRAS* wild-type

   *3: Infusional 5-FU + *l*-LV

FOLFOX-based therapy is more frequently selected as first-line treatment than FOLFIRI-based therapy, and bevacizumab is widely used for *KRAS* wild-type colorectal cancer as well. As a result, FOLFOX + bevacizumab combination therapy is the most common first-line treatment in Japan (in-house document).

It is recommended that in principle, a regimen not used in first-line treatment should be used for second-line treatment. More specifically, IRI-based regimens are recommended as a second-line treatment of patients who have received an OXA-based regimen as a first-line treatment, while OXA-based regimens are recommended for patients who have received an IRI-based regimen. This principle also applies to molecular-targeted drugs concomitantly used for second-line treatment. For *KRAS* wild-type colorectal cancer, bevacizumab is recommended as a second-line treatment of patients who have received an anti-EGFR antibody as a first-line treatment, while switching to an anti-EGFR antibody or continued use of bevacizumab is an option as a second-line treatment of patients who have received bevacizumab as a first-line treatment. Regimens that can be used for second-line treatment are as follows.

1. If subject becomes resistant to regimen including OXA
   1) FOLFIRI ± bevacizumab or IRI alone or IRI + S-1 (IRIS)
   2) FOLFIRI (or IRI alone) + cetuximab or panitumumab (*KRAS* wild-type)
2. If subject becomes resistant to regimen including IRI
   1) FOLFOX or CapeOX (XELOX) ± bevacizumab
3. If patient becomes resistant to regimen including fluropyrimidines, OXA, IRI
   1) IRI + cetuximab or panitumumab (*KRAS* wild-type)
   2) Cetuximab or panitumumab monotherapy (*KRAS* wild-type)

For third-line treatment and onwards, IRI + cetuximab or panitumumab combination therapy (*KRAS* wild-type) and cetuximab or panitumumab monotherapy (*KRAS* wild-type), and regorafenib monotherapy, TAS-102 monotherapy or symptomatic therapies are currently recommended.

4.1.3 Efficacy and safety of panitumumab in patients with unresectable, advanced/recurrent colorectal cancer

4.1.3.1 Panitumumab

EGFR is a member of the ErbB family of transmembrane receptor tyrosine kinases constantly expressed in epithelial-derived tissues, has been shown to be overexpressed in various types of solid tumors. Colorectal cancer is characterized by high EGFR expression, and the EGFR signaling pathway has been shown to play in the pathogenesis and progression of tumors. Binding of epidermal growth factor (hereinafter referred to as EGF), the major ligand of EGFR, to EGFR is considered to induce auto-phosphorylation of EGFR and activation of various signaling pathways, resulting in induction of cellular proliferation, inhibition of apoptosis, and increased production of inflammatory cytokines and angiogenesis factors. Panitumumab is a human IgG2 monoclonal antibody that binds to EGFR with specificity and high affinity, and inhibits the proliferation of tumor cells by competitively inhibiting the binding of the ligand to EGFR[3)].

4.1.3.2 Clinical study results for panitumumab in the U.S. and Europe

As a clinical trial of panitumumab monotherapy for colorectal cancer, a phase III study was conducted to compare best supportive care (hereinafter referred to as BSC) vs. BSC + panitumumab therapy in patients with unresectable, recurrent/advanced, EGFR-positive colorectal cancer that became resistant to fluoropyrimidine agents, OXA, and IRI (BSC group, 232 patients; BSC + panitumumab group, 231 patients)[4)]. The median of the primary endpoint of progression free survival (hereinafter referred to as PFS) with BSC alone at 7.3 weeks, whereas with BSC + panitumumab therapy at 8weeks, significantly longer than that of BSC, showed the efficacy of panitumumab therapy (hazard ratio [HR], 0.54; two-sided 95% confidence interval [CI], 0.44 to 0.66, $p< 0.0001$). The secondary endpoint of OS was not significantly different between the two groups (HR, 1.00, two-sided 95% CI 0.82 to 1.22, $p = 0.81$), however, this may be primarily due to the fact that 173 subjects (75%) in the BSC group received follow-up therapy with panitumumab. Also, a phase III randomized control study comparing cetuximab monotherapy and panitumumab monotherapy in patients with *KRAS* wild-type unresectable, recurrent/advanced colorectal cancer (anti-EGFR antibody untreated) after they became resistant to fluoropyrimidine agents, OXA, and IRI has been reported (ASPECCT study).[17)] In this study, the median of OS which is the primary endpoint was 10.4 months for the panitumumab group (499 subjects) compared to 10.0 months for cetuximab group (500 subjects) and this indicated that panitumumab is non-inferior to cetuximab (HR = 0.97, two-sided 95% CI 0.84 to 1.11) PFS which is the secondary endpoint were 4.1 months for panitumumab group and 4.4 months for cetuximab group and showed no difference (HR = 1.00, two-sided 95% CI 0.88 to 1.14).

With regard to clinical study of combination of chemotherapy and panitumumab, a phase III clinical study (PRIME Study) has been reported, in which FOLFOX4 monotherapy vs. FOLFOX4 therapy + panitumumab (given at a dose of 6 mg/kg every 2 weeks) as a first-line treatment was compared in a total of 1,183 patients (593 in monotherapy group, 590 in panitumumab group)[5]. The primary endpoint of median PFS in *KRAS* wild-type patients was 9.6 months and significantly longer in the FOLFOX4 + panitumumab group as compared with 8.0 months in the FOLFOX4 alone group (HR, 0.80; two-sided 95% CI, 0.66 to 0.97; p = 0.02). Of Grade 3/4 adverse events, panitumumab-related adverse events such as dermatologic toxicities, diarrhoea, and hypomagnesaemia occurred more frequently in the FOLFOX4 + panitumumab group, but there were no major differences in the incidence of other adverse events between the two groups. Grade 3 infusion reaction occurred in 2 patients (Table 4.a).

Table 4.a Grade 3/4 adverse events reported in *KRAS* wild-type patients in the PRIME study

Adverse event	FOLFOX4 + panitumumab (n = 322)		FOLFOX4 alone (n = 327)	
	n	%	n	%
Any adverse drug reaction	270	84	227	69
Leukopenia	136	42	134	41
Skin disorder	116	36	7	2
Diarrhoea	59	18	29	9
Nerve disorder	52	16	51	16
Hypokalaemia	32	10	15	5
Malaise	30	9	10	3
Stomatitis	28	9	2	< 1
Hypomagnesaemia	20	8	1	< 1
Paronychia	11	3	0	0
Pulmonary embolism	9	3	5	2
Febrile neutropenia	8	2	7	2
infusion reaction	2	< 1	-	-

With regard to second-line treatment, a phase III clinical study (Study 20050181) has been conducted, in which FOLFIRI monotherapy vs. FOLFIRI therapy + panitumumab (given at a dose of 6 mg/kg every 2 weeks) was compared[6]. The primary endpoints were PFS and OS in *KRAS* wild-type patients. In *KRAS* wild-type patients, PFS was 5.9 months and significantly longer in the FOLFIRI + panitumumab group than 3.9 months in the FOLFIRI alone group (HR = 0.73, two-sided 95% CI 0.59 to 0.90, p = 0.004). On the other hand, the OS median were 12.5 months in the FOLFIRI alone group and 14.5 months in the FOLFIRI + panitumumab group (HR = 0.85, two-sided 95% CI 0.70 to 1.04, p=0.12) and showed no significant difference. The response rate

(hereinafter referred to as RR) was 35% and higher in the FOLFIRI + panitumumab group as compared with 10% in the FOLFIRI alone group. Of Grade 3/4 adverse events, the incidence of dermatologic toxicities was higher and the incidences of diarrhoea and hypomagnesaemia tended to be higher in the FOLFIRI + panitumumab group; however, there were no major differences in the incidence of toxicities including hematologic toxicities between the two groups, and the incidence of infusion reaction was not more than 1%.

Both the PRIME Study[5)] and Study 20050181[6)] described above, in which the presence/absence of *KRAS* was prospectively studied, showed that combination therapy containing panitumumab was not effective in *KRAS*-mutant patients, suggesting that *KRAS* mutation is predictive of poor response to anti-EGFR antibody therapy.

4.1.3.3 Clinical study results for panitumumab in Japan

In a Japanese phase I clinical study of panitumumab, panitumumab was administered at the same dosing regimens with which the drug was confirmed to be safe and effective in overseas studies; i.e., a dose of 2.5 mg/kg once weekly, 6 mg/kg once every 2 weeks, and 9 mg/kg once every 3 weeks. Each of these dosing regimens was evaluated in 6 patients, and tolerance was ratified in overseas clinical trial.

In a Japanese phase II clinical study of panitumumab monotherapy, [7)] 52 patients with previously treated, unresectable colorectal cancer were enrolled. In this study, the 6 mg/kg biweekly regimen of panitumumab, which was the recommended dosing regimen in the overseas phase III clinical study, was well tolerated, and the incidence of adverse events was similar to that observed in the U.S. and Europe (Table 4.b). In addition, 7 patients (13.5%) had partial response (hereinafter referred to as PR), and this Japanese study yielded an RR of 13.5% (two-sided 95% CI: 5.6 to 25.8),a time to treatment failure of 11.4 weeks (two-sided 95% CI: 8.4 to 15.0), a PFS of 8.0 weeks (two-sided 95% CI: 7.4 to 11.4), and an OS of 9.3 months (two-sided 95% CI: 7.1 to 12.8), similar to those observed in clinical studies in the U.S and Europe.

On the basis of the above results, panitumumab was approved in April 2010 for the treatment of unresectable, advanced/recurrent colorectal cancer in Japan as well.

Table 4.b Common adverse events (≥ 20%) noted in a Japanese phase II clinical study of Panitumumab monotherapy

Adverse event	Panitumumab Monotherapy (n = 52)			
	Any Grade		Grade 3 or higher	
	n	%	n	%
Any adverse drug reaction	51	98	6	12
Skin disorder	51	98	3	6

Adverse event	Panitumumab Monotherapy (n = 52)			
	Any Grade		Grade 3 or higher	
	n	%	n	%
Acne	42	81	1	2
Dry skin	32	62	0	
Skin rash	24	46	1	2
Pruritus	17	33	0	
Paronychia	17	33	1	2
Hypomagnesaemia	17	33	0	0
Malaise	13	25	0	0
Stomatitis	12	23	0	0
Anorexia	11	21	1	2

4.1.3.4 Specified drug use surveillance results (all patients surveillance) in Japan

In the post- marketing surveillance conducted for a fixed period where all the patients treated were registered, [8)] the median of treatment period (first day of treatment to the final day of treatment) for the 3,085 patients who were subject to safety evaluation was 113 days (range: 1 to 559 days), incidence of adverse reaction was 84.1% (25.8% ≥ Grade 3), of which the panitumumab monotherapy group with 1,254 patients was 80.1% (19.7% ≥ Grade 3), panitumumab + chemotherapy combination group with 1,831 patients was 86.9% (30.0% ≥ Grade 3). The occurrence status of intensively investigated adverse reaction items are listed in Table 4.c.

Table 4.c Common adverse events in specified drug use surveillance in Japan

All patient surveillance	Panitumumab monotherapy group (n=1,254)				Panitumumab + chemotherapy combination group (n=1,831)			
	Any Grade		Grade 3 or higher		Any Grade		Grade 3 or higher	
Intensively investigated item	n	%	n	%	n	%	n	%
Skin & subcutaneous tissue disorders (SOC)	918	73.2	118	9.4	1446	79.0	274	15.0
Paronychia	272	21.7	33	2.6	459	25.1	99	5.4
Interstitial lung disease*	16	1.3	-	-	23	1.3	-	-
Infusion reaction	17	1.4	1	0.1	30	1.6	5	0.3
Hypomagnesaemia	257	20.5	61	4.9	263	14.4	62	3.4
Hypocalcaemia	59	4.7	16	1.3	77	4.2	26	1.4
Cardiac disorders (SOC)	2	0.2	0	0.0	5	0.3	1	0.1

SOC: System Organ Class

*: Interstitial pneumonia subcommittee criteria

4.1.4 Efficacy and safety of TAS-102 for unresectable, advanced/recurrent colorectal cancer

4.1.4.1 TAS-102

TAS-102 is a new nucleoside anticancer agent formulated with trifluridine (FTD) and tipiracil (TPI) prepared at a molar ratio of 1 : 0.5. FTD is an anticancer active ingredient of TAS-102 and TPI is an inhibitor specific to thymidine phosphorylase (TPase) which is a FTD decomposing enzyme.[9)] FTD will show anti-tumor effect when administered orally and taken in by DNA, while on the other hand, FTD will be metabolized promptly through first-pass effect of oral administration. Therefore, in order to have FTD taken in by DNA efficiently, it is necessary to inhibit TPase that engages in metabolizing FTD and it is necessary to administer FTD in combination with TPI. In the non-clinical study, in a nude mouse subcutaneously implanted with human tumor-derived cell line, as the FTD amount taken in DNA and tumor proliferation inhibitory effect had correlated it was presumed that tumor proliferation inhibitory effect of TAS-102 is based on FTD and tumor proliferation inhibitory effect shows effectiveness when FTD is taken in by DNA. Also, when FTD alone is orally given to monkies, FTD could hardly be observed in blood, whereas in combination with TPI that inhibits TPase which is a FTD decomposing enzyme, FTD blood concentration was maintained.

4.1.4.2 Clinical study results for TAS-102

In Japan, after the phase I study in patients with solid tumors (J001 study) had been conducted, a phase II control study (J003 study) with OS as primary endpoint and PFS, DCR, etc. as secondary endpoints and the objective of assessing the superiority of TAS-102 group over placebo group in patients (number of safety assessed subjects: TAS-102 group 113, placebo group 57, efficacy assessed: TAS-102 group 112, placebo group 57) that have received previous treatment of 2 regimens including fluoropyrimidine agents, OXA, and IRI and with refractory or intolerant, unresectable, advanced/recurrent colorectal cancer was conducted. [10)] TAS-102 was given 35 mg/m^2/dose orally twice daily for 5 consecutive days, followed by 2 days of washout and after this was repeated twice, 14 days washout was implemented. As a result, OS prolongation was observed in the TAS-102 group compared to the placebo group. In the TAS-102 group, the OS median was 9.0 months, and by independent diagnostic imaging organization PFS median was 2.0 months, DCR was 43.8% (49/112 subjects).Common adverse events (occurrence 10%) noted in Japanese clinical study in 119* subjects are shown in Table 4.d.

*: 6 subjects who were given the same dosage and regimen as the J003 study in the Japanese phase I study (J001 study) were added to the 113 subjects of the Japanese phase II study (J003 study)

Table 4.d Common adverse events (occurrence 10%) noted in Japanese clinical study

Adverse event	Any Grades (n = 119)		Grade 3 or higher (n = 119)	
	n	%	n	%
Hematocrit decreased	34	28.6	1	0.8
Haemoglobin decreased	76	63.9	22	18.5
Lymphocyte count decreased	40	33.6	13	10.9
Neutrophil count decreased	87	73.1	61	51.3
Platelet count decreased	49	41.2	5	4.2
Red blood cell count decreased	38	31.9	1	0.8
White blood cell count decreased	91	76.5	36	30.3
Diarrhoea	40	33.6	6	5.0
Nausea	75	63.0	3	2.5
Stomatitis	18	15.1	-	-
Vomiting	34	28.6	3	2.5
Fatigue	63	52.9	7	5.9
Blood albumin decreased	13	10.9	-	-
Blood bilirubin increased	23	19.3	1	0.8
Weight decreased	14	11.8	-	-
Protein urine present	14	11.8	-	-
Decreased appetite	66	55.5	3	2.5

On the other hand, a phase III global study (RECOURSE study) with OS as primary endpoint and PFS, DCR, etc. as secondary endpoints and the objective of assessing the superiority of TAS-102 over placebo in patients (number of safety assessed subjects: TAS-102 group 533, placebo group 265, efficacy assessed: TAS-102 group 534, placebo group 266) that have received previous chemotherapy of 2 regimens and with refractory or intolerant to fluoropyrimidine agents, IRI,OXA, bevacizumab and anti-EGF-R antibody agents (*KRAS* wild-type), unresectable, advanced/recurrent colorectal cancer, was conducted.[11)] As a result, OS significantly prolonged in the TAS-102 group compared to placebo group. In the TAS-102 group, the OS median was 7.1 months, and by independent diagnostic imaging organization PFS median was 2.0 months, DCR was 44% (221/502 subjects).

Common adverse events (occurrence 10%) noted in the phase III global clinical study in 533 subjects are shown in Table 4.e.

Table 4.e Common adverse events (occurrence 10%) noted in the phase III global clinical study

Adverse event	Any Grades (n = 533)		Grade 3 or higher (n = 533)	
	n	%	n	%
Aneamia	168	31.5	65	12.2
Neutropenias	153	28.7	107	20.1
Neutrophil count decreased	145	27.2	83	15.6
White blood cell count decreased	140	26.3	52	9.8
Platelet count decreased	77	14.4	13	2.4
Diarrhoea	126	23.6	12	2.3
Nausea	210	394	5	0.9
Asthenia	58	10.9	9	1.7
Fatigue	132	24.8	11	2.1
Decreased appetite	141	26.5	9	1.7

Regarding combination of TAS-102 and antibody drugs, a phase I/II study in combination with bevacizumab was conducted in Japan. [12)] Patients with colorectal cancer refractory/intolerant to anticancer agent therapies including 5-FU, OXA, IRI, and anti VEGF inhibitors (bevacizumab, etc.), anti EGFR antibody agents (in cases of RAS wild-type) and has no treatment history of regorafenib and TAS-102, and DLT was not observed in the phase I part (6 subjects), RD was determined at 35 mg/m^2 of TAS-102 given twice daily and 5 mg/day of bevacizumab. For efficacy, 21 subjects (total from phase I part and phase II part) were analyzed and PFS at week 16 was 42.9%. Also, from the assessment by the attending physician PFS median was 24.1 weeks, DCR was 72%. Neutropenia as drug related adverse event (Grade 3: 56%, Grade 4: 12%), leukopenia (Grade 3: 40%), febrile neutropenia (Grade 3: 16%) were many but no study related deaths. In 17 subjects (68%) start of treatment was delayed, in 6 subjects (24%) dose reduction of TAS-102 was necessary, many of the causes were neutrophenia. Therefore, tolerance and efficacy has been observed in combination therapy with TAS-102 and bevacizumab for unresectable, advanced/recurrent colorectal cancer after becoming refractory to standard treatment.

4.1.5 *RAS* (*KRAS*/*NRAS*) mutation and panitumumab in unresectable, advanced/recurrent colorectal cancer

In a phase III randomized control study (Study 20040408[4)]) of panitumumab monotherapy that investigated its efficacy as a third-line treatment in patients with unresectable, advanced/recurrent colorectal cancer after receiving standard treatment, the enrolled subjects were analyzed for the relationship of the presence or absence of mutations in the genes of *KRAS* exons 3 (codon 61) and 4 (codons 117, 146), *NRAS* exons 2 (codons 12, 13), 3 (codon 61) and 4 (codons 117, 146) in the

tumor using DNA sequencing by the Sanger method and WAVE-based SURVEYOR® Scan Kit. In patients with *KRAS* wild-type and *NRAS* wild-type colorectal cancer (hereinafter referred to as RAS wild-type), the PFS median was 14.1 weeks and significantly prolonged by 7.1 weeks in the panitumumab combination group as compared with 7.0 weeks in the BSC group (HR = 0.36, two sided 95% CI 0.25 to 0.52, p<0.001). On the other hand, in patients with RAS mutation (*KRAS* or *NRAS* mutation), the median PFS was 7.3 weeks in the BSC group as compared with 7.4 weeks in the panitumumab combination group and did not show significant difference. (HR = 0.97, two sided 95% CI 0.73 to 1.29). [13)]

Among the patients enrolled in the PRIME study, were analyzed for the relationship of the presence or absence of mutations in the genes of *KRAS* exons 2, 3, 4, *NRAS* exons 2, 3, 4, and BRAF exon 15 (codon 600) with PFS and OS. [5)] In patients with RAS wild-type, the OS median was 25.8 months and significantly prolonged by 5.6 month in the FOLFOX4 + panitumumab group as compared with 20.2 months in the FOLFOX4 alone group (HR = 0.77, two sided 95% CI 0.64 to 0.94, p = 0.009). On the other hand, in patients with RAS mutation, the OS median was 15.5 months and significantly shorter in the FOLFOX4 + panitumumab group as compared with 18.7 months in the FOLFOX4 alone group (HR = 1.21, two sided 95% CI 1.01 to 1.45, p = 0.04). [14)]

Also, in addition to the above studies, patients with *KRAS* (exons 3 and 4) and *NRAS* (exons 2, 3 and 4) mutations other than *KRAS* exon 2 showing ineffectiveness to anti-EGFR antibody drugs in several post hoc analysis has been reported, [15)]and for patients determined as having wild-types and currently measuring *KRAS* exon 2 only, it has been recognized that presence/absence of other RAS (*KRAS*/*NRAS*, hereinafter referred to as RAS) mutations should be added, and "Guidance for measuring RAS (*KRAS*/*NRAS*) mutations in colorectal cancer patients" [16)] has been published from Japanese Society of Medical Oncology.

4.2 Rationale for the proposed study

For the treatment of *KRAS* wild-type, unresectable, advanced/recurrent colorectal cancer it is recommended to use molecular target drugs of either anti-VEGF antibody agents or anti-EGFR antibody agents in combination with FOLFOX or FOLFIRI treatment. OXA combination treatment + anti-VEGF antibody agent for first-line treatment, and if IRI + anti-VEGF antibody agent is used in second-line treatment, anti-EGFR antibody agents alone based on the results from 20020408 study[4)] or ASPECCT study[17)], or IRI + anti-EGFR antibody agents based on results from BOND study[18)] or GERCOR study[19)], etc. for third-line treatment is used often.

Combination therapy with anti-EGFR antibody agents and chemotherapy has shown that it also has antitumor effect in patients that have become resistant to chemotherapy. In the BOND study in

which cetuximab alone group and cetuximab + IRI combination group were compared in patients with colorectal cancer that have become resistant to IRI, in spite of the fact that the patient group had already been IRI resistant, it has been reported that cetuximab + IRI combination group had superior antitumor effect and PFS (for RR, cetuximab + IRI combination group was 22.9% [two-sided 95% CI 17.5 to 29.1%], IRI group was 10.8% [two-sided 95% CI 5.7 to 18.1%], P=0.007; for PFS, cetuximab + IRI combination group was 4.1 months, IRI group was 1.5 months, P<0.001 by the log-rank test). [18] Also in the phase II GERCOR study[19] where panitumumab and IRI combination therapy was used in patients with colorectal cancer refractory to standard treatment, in spite of the fact that it included patients that had already become IRI resistant, anti-tumor effect was observed with combination use of panitumumab and IRI, and indicated that panitumumab and IRI combination therapy was a superior treatment than that of panitumumab monotherapy (PFS median in *KRAS* wild-type was 6.3 months, 95% CI 3.7 to 8.7).

As indicated in Section 4.1.4.2, regarding combination use of TAS-102 and antibody agents, tolerance and efficacy has been observed with TAS-102 and bevacizumab combination therapy in patients with unresectable, advanced/recurrent colorectal cancer after being refractory to standard treatment. For combination use of panitumumab and TAS-102, currently there is no clinical data that would confirm its efficacy, while in non-clinical studies in vitro tests show anti-tumor effect increases by combination use of FTD which is the active component of TAS-102 and panitumumab compared to using them alone in *KRAS* wild-type colorectal cancer cell strain (Figure 4.a, in-house data).

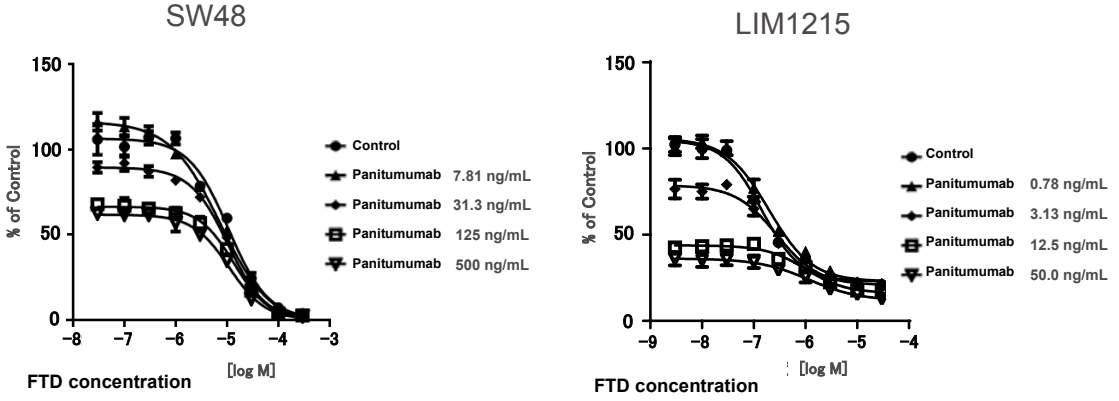


Figure 4.a Anti-tumor effect from combination use of FTD and panitumumab in *KRAS* wild-type colorectal cancer cell strain (SW48 and LIM1215, both are *KRAS*/BRAF wild type)

In a colorectal cancer cell strain trans planted mouse model, it was indicated that a higher anti-tumor effect may be obtained with combination use of panitumumab and TAS-102 compared to preparing them alone, and also weight decrease, etc. or increase of other toxicities have not been observed. [20] Although the mechanism of action is not known for this combination use effect, from the in vitro test

using colorectal cancer cell strain, FTD which is an active component of TAS-102 activates the phosphorylation of EGFR and AKT or MAPK protein that is located downstream from EGFR, and also erlotinib which is a tyrosine kinases inhibitor showed synergy effect of inhabitation of cell proliferation by simultaneous action with FTD and also indicated that erlotinib down regulates phosphorylation of AKT or MAPK protein by FTD.[21)] From these reasons, it was considered that a higher effect may be expected from combination use of TAS-102 and panitumumab compared to using them alone.

As mentioned earlier, for third-line treatment for colorectal cancer with treatment history of FOLFOX therapy or FOLFIRI therapy, taking in account of the results, etc. of the 20020408 study[4)] in which treatment with panitumumab alone and BSC were compared, the ASPECCT study[17)] in which panitumumab monotherapy and cetuximab monotherapy were compared, the NCIC CTG CO.17 study[22)] in which treatment with cetuximab alone and BSC were compared, the BOND study[18)] in which treatment groups of cetuximab alone and cetuximab and IRI combination use were compared and the GERCOR study[19)] in which effect of combination use of IRI + panitumumab was assessed, treatment with either cetuximab or panitumumab alone or combination use of IRI + cetuximab or IRI + panitumumab are recommended by the "Guidelines for Treatment of Colorectal Cancer (2014)".[2)] Actually, for subjects who did not show serious adverse event in IRI among patients with treatment history with fluropyrimidines, IRI, OXA, it is expected that IRI + anti-EGFR antibody combination therapy will be a treatment option, although it has not been proven that IRI + anti-EGFR antibody combination therapy has longer survival period compared to cetuximab or panitumumab monotherapy. If panitumumab + TAS-102 combination therapy has higher effectiveness than anti-EGFR antibody monotherapy and similar effect as IRI + anti-EGFR antibody in the same patient group, there will be major benefits for the patient such as avoidance of adverse event in IRI.

Comparison of adverse events in treatments with TAS-102 alone and panitumumab alone is shown in the table below. Adverse events for TAS-102 are from Japanese phase II study and for panitumumab are from Specified drug use surveillance results (all patients surveillance) in Japan, incidence of ≥ 10% has been extracted and presented Table 4.f and Table 4.g. As adverse events in both drugs do not hardly overlap besides stomatitis, and adverse events besides stomatitis from TAS-102 were all ≤ Grade 2, both drugs are considered usable in combination fairly safely.

Table 4.f Comparison of rate of adverse events

in panitumumab alone among common adverse events (incident ≥ 10%) in treatments with TAS-102

Common adverse events in TAS-102 (incident ≥ 10%)	TAS-102 (n = 119)		Panitumumab alone (n = 1254)	
	n	%	n	%
Hematocrit decreased	34	28.6	-	-
Haemoglobin decreased	76	63.9	1	0.1
Lymphocyte count decreased	40	33.6	0	0
Neutrophil count decreased	87	73.1	0	0
Platelet count decreased	49	41.2	4	0.3
Red blood cell count decreased	38	31.9	-	-
White blood cell count decreased	91	76.5	5	0.4
Diarrhoea	40	33.6	24	1.9
Nausea	75	63.0	9	0.7
Stomatitis	18	15.1	123	9.8
Vomiting	34	28.6	4	0.3
Fatigue	63	52.9	9	0.7
Blood albumin decreased	13	10.9	0	0
Blood bilirubin increased	23	19.3	1	0.1
Weight decreased	14	11.8	1	0.1
Protein urine present	14	11.8	2	0.2
Decreased appetite	66	55.5	25	2.0

Table 4.g Comparison of rate of adverse events

in TAS-102 among common adverse events (incident ≥ 10%) in treatment with panitumumab alone

Common adverse events in panitumumab alone (incident ≥ 10%)	Panitumumab alone (n = 1254)		TAS-102 (n = 119)	
	n	%	n	%
Paronychia	272	21.7	1	0.8
Hypomagnesaemia	223	17.8	-	-
Dermatitis acneiform	619	49.4	-	-
Dry skin	265	21.1	1	0.8

From the above, this study was planned as it was determined that assessment of recommended dose, efficacy and safety of panitumumab in combination with TAS-102 was necessary in RAS wild-type, unresectable, advanced/recurrent colorectal cancer. For combination therapy, panitumumab and TAS-102 were used as alone treatment and combined. Therefore, panitumumab will be given at a dose of 6 mg/kg every 2 weeks, TAS-102 will be given 35 mg/m^2/dose for 5 consecutive days orally followed by 2 days of washout and after repeating this twice, 14 days of washout will be implemented and if safety is confirmed in the phase I part, the dosage and administration will be the

recommended dose for the combination therapy and the same dosage and administration will be adopted in the phase II part. If it is determined intolerable in the phase I part, continuation of study will be considered and dose reduction will be assessed when necessary.

5.0 OBJECTIVE AND ENDPOINTS OF THE STUDY

5.1 Objective

Phase I part

To assess the recommended dose (RD) of panitumumab in combination with TAS-102 in patients with RAS wild-type, unresectable, advanced/recurrent colorectal cancer.

Phase II part

To assess the efficacy and safety of panitumumab in combination with TAS-102 in RAS wild-type, unresectable, advanced/recurrent colorectal cancer.

5.2 Definition of endpoints

5.2.1 Definition of endpoints for phase I part

Primary endpoint:

Incidence of DLT in panitumumab treatment in combination with TAS-102

5.2.2 Definition of endpoints for phase II part

(Including subjects who received RD in phase I part)

Primary endpoint:

Efficacy

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

Secondary endpoints:

Safety

Percentage of subjects with adverse events

Efficacy

Overall survival (OS)

Progression-free survival (PFS)

Response rate (RR)

Duration of response (DOR)

Disease control rate (DCR)

Time to treatment failure (TTF)

Additional endpoints:

Follow-up therapy and its rate

5.3 Rationale for the endpoints

5.3.1 Primary endpoint

In the phase I part, incidence of DLT was set as primary endpoint to assess the tolerability and safety of panitumumab in combination with TAS-102 in patients with unresectable, advanced/recurrent colorectal cancer and determine RD.

In the phase II part, PFS rate at 6 months was set as primary endpoint as an important criteria in assessing the efficacy of combination use of TAS-102 with panitumumab monotherapy in patients with unresectable, advanced/recurrent colorectal cancer.

5.3.2 Secondary endpoints

The OS, PFS, RR, DOR, DCR, and TTF were selected as the secondary endpoint, because they reflect the anti-tumor efficacy. In addition, adverse events were selected as the secondary endpoint, because safety is also an important factor in treatment selection in phase II part.

6.0 CLINICAL STUDY DESIGN

6.1 Clinical study design

This phase I/II study is a multi-center, open-label single-arm study that consists of a phase I part (dose de-escalation) which will assess the tolerability and RD of Panitumumab in combination with TAS-102 as primary objective, and a phase II part which will assess the efficacy and safety of Panitumumab in combination with TAS-102 as primary objective in patients with RAS wild-type unresectable, advanced/recurrent colorectal cancer. In the phase I part, the subjects will be included sequentially into Cohort 1 and 2, 3 subjects each with the same dosage and administration. In the phase II part, 46 subjects will be included additionally for RD confirmed in the phase I part.

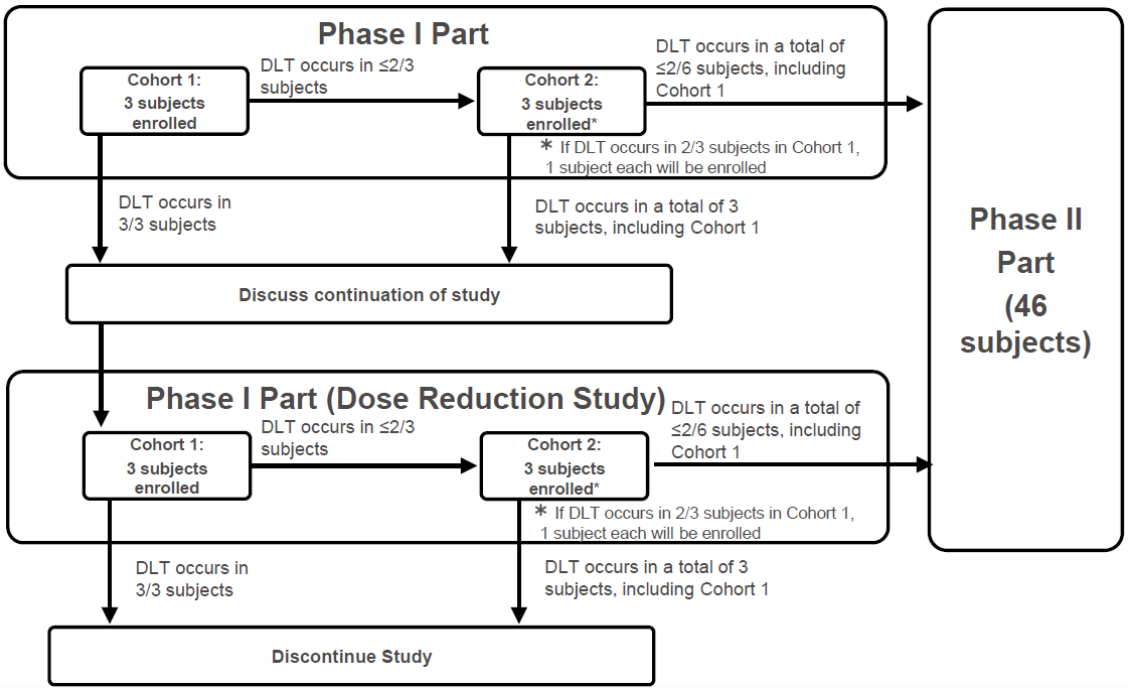


Figure 6.a Outline of study design

In the phase I part, each cohort will be conducted with 3 subjects, the sponsor will assess tolerability of the dosage and administration based on the incidence of Dose Limiting Toxicity (hereinafter referred to as DLT) during the assessment period and determine whether or not to move on to the next cohort (opinion from the Data Monitoring Committee [hereinafter referred to as DMC] will be confirmed appropriately upon determination). Therefore, in Cohort 1, if occurrence of DLT is ≤ 2 subjects out of 3, the dosage and administration will be determined tolerable and will move on to Cohort 2. However, if DLT is observed in 2 subjects during DLT assessment period in Cohort 1, subjects will be included one at a time in Cohort 2 in consideration for safety to assess DLT.

Similarly 3 subjects will be included in Cohort 2 and DLT will be assessed in a total of 6 subjects of Cohort 1 and 2 at most. If DLT is observed in 3 subjects included in Cohort 1, or DLT is observed in 3 subjects from a total of 6 subjects of Cohort 1 and 2, the sponsor will promptly request to postpone new enrollment of subjects to each site and after consultation with the Research Steering Committee and DMC on the continuation of the study, will determine whether or not to continue the study.

If study is to be continued, taking in account of the adverse event that occurred, either panitumumab or TAS-102 or both drugs will be reduced one step and re-conducting the phase I part similarly will be considered. If DLT is observed in 3 subjects after reducing 1 step of panitumumab or TAS-102 or both drugs, the study will be discontinued.

If DLT is observed in ≤ 2 subjects from a total of 6 subjects of Cohort 1 and 2, the sponsor will comprehensively assess with the Research Steering Committee based on the safety data of the phase I part, and after confirming the opinion of DMC, will determine the transit to phase II part.

In the phase II part, in addition to the 6 subjects who received RD dose in the phase I part, a target of 46 subjects are to be accumulated (a total of 52 subjects).

6.2 Rationale for study design

6.2.1 Study population

Survival period for unresectable, advanced/recurrent colorectal cancer patients is approximately two and a half years and still prognostic is poor. Although systemic chemotherapy is used for unresectable cases as first-line treatment, recovery is difficult and PFS after initial chemotherapy is about one year, second-line chemotherapy PFS is about half a year, and in most cases third-line, fourth-line treatment is necessary. Therefore, this became the object of this clinical research as development of appropriate treatment for unresectable cases that have become refractory/intolerant to existing chemotherapy is an important issue. The patients should also be RAS wild-type, because the above mentioned analysis results in the PRIME study[5)] suggest that panitumumab may be the most effective in these patients.

KRAS/*NRAS* test will be performed using the in vitro diagnostic that has been approved for marketing.

6.2.2 Treatment regimens and planned number of subjects

6.2.2.1 Reasons for selecting panitumumab + TAS-102 combination therapy as the treatment regimen

As described in Section 4.1.2, the following regimens using FOLFOX and FOLFIRI treatment and methods to use bevacizumab, panitumumab and cetuximab in combination, are shown in the Guidelines for Treatment of Colorectal Cancer (2014)[2)] as the first-line treatment and second-line treatment for patients with unresectable, advanced/recurrent colorectal cancer. In Japan, FOLFOX-based therapy is more frequently selected as first-line treatment for unresectable, advanced/recurrent colorectal cancer than FOLFIRI-based therapy, and bevacizumab is widely used for *KRAS* wild-type colorectal cancer as well. As a result, FOLFOX + bevacizumab combination therapy is the most common first-line treatment in Japan. Further, if it becomes refractory or intolerant to these first-line treatment, FOLFIRI+ bevacizumab is used widely as second-line treatment (in-house document). Furthermore, if it becomes refractory or intolerant to these second-line treatments, the following regimens are for third-line treatment and onwards.

1. Panitumumab monotherapy or cetuximab monotherapy
2. IRI + panitumumab combination therapy or IRI + cetuximab combination therapy
3. Regorafenib monotherapy
4. TAS-102 monotherapy
5. Symptomatic therapies

On the other hand, from the results of the randomized, double blinded, placebo controlled comparative study (Japanese phase II control study) in which unresectable, advanced/recurrent colorectal cancer that have received previous treatment of 2 regimens including fluoropyrimidine agents, OXA, and IRI and became refractory or intolerant was assessed, and it was reported that overall survival prolonged significantly compared to placebo administration and TAS-102 obtained approval in March 2014 for "unresectable, advanced/recurrent colorectal cancer (restricted to where standard treatment is difficult)" as indication. Also, from the results of the phase III global study (RECOURSE study[11)]) in which colorectal cancer patients had no change to standard therapy, it was reported that overall survival prolonged significantly compared to placebo and TAS-102 has become one of the options for third-line treatment as indication was changed and approved to "unresectable, advanced/recurrent colorectal cancer" in March 2015.

As mentioned in Section 4.2, anti-EGFR antibody agents and chemotherapy has shown that it also has anti-tumor effect in patients that have become resistant to chemotherapy. As for panitumumab and TAS-102 also, further anti-tumor effect can be expected from combination use. For combination

therapy to be assessed in this clinical research, panitumumab and TAS-102 were used as alone treatment and combined. Therefore, panitumumab will be given at a dose of 6 mg/kg every 2 weeks, TAS-102 will be given 35 mg/m^2/dose for 5 consecutive days orally followed by 2 days of washout and after repeating this twice, 14 days of washout will be implemented and if safety and tolerability is confirmed, the dosage and administration will be the RD for the combination therapy.

6.2.2.2 Rationale for planned number of subjects

In the phase I part for the assessment of tolerability and RD of panitumumab and TAS-102 combination therapy, 6 to 12 subjects were included according to the "Guidelines for clinical evaluation methods of anti-cancer drugs" (PFSB/ELD notification No. 1101001, 01/Nov/2005).

Also, in this study as efficacy will be assessed on PFS rate as primary endpoint, according to the above guideline and precedent overseas clinical trial results, number of subjects were set as to confirm the expected PFS rate to overwhelm the PFS rate threshold.

In the panitumumab monotherapy vs. BSC as third-line treatment control trial in patients with unresectable, advanced/recurrent colorectal cancer (20020408 study[4)]), the PFS median were 8.0 weeks for the panitumumab group and 7.3 weeks for the BSC group. In retrospectively conducted *KRAS* wild-type population and *KRAS*/*NRAS* wild-type population, PFS median were 12.3 weeks and 14.1 weeks respectively in the panitumumab group. On the other hand, in the panitumumab monotherapy vs. cetuximab monotherapy control study (ASPECCT study) in patients with *KRAS* wild-type unresectable, advanced/recurrent colorectal cancer that became resistant to fluoropyrimidine agents, OXA, and IRI[17)], the secondary endpoint PFS were 4.1 months for panitumumab and 4.4 months for cetuximab and showed no difference (hazard ratio [HR], 1.00; two-sided 95% confidence interval [CI], 0.88–1.14). Further, PFS rate at 6 months was 33% (two-sided 95% CI, 29% to 37%) for the panitumumab group.

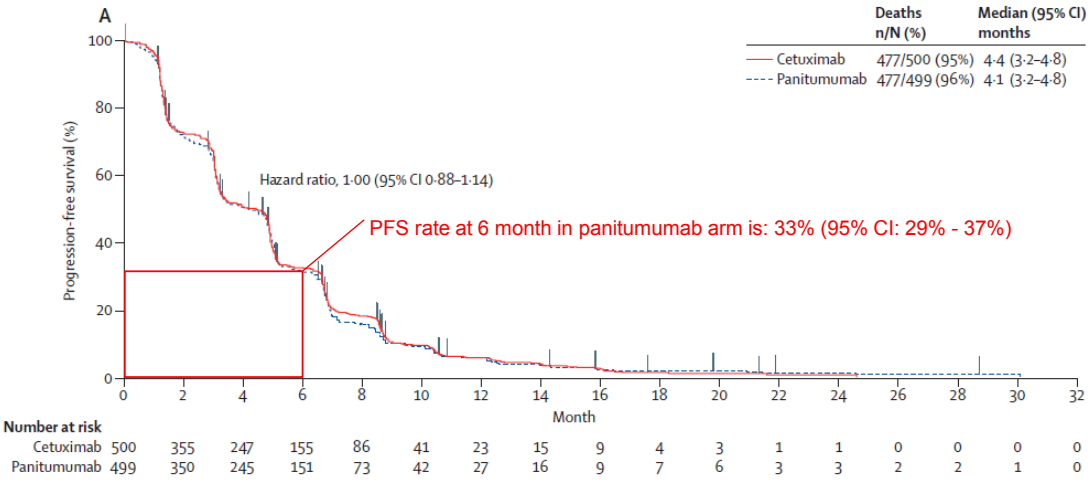


Figure 6.b ASPECCT study Progression-free survival

On the other hand, for TAS-102, in the domestic phase II study in previously treated subjects with metastatic, unresectable, colorectal cancer refractory or intolerant to fluoropyrimidine agents, OXA, and IRI, and has treatment history of 2 regimens of standard chemotherapy, the secondary endpoint PFS median assessed by the Investigator were 1.0 months in the placebo group but significantly prolonged to 2.7 months in the TAS-102 group (HR = 0.35, two-sided 95% CI 0.25–0.50, p<0.0001)

As increased anti-tumor effect can be expected by using TAS-102 in combination with panitumumab treatment which is the standard treatment for patients with unresectable, advanced/recurrent colorectal cancer, the PFS rate at 6 months in this study was assumed to be 48% and this was set as the expected value for the panitumumab treatment in combination with TAS-102 therapy in patients with RAS wild-type unresectable, advanced/recurrent colorectal cancer. *Also, for the threshold where* further development for panitumumab treatment in combination with TAS-102 may be considered not necessary, it was assumed to be 29% from the CI lower limit of the PFS rate at 6 months in the ASPECCT study. [17)]

For the main analysis, based on the observed PFS rate at 6 months from start of treatment, binomial test will be conducted on the null hypothesis “the true PFS rate at 6 months from start of treatment will be not more than the PFS threshold rate where value is determined invalid”. With the PFS threshold rate at 29%, PFS expected rate at 48% at 6 months from start of treatment, and one-sided significant level at 5%, power at 80%, the necessary number of subjects will be 47. Taking into consideration of ineligible or discontinued subjects at approximately 10%, the target number of subjects was set to 52 (including subjects that received RD in the phase I part).

6.3 Discontinuation of entire clinical study or discontinuation of clinical study at a study site

6.3.1 Criteria for discontinuation of entire clinical study

The sponsor should immediately discontinue the study when at least one of the following criteria is applicable.

- When new information or other evaluation on the safety or efficacy of protocol treatment becomes available which shows a change in the known risk/benefit profile of the concerned compound, and risks/benefits are no longer tolerable for subject participation in the study.
- When suspension or discontinuation of the clinical study is notified by the DMC.
- Occurrence of serious violation of Ethical Guideline for Clinical Research or ICH-GCP which may endangers safety of subjects.

6.3.2 Criteria for discontinuation of clinical study at a study site

A study site may be notified to discontinue clinical study if the site (including the investigator) is found in significant violation of Ethical Guideline for Clinical Research, ICH-GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures of clinical study suspension and discontinuation of entire clinical study or study at a study site

In the event that the sponsor, the study site director or the investigator decides to suspend or discontinue the entire clinical study or clinical study at a study site, a study-specific procedure will be provided by the sponsor. The procedure will be followed by applicable study sites during the course of clinical study suspension or discontinuation.

6.4 Procedures for protocol amendment

When protocol amendment is required, the sponsor and the research steering committee chairman will assess and determine the propriety of the amendment.

The protocol will be amended when the following purposes are applicable, and when an amendment is made, the content will be notified to all study site investigators. Then, investigators should confirm the content of the amendment of the protocol and submit a letter of agreement to the sponsor to prove agreement for protocol amendment.

[When amendment of protocol is required]

1. Change or addition of objective
2. Change or addition of efficacy, safety evaluation method
3. Addition of test (frequency, items) or change in test method that may increase the burden of the subject
4. Dose alteration (including addition of treatment group)
5. Critical change or addition to inclusion/exclusion criteria
6. Change in planned number of subjects
7. Change of plan or description of content due to occurrence of serious adverse event, etc.
8. Following discussion between the sponsor and the research steering committee chairman, that it is determined to be applicable to critical change

Upon receiving the above notification, investigators of the study sites will be reviewed by the ethics review board again and must obtain approval from the study site director according to the regulations at each site when necessary.

7.0 SELECTION OF STUDY SUBJECTS AND ENROLLMENT

Prior to enrollment, it is necessary to confirm all inclusion/exclusion criteria including test results.

7.1 Inclusion criteria at enrollment

Patient's eligibility will be determined based on the following criteria.

1. In the opinion of the investigator* or the subinvestigator, the patient is capable of understanding and complying with protocol requirements.

   *: A personnel taking part in conducting the study and presides over the study related activities within the belonging study site.

2. Patients who signs and dates a written ICF prior to the initiation of any study procedures
3. Patients aged ≥ 20 to < 75 years at the time of informed consent
4. Patients with unresectable adenocarcinoma originating in the large intestine (excluding carcinoma of the appendix and anal canal cancer)
5. Patients who have measurable lesion (refer to Appendix A) according to Response Evaluation Criteria in Solid Tumors (hereinafter referred to as RECIST) ver 1.1
6. Patients with colorectal cancer refractory or intolerant* to chemotherapy including fluropyrimidines, oxaliplatin (OXA), irinotecan (IRI) and angiogenesis inhibitors (bevacizumab, aflibercept, ramycirumab, etc.)

   *: Refractory or intolerant if applicable to any of the following

   1) If recurrence is observed during supportive chemotherapy before or after surgery or from imaging diagnosis within 6 months of completion.

   2) If imaging or clinical progression is observed during or within 3 months from the last administration of chemotherapy for advanced cancer

   3) When it is determined that resumption is not possible due to intolerable adverse event toxicities (serious allergic reaction, accumulative neuropathy, etc.)

7. Patients classified as *KRAS/NRAS* wild-type** by *KRAS*/*NRAS* testing*.

   *: *KRAS*/*NRAS* test will be performed using the in vitro diagnostic that has been approved for marketing.

   **: All codons listed below are required to be wild-type. If any codon is unmeasured or unmeasurable, it will not be defined as wild-type.

KRAS	EXON	2	3	4
	codon	12, 13	59, 61	117, 146
NRAS	EXON	2	3	4
	codon	12, 13	59, 61	117, 146

8. Patients who may receive oral administration
9. Patients who satisfy the following criteria for the major organ function in tests performed within two weeks (14 days) prior to enrollment.
   (1) Neutrophil count 1.5×10^3/L
   (2) Platelet count 10.0×10^4/L
   (3) Hemoglobin 8.0 g/dL
   (4) Total blood bilirubin 1.5 mg/dL
   (5) AST 100 IU/L (200 IU/L if liver metastases are present)
   (6) ALT 100 IU/L (200 IU/L if liver metastases are present)
   (7) Serum creatinine 1.5 mg/dL
10. Eastern Cooperative Oncology Group (hereinafter referred to as ECOG) performance status (P.S.) has been determined as 0-1.
11. Life expectancy of 3 months (90 days) after enrollment.

7.2 Exclusion criteria at enrollment

A patient who meets any of the criteria below will not be included in this study.

1. Patients who have treatment history of anti-EGFR antibody drugs (cetuximab, panitumumab), regorafenib and TAS-102
2. Patients who have received radiotherapy and chemotherapy for primary disease as previous treatment and ≥ 2 weeks (14 days) have not passed since the last treatment at scheduled start day of treatment. However, excluding therapy received for pain relief of bone metastasis site
3. Patients with known brain metastasis or strongly suspected of brain metastasis
4. Patients with synchronous cancers or metachronous cancers with a disease-free period of 5 years (excluding colorectal cancer) excluding mucosal cancers cured or be possibly cured by regional resection (esophageal, stomach, and cervical cancer, non-melanoma skin cancer, bladder cancer, etc.)
5. Patients with body cavity fluid that requires treatment (pleural effusion, ascites, pericardial effusion, etc.)
6. Patients who do not want to use contraception to prevent pregnancy, and women who are pregnant or breast-feeding, or test positive for pregnancy
7. Patients who have received other study drugs and ≥ 4 weeks (28 days) have not passed since at scheduled start day of treatment.
8. Patients with disease requiring systemic steroids for treatment (excluding topical steroids)
9. Patients with history or obvious and extensive computerized tomography (hereinafter referred to as CT) findings of interstitial pulmonary disease (interstitial pneumonia, pulmonary fibrosis,

etc.)

10. Patients with serious concurrent medical condition (intestinal paralysis, gastrointestinal obstruction, intestinal obstruction, uncontrollable diarrhoea, diabetes mellitus being treated with continuous use of insulin or that is difficult to control, renal failure, hepatic failure, psychiatric disorder, cerebrovascular disorder, gastrointestinal ulceration requiring blood transfusion)
11. Patients with serious drug hypersensitivity (excluding allergic reaction to OXA)
12. Patients with local or systemic active infection requiring treatment, or fever indicating infection
13. Patients with heart failure or serious heart disease of class II by New York Heart Association (NYHA).
14. Patients with active hepatitis B
15. Patients with known HIV infection
16. Patients who have adverse event from previous treatment that has not recovered to at least Grade 1 (Grade 2 for peripheral sensory neuropathy) by Common Terminology Criteria for Adverse Events (hereinafter referred to as CTCAE, Japanese edition JCOG version v4.03) (excluding hemoglobin content)
17. Patients with known BRAF mutation.
18. Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study (such as patients who may be coerced to give consent)

7.3 Procedures for registration and protocol treatment

7.3.1 Procedures for registration and initiation of protocol treatment

The investigator or subinvestigator will register subjects according to the following procedure.

1. The investigator, subinvestigator or study collaborator should pre-register the subject who has been given written information on informed consent by entering the identification code and date of informed consent discussion into the Web case registration system. *

PPD

*: The study collaborator may enter data into the Web case registration system by instruction of the investigator or the subinvestigator.

2. After pre-registration, the investigator, subinvestigator or study collaborator should enter the necessary items into the Web case registration system (formal registration) for a subject who has given consent. After formal registration, eligibility of a prospective subject is judged by the Web case registration system and the registration will be completed.

3. The investigator, subinvestigator and study collaborator will check the registration result on the Web case registration system. The registration result will be sent via e-mail from the Web case registration system to the investigator, subinvestigator and study collaborator.

4. The investigator or the subinvestigator should start the protocol treatment within 2 weeks (14 days) of registration (including the same day of week as the day of enrollment). However, if protocol treatment cannot be initiated within 4 weeks of registration or predicted that the initiation of protocol will be after 4 weeks from registration, this must be reported to the study office before protocol treatment initiation. See Section 1.3 for study office contacts.

7.3.2 Contacts for enrollment procedure

Case enrollment center: PPD

- E-mail: PPD

[E-mail receipt confirmation]

PPD

- Tel: PPD

[Reception hours]

PPD

8.0 PROTOCOL TREATMENT

The protocol treatment, contraindicated drugs/therapies, and recommended supportive care/combination therapies in this study are explained in this section. The drugs used for this study should be ethical drugs used by the study site. See the latest package insert for details and handling of each drug.

8.1 Definition of protocol treatment

With protocol treatment in principle, combination therapy with panitumumab and TAS-102 stipulated in the "8.2 treatment regimen" will be conducted, and even if any of the criteria for suspension or discontinuation of each drug is met, treatment with other drugs will be continued unless any of the criteria for discontinuation of protocol treatment is met (such as in case of PD).

Protocol treatment in principle will be initiated within 14 days of entry.

8.2 Treatment regimen

The treatment regimen shown below should be administered (28 days [Day1-28] as one course) until any of the criteria specified in "8.7 Criteria for discontinuation of protocol treatment for each subject" is met. For administration of each drug, see "8.3 Recommended dose of protocol treatment", "8.4 Criteria for administration" and "8.5 Criteria for protocol treatment change".

Table 8a Treatment regimen of combination therapy with panitumumab + TAS-102

Drug	Dose	Method of administration	Date of administration
Panitumumab	6 mg/kg	IV drip infusion 60 min*	Day 1, 15
TAS-102	35 mg/m^2	Oral administration (twice daily**)	Day 1-5 Day 8-12

*: When the dose at one time exceeds 1,000 mg, intravenously administer it over 90 min or longer after dilution with JP physiological saline to make approximately 150 mL.

**: Within 1 hour of breakfast and dinner as reference. When TAS-102 is given at fasting state, elevation of Cmax of trifluridine (FTD) is observed, therefore fasting should be avoided.

***: Oral drug intake will start from Day 1 after dinner or the next morning and to oral drug intake on Day 6 after breakfast or after dinner will be the 5 day intake (however, in the phase I part, after dinner on Day 1 will be the start).

****: Oral drug intake will start from Day 8 after dinner or the next morning and to oral drug intake on Day 13 after breakfast or after dinner will be the 5 day intake (however, in the phase I part, after dinner in Day 8 will be the start).

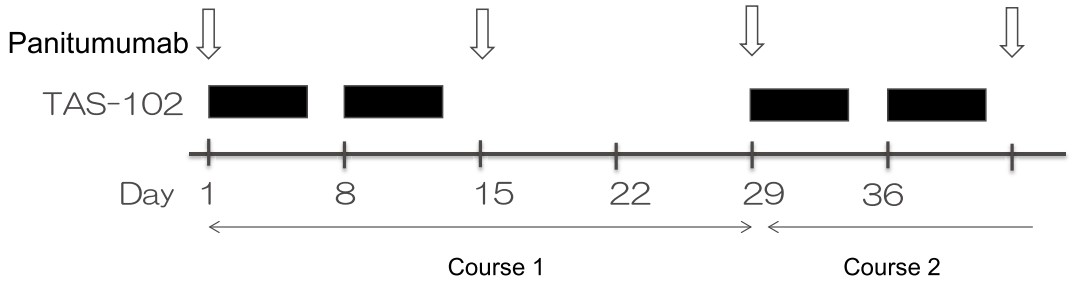


Figure 8.a Combination therapy with panitumumab and TAS-102

8.3 Recommended dose of protocol treatment

The dose will be calculated based on the body surface area (calculated using the DuBois & DuBois formula) and body weight at the time of study entry. Dose for panitumumab is round down in unit of 10 mg for reference, TAS-102 will be as Table 8.b and 8.c. At the time of entry, the data center will announce the reference dose and this should be recalculated and confirmed at the study site. The dose should be recalculated for 10% change in body weight, in principle, but at the discretion of the investigator or the subinvestigator. If more than 10% change in body weight is observed further after the recalculation the same method should be taken. However, TAS-102 dosage will be adjusted by course and adjustment from the middle of the course will not be conducted. Even if suspended during treatment period, drug will not be re-taken and drug will be taken according to stipulated treatment schedule (after 1 to 5 days, 8 to 12 days from initial administration of each course). Also, if subject missed any dose, remaining drug should not be taken.

Table 8.b TAS-102 dosage

TAS-102 dosage (twice daily)	**Body surface area (m^2)**	**One dose (mg)**	**Dose per day (mg)**	**One dosage**	
				15 mg tablet	20 mg tablet
35 mg/m^2 (70 mg/m^2/day)	< 1.07	35	70	1	1
	1.07 – 1.22	40	80	0	2
	1.23 – 1.37	45	90	3	0
	1.38 – 1.52	50	100	2	1
	1.53 – 1.68	55	110	1	2
	1.69 – 1.83	60	120	0	3
	1.84 – 1.98	65	130	3	1
	1.99 – 2.14	70	140	2	2
	2.15	75	150	1	3

Table 8.c TAS-102 dosage when dose is adjusted

TAS-102 dosage (twice daily)	Body surface area (m^2)	One dose (mg)	Dose per day (mg)	One dosage	
				15 mg tablet	20 mg tablet
Drug reduction (35 mg/m^2 to 30 mg/m^2)					
30 mg/m^2 (60 mg/m^2/day)	< 1.09	30	60	2	0
	1.09 – 1.24	35	70	1	1
	1.25 – 1.39	40	80	0	2
	1.40 – 1.54	45	90	3	0
	1.55 – 1.69	50	100	2	1
	1.70 – 1.94	55	110	1	2
	1.95 – 2.09	60	120	0	3
	2.10 – 2.28	65	130	3	1
	2.29	70	140	2	2
Drug reduction (30 mg/m^2 to 25 mg/m^2)					
25 mg/m^2 (50 mg/m^2/day)	< 1.10	25	50	2 (after dinner)	1 (after breakfast)
	1.10 – 1.29	30	60	2	0
	1.30 – 1.49	35	70	1	1
	1.50 – 1.69	40	80	0	2
	1.70 – 1.89	45	90	3	0
	1.90 – 2.09	50	100	2	1
	2.10 – 2.29	55	110	1	2
	2.30	60	120	0	3
Drug reduction (25 mg/m^2 to 20 mg/m^2)					
20 mg/m^2 (40 mg/m^2/day)	< 1.14	20	40	0	1
	1.14 – 1.34	25	50	2 (after dinner)	1 (after breakfast)
	1.35 – 1.59	30	60	2	0
	1.60 – 1.94	35	70	1	1
	1.95 – 2.09	40	80	0	2
	2.10 – 2.34	45	90	3	0
	2.35	50	100	2	1

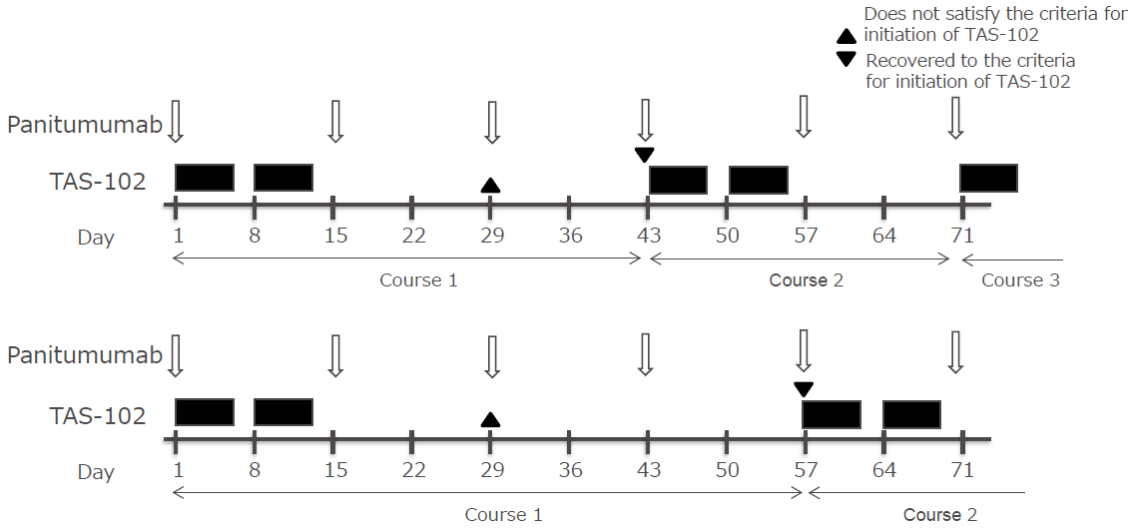
*: If TAS-102 is to be given 50 mg/day, 20 mg will be given after breakfast, 30 mg after dinner.

8.4 Criteria for administration

In principle, the day (Day 29) that is 4 weeks after the starting day of treatment (Day 1) in the previous course will be Day 1 of the subsequent course (however, if the actual starting day is the next morning, the day before the starting day will be Day 1). Postponement or acceleration due to holidays is allowed. See ”Table 9c. Allowance range for protocol treatment and laboratory tests”.

It should be confirmed that all of the criteria for initiation of protocol treatment (Table 8.d, Table 8.e) are satisfied on the starting day of treatment of each course. However, the latest data obtained from 2 days before treatment to the starting day of treatment may be used as test value.

Treatment will be postponed when any of the criteria for each drug is not met, and will be started after confirming that the symptom and laboratory data satisfy all of the criteria, and if only one drug satisfies the criteria for start of treatment then monotherapy with that drug may be allowed. However, at the starting point of the second course of the phase I part, both drugs are required to meet the treatment initiation criteria. If start of treatment with TAS-102 is postponed, the starting day thereafter (if the actual staring day is next morning, the day before) will be Day 1 of the course and that will be the schedule starting point, and if treatment with TAS-102 is determined to be discontinued and monotherapy with panitumumab is to be continued, the starting day of monotherapy with panitumumab will be defined as the start of course (Day 1), and the course will be defined as to give panitumumab on Day 1 and Day 15 between Day 1 and Day 28. However, while monotherapy with panitumumab is ongoing and treatment does not start beyond 42 days from scheduled start of treatment (starting day of treatment of previous course as Day 1, if treatment does not start by Day 57), protocol treatment will be discontinued. Postponement of start of treatment due to holidays is allowed.



Also, if start of treatment with panitumumab is postponed or discontinued, the starting day of treatment with TAS-102 (if the actual staring day is next morning, the day before) will be Day 1 of the course and that will be starting point for the schedule thereafter. However, while monotherapy with TAS-102 is ongoing and treatment does not start beyond 28 days from scheduled start of treatment (starting day of treatment of previous course as Day 1, if treatment does not start by Day

57), protocol treatment will be discontinued. Postponement of start of treatment due to holidays is allowed.

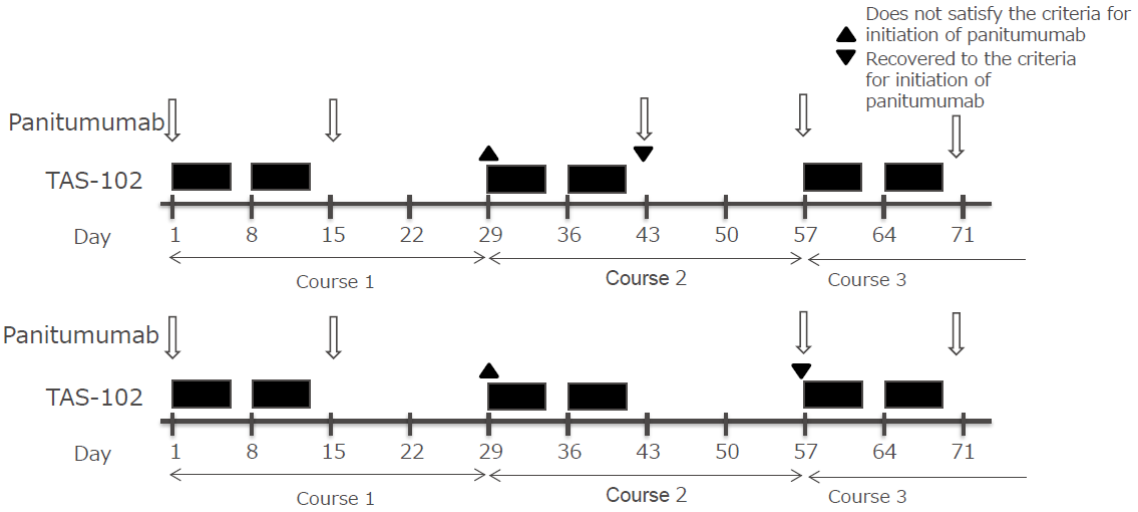


Table 8.d. Criteria for initiation of treatment with panitumumab

Item	Criteria for initiation
Skin symptom (e.g., rash acneiform, dry skin, paronychia)	≤ Grade 2
Hypomagnesaemia *	≤ Grade 2
Treatment may be postponed when suspension is needed at the discretion of the investigator or the subinvestigator due to adverse events not listed above.	

*: When accompanied by abnormal ECG findings requiring treatment such as significant QTc prolongation, discontinuation or suspension of panitumumab should be considered irrespective of the severity of hypomagnesaemia.

Table 8.e Criteria for initiation of treatment with TAS-102

Item	Criteria for initiation
Hemoglobin concentration	≥8.0 g/dL
Neutrophil count	≥ 1.5×10^3 μL
Platelet count	≥ 7.5×10^4/μL
Total bilirubin	≤ 1.5 mg/dL
AST	≤ 100 IU/L (≤ 200 IU/L with liver metastasis)
ALT	
Serum creatinine	≤ 1.5 mg/dL
Periphial sensory neuropathy	≤ Grade 2
Other non-hematological toxicity	(excluding alopecia, dygeusia, pigmentation, underlying disease related symptoms) ≤ Grade 1
Treatment may be postponed when suspension is needed at the discretion of the investigator or the subinvestigator due to adverse events not listed above.	

8.5 Criteria for protocol treatment change

8.5.1 Criteria for suspension/dose reduction of panitumumab

The criteria for suspension/dose reduction and doses of panitumumab are shown in Table 8.f and Table 8.g, respectively.

Table 8.f Criteria for suspension/dose reduction of panitumumab

Item	Grade	Dose adjustment for the next dose of panitumumab
Skin disorder	≥ 3	Dose reduction by **1** level after suspension However, treatment at a dose of **6 mg/kg** is allowed without dose reduction when it recovers to **Grade 2** or less within **6** weeks (**42** days).
Hypomagnesaemia *		
Pulmonary fibrosis (interstitial pneumonia)	≥ 2	Discontinue protocol treatment
Infusion reaction (reaction from injection) **, ***	≥ 3	Discontinuation (no resumption)
Dose reduction/suspension is allowed as necessary at the discretion of the investigator or the subinvestigator due to adverse events not listed above.		

*: When accompanied by abnormal ECG findings requiring treatment such as significant QTc prolongation, discontinuation or suspension of panitumumab should be considered irrespective of the severity of hypomagnesaemia.

**: Allergic reaction, anaphylactoid reaction, and chills, fever, and dyspnea occurring within 24 hours after the initial dose

***: If infusion reaction is observed, immediately discontinue administration. The course may be resumed at the discretion of the study site. In the event that Grade 1 or 2 infusion reaction occurs during infusion, careful administration will be allowed after appropriate supportive therapy has been given or infusion speed has been decreased by 50%, etc., upon administration of subsequent course.

Table 8.g Doses of panitumumab

Dose reduction level	Panitumumab
Initial dose	6 mg/kg
-1	4.8 mg/kg
-2	3.6 mg/kg
-3	Discontinuation (no resumption)

The administration of panitumumab may be postponed (skipped) and only TAS-102 therapy performed when the subject meets the panitumumab suspension criteria (in this case, the day of starting the next course (Day 1) will be the day of starting TAS-102 therapy). When the actual day of initiating administration starts on the morning of the next day, the day before starting administration will be Day 1. For the next dose of panitumumab, treatment will be resumed after it is confirmed that the subject does not meet the criteria for suspension of panitumumab, but if panitumumab cannot be administered for more than 28 days after the scheduled day of treatment initiation, panitumumab treatment will be discontinued.

8.5.2 Criteria for suspension/dose reduction of TAS-102

The criteria for suspension/dose reduction and doses of TAS-102 are shown in Tables 8.h-j.

Table 8.h Criteria for suspension of TAS-102

Item	Suspension criteria
Hemoglobin concentration	< 7.0 g/dL
Neutrophil count	< $1.0 \times 10^3/\Lambda$
Platelet count	< $5.0 \times 10^4/\Lambda$
Total bilirubin	> 2.0 mg/dL
AST	> 100 U/L
ALT	(> 200 U/L with liver metastasis)
Serum creatinine	> 1.5 mg/dL
Periphial sensory neuropathy	Grade 3 or higher
Other non-hematologic toxicity	Grade 3 or higher
Dose suspension is allowed as necessary at the discretion of the investigator or the subinvestigator due to adverse events not listed above.	

If adverse events meeting the criteria for dose reduction of TAS-102 shown in Table 8.i occur during the previous course (including the suspension period), dose will be reduced in course units, with a daily dose unit of reduction of 10 mg/day, when TAS-102 is resumed. However, the minimum dose will be 40 mg/ m^2/day (Table 8.j).

Table 8.i Criteria for dose reduction of TAS-102

Item	Criteria for dose reduction
Neutrophil count	< $0.5 \times 10^3/\Lambda$
Platelet count	< $5.0 \times 10^4/\Lambda$
Dose reduction is allowed as necessary at the discretion of the investigator or the subinvestigator due to adverse events not listed above.	

Table 8.j Doses of TAS-102

Dose reduction level	TAS-102
Initial dose	35 mg/m^2 (70 mg/m^2/day)
-1	30 mg/m^2 (60 mg/m^2/day)
-2	25 mg/m^2 (50 mg/m^2/day)
-3	20 mg/m^2 (40 mg/m^2/day)
-4	Discontinuation (no resumption)

When the subject meets the criteria for suspension of TAS-102, administration of TAS-102 will be suspended, and only panitumumab therapy will be administered. For the next dose of TAS-102,

TAS-102 treatment will be resumed after it is confirmed that the subject meets the criteria for initiation of TAS-102 treatment (however, when the subject satisfies the criteria for initiation of treatment from Day 13 to Day 28 of the suspension period, treatment will be resumed on Day 29). However, if TAS-102 cannot be administered for more than 28 days from the scheduled day of initiation of treatment, treatment with TAS-102 will be discontinued. (At this time, the day of initiating panitumumab monotherapy after it is determined that treatment with TAS-102 will be discontinued will be defined as the day for starting the course (Day 1), and the course will be defined as the administration of panitumumab between Day 1 and Day 28 on Days 1 and 15.)

8.6 Criteria for dose increase of protocol treatment

The dose should not be increased after dose reduction for any of the drugs.

8.7 Criteria for discontinuation of protocol treatment for each subject

The number of doses is not specified. However, protocol treatment should be discontinued when any of the criteria for discontinuation of protocol treatment listed below is met. The date of discontinuation of protocol treatment is defined as the date when the investigator or the subinvestigator decides on discontinuation of protocol treatment. The investigator or the subinvestigator should record the main reason for discontinuation of protocol treatment in the case report form (hereinafter referred to as CRF) according to the classification described below. For subjects discontinuing before enrollment, see 9.3 Records of subjects who discontinued before enrollment.

1. Lack of efficacy (exacerbation)
   When PD is evident in the clinical or imaging evaluation
2. Adverse event
   Discontinuation of treatment due to an adverse event in the opinion of the investigator or the subinvestigator, or according to the protocol treatment discontinuation criteria. However, death during protocol treatment will be classified in “4. Death during protocol treatment” and not in this item.
   Protocol treatment is postponed due to adverse event for 58 days or more after the day of starting the last course. However, postponement due to holidays is allowed.
3. Voluntary discontinuation
   A subject wishes to discontinue study participation. The reason for discontinuation should be recorded in CRF when it is clarified.

Note: Attempts should be made as best as possible to clarify the reason for voluntary discontinuation. (Discontinuation due to adverse event or lack of efficacy should not be classified as "voluntary discontinuation").

4. Death during protocol treatment
   Death before discontinuation of protocol treatment is decided. Date of death, reason of death (protocol treatment related, primary disease, others) should be described in the CRF.

5. Significant deviation from the protocol
   When study continuation may cause intolerable risk to the health of a subject because the subject was found not to satisfy the inclusion criteria specified in the protocol after enrollment or the protocol has not been observed.

6. Lost to follow-up
   When subject fails to make visits and cannot be contacted. The attempts that were made to contact the subject should be recorded in the source documents.

7. Discontinuation of the entire study
   For example, when the sponsor decides to discontinue the clinical study upon the recommendation of the DMC. See 6.3.1 Criteria for discontinuation of entire clinical study for details.

8. Pregnancy
   When a female subject is found to be pregnant.

   Note: Study participation should be immediately discontinued when pregnancy is known. See "9.2.13 Pregnancy" for procedures.

9. Others
   When the investigator or the subinvestigator decides that protocol treatment should be discontinued for other reasons. Details should be described in the CRF.

8.8 Procedures for Discontinuation or Withdrawal of a Subject

The investigator or the subinvestigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 8.7. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary reason for termination must be recorded in the CRF by the investigator or the subinvestigator. In addition, efforts should be made to perform all tests/observations/evaluation scheduled at the time of discontinuation.

8.9 DLT

In this study, DLT will be assessed based on the toxicity in 6 subjects at maximum enrolled in phase I part. The sponsor will confirm the opinion of the DMC in a suitable manner when evaluating DLT.

8.9.1 DLT Evaluation Period

The DLT evaluation period will be the period from Day 1 of Course 1 of protocol treatment to Day 1 of Course 2. However, it is mandatory that the treatment initiation criteria for both panitumumab and TAS-102 be satisfied in order to start Course 2 of protocol treatment. Furthermore, the DLT evaluation period will be the period until the test day at discontinuation of protocol treatment for subjects who could not start Course 2 of protocol treatment until Day 57 due to adverse events and discontinued the protocol treatment.

8.9.2 Subjects Included in the DLT Evaluation

Subjects enrolled in the phase I part of the study will be included in the DLT evaluation. 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/m^2) on Days 1-5 and Days 8-12.

8.9.3 DLT Criteria

DLT is defined as any adverse event for which a causal relationship with protocol treatment cannot be denied falling in the following categories. Adverse events will be graded according to the "Common Terminology Criteria for Adverse Events (CTCAE), ver. 4.03." Further, DLT will be assessed from Day 1 of course 1 of protocol treatment, and if DLT does not occur by Day 1 of course 2, it will be handled as no occurrence of DLT in the subject. Adverse events that can clearly be denied of causal relationship with the protocol treatment will not be considered DLT. If serious adverse event or unexpected adverse event occurs which causal relationship with the protocol treatment cannot be denied other than the following, it may be determined as to whether or not to handle it as DLT in consultation with the Investigator, the Research Steering Committee and the sponsor.

1. Persistent Grade 4 neutropenia for more than 7 days under maximum supportive therapy

2. Febrile neutropenia
3. Blood platelete decreased of Grade 3 requiring platelet transfusion or blood platelete decreased of Grade 4
4. If start of second course is delayed for more than 14 days due to adverse event related to protocol treatment
5. Grade 3 or higher non-hematologic toxicity that is clinically problematic however the following will not be applicable as DLT.

   - Grade 3 gastrointestinal symptoms that can be controlled with supportive care (appropriate use of antiemetics, antidiarrheals, etc.)

   - Grade 3 or higher electrolyte abnormalities that are not deemed clinically problematic

8.10 Replacement/Addition of Subjects

Should there be, during the DLT evaluation period in the phase I part of the study, a major deviation from the protocol affecting the DLT evaluation for a reason other than an adverse event classified as a DLT or if DLT cannot be evaluated appropriately, that subject can be excluded from the DLT evaluation and a new subject can be enrolled and added to that cohort.

8.11 Contraindicated drugs/therapies

The drugs and therapies shown below are contraindicated from informed consent until discontinuation of protocol treatment. The investigator or the subinvestigator should instruct the subjects not to use any drugs including over-the counter drugs other than the prescribed drugs without prior consultation.

- Chemotherapy for primary disease other than protocol treatment
- Hormone therapy for primary disease
- Immunotherapy for primary disease
  - Cellular immunotherapy
  - Vaccine therapy
  - Cytokine therapy
    Except for G-CSF
  - Biological Response Modifiers (BRM) therapy
  - Antibody therapy
  - Gene therapy
- Other antibody therapy (except for denosumab)
- Flucytosine (antifungal)

- Radiotherapy for primary disease
  Except for treatment for pain relief of bone metastasis site is allowed.
- Hyperthermia therapy for primary disease
- Study drug and unapproved drug

8.12 Recommended supportive care and combination medications

The supportive care and concomitant medications shown below are recommended during the study period (from obtaining consent until discontinuation of protocol treatment). The absence of supportive care or concomitant medications does not constitute a protocol deviation.

- Neutropenia
  Granulocyte colony stimulating factor (hereinafter referred to as G-CSF) should be administered The type of G-CSF products administered should depend on the insurance coverage.
- Nausea/vomiting
  Premedication including prophylactic administration of antiemetics is allowed. Premedication with 5-HT3 (serotonin) receptor antagonists, NK1 (neurokinin 1) receptor antagonists, steroids, and antihistamines may be carried out using the method employed at each study site.
- Diarrhoea
  Fluids and electrolyte balance will be followed adequately, and suitably supplemented, as necessary. If careful observation suggests that it is necessary, administration of an antidiarrheal such as loperamide hydrochloride may be considered.
- Allergic reaction
  Treatment with adrenal corticosteroids, antihistamines, etc. may be considered at the time of onset or for premedication at the start of the subsequent course. Careful administration of panitumumab by slowing the infusion speed may be considered.
- Pulmonary fibrosis (interstitial pneumonia)
  If it occurs, it should be treated according to the severity (e.g., steroid pulse therapy).
- Hepatitis B
  Refer to JSH Guidelines for the Management of Hepatitis B virus infection (http://www.jsh.or.jp/doc/guidelines/HBV_GL_ver2.201406.pdf**)** and take appropriate action and monitoring.
- Others
  Drugs for treatment of adverse events may be coadministered at the discretion of the investigator or the subinvestigator. Symptomatic therapies which have been continued from before the start of this study are allowed.

In addition, it is recommended that the supportive care shown below be performed at the discretion of the investigator or the subinvestigator when any of panitumumab-related adverse events listed below is observed. The absence of supportive care does not constitute a protocol deviation.

- Skin disorder
  - Tetracycline antibiotic (e.g. oral minocycline)

- External salicylic acid petrolatum (10%)
- External steroid therapy (example)
  - Face: hydrocortisone butyrate (0.1%)
  - Trunk: difluprednate (0.05%)
- Moisturizer (example): heparin analog lotion
- Sunscreen (example): not containing 4-aminobenzoic acid, SPF (Sun Protection Factor) 30, PA (Protection grade of UVA)++. Apply before going out to block ultraviolet rays (UVA and UVB).

Dermatopathy prevention with humectants, suntan lotion, antibiotic or external steroids may be carried out using the method employed at each study site, based on non-Japanese[29)] and Japanese reports[30)], etc.

- Electrolyte abnormality (e.g., hypomagnesaemia, hypocalcaemia)
  - ECG: ECG may be performed to determine whether there are abnormal ECG findings requiring treatment such as significant QTc prolongation. When any abnormal ECG findings requiring treatment are observed, suspension of panitumumab should be considered irrespective of the serum magnesium concentration.
  - Magnesium supplementation (example): intravenous infusion of magnesium sulfate (10 mmol) over 60 min

8.13 Recommended follow-up therapy

Approved drugs (e.g., regorafenib) should be used as appropriately as possible.

9.0 PROTOCOL, EVALUATION ITEMS AND PROCEDURES FOR OBSERVATIONS

9.1 Study calendar

The investigator or the subinvestigator should collect data according to "Table 9.a Study calendar (phase I part of the study)" in the phase I part of the study and "Table 9.b Study calendar (phase II part of the study)" in the phase II part of the study. The same investigator or the subinvestigator should perform tests/observations/evaluation of subjects in principle. For the allowance range of protocol treatment and various laboratory tests, see "Table 9.c. Allowance range for protocol treatment and laboratory tests"

Table 9.a Study calendar (phase I part of the study)

Item	At enrollment	Protocol treatment period							Follow-up period[#]
		Course 1				Second and later courses		Discontinuation of protocol treatment †	
Reference day: Number of days counted from the first day of each course	-14, -1	1	8	15	22	1	15		
Informed consent obtained*[1]	●								
Patient Background	●								
RAS status*[2]	●								
Clinical findings*[3]	●	●	●	●	●	●	●	●	
Height*[2]	●								
Body weight*[4]	●*[7]	○	○	○	○	○	○		
ECOG P.S. *[3]	●*[7]	●	○	○	○	●	○	●	
Compliance*[3]		●	○	○		●	○		
Hematology*[5]	●*[7]	●	●	●	●	●	●	●	
Serum chemistry*[5]	●*[7]	●	●	●	●	●	●	●	
Immunology (HBs antigen)*[6]	●								
Tumor marker		●*[8]				<- ●*[9] ->		●	
Imaging tests (thoracoabdominal-pelvic CT/MRI)	●*[10]					<- ●*[9] ->		○*[11]	○
Follow-up treatment									●
Survival survey									●
Adverse events	−	<- ● ->							○

●: Mandatory, ○: Perform as necessary
†: Perform within 28days of discontinuation or earlier date than start of follow-up treatment.
#: Perform every 6 months as a guide with protocol discontinuation date as starting point.
*1: Consent must be obtained before enrollment. Further, consent should be obtained after RAS status has been identified.
*2: Values obtained after the diagnosis of colorectal cancer may be used.
*3: When the visit day is the treatment day, this will be done before administration.
*4: Measurement is not mandatory during protocol treatment period. Even if measured, it is unnecessary to record in the CRF.
*5: Testing will be performed from 2 days before to the day of the visit during each course.
*6: Test results from up to one year before obtaining consent may be used. It is unnecessary to record this in the CRF. However, follow JSH Guidelines for the Management of Hepatitis B virus infection for the measurement of HBs antibody, HBc antibody and HBV-DNA.
*7: If done within 14 days before enrollment, results from before obtaining informed consent may be used.

*8: If it has been performed within 28days before treatment day, the test for Course 1 may be omitted.
*9: Measure once every 8 weeks (56 days) with Day 1 of Course 1 as starting point. However, reduce the frequency to once every 12 weeks (84 days) when one year has passed since initiation of protocol treatment.
*10: Imaging test will be performed within 4 weeks (28 days) prior to enrollment (including the same day of week as the day of enrollment). The results of imaging diagnosis/test performed before obtaining consent may be used if it is performed within 4 weeks (28 days) prior to enrollment.
*11: This is only done when the subject is discontinued for a reason other than imaging results (PD).

Table 9.b Study calendar (phase II part of the study)

Item	At enrollment	Protocol treatment period						Follow-up period#
		Course 1			Second and later courses		Discontinuation of protocol treatment †	
Number of days counted from the first day of each course	-14, -1	1	15	22	1	15		
Informed consent obtained*1	●							
Patient Background	●							
RAS status*2	●							
Clinical findings*3	●	●	●	●	●	●	●	
Height*2	●							
Body weight*4	●*7	○	○	○	○	○		
ECOG P.S. *3	●*7	●	○	○	●	○	●	
Compliance*3		●	○		●	○		
Hematology*5	●*7	●	●	●	●	●	●	
Serum chemistry*5	●*7	●	●	●	●	●	●	
Immunology (HBs antigen)*6	●							
Tumor marker		●*8			<-●*9->		●	
Imaging tests (thoracoabdominal-pelvic CT/MRI)	●*10				<-●*9->		○*11	○
Follow-up treatment								●
Survival survey								●
Adverse events	−	<- ● ->						○

●: Mandatory, ○: Perform as necessary
†: Perform within 28days of discontinuation or earlier date than start of follow-up treatment.
#: Perform every 6 months as a guide with protocol discontinuation date as starting point.
*1: Consent must be obtained before enrollment. Further, consent should be obtained after RAS status has been identified.
*2: Values obtained after the diagnosis of colorectal cancer may be used.
*3: When the visit day is the treatment day, this will be done before administration.

*4: Measurement is not mandatory during protocol treatment period. Even if measured, it is unnecessary to record in the CRF.
*5: Testing will be performed from 2 days before to the day of the visit during each course.
*6: Test results from up to one year before obtaining consent may be used. It is unnecessary to record this in the CRF. However, follow JSH Guidelines for the Management of Hepatitis B virus infection for the measurement of HBs antibody, HBc antibody and HBV-DNA.
*7: If done within 14 days before enrollment, results from before obtaining informed consent may be used.
*8: If it has been performed within 28 days before treatment day, the test for Course 1 may be omitted.
*9: Measure once every 8 weeks (56 days) with Day 1 of Course 1 as starting point. However, reduce the frequency to once every 12 weeks (84 days) when one year has passed since initiation of protocol treatment.
*10: Imaging test will be performed within 4 weeks (28 days) prior to enrollment (including the same day of week as the day of enrollment). The results of imaging diagnosis/test performed before obtaining consent may be used if it is performed within 4 weeks (28 days) prior to enrollment.
*11: This is only done when discontinuation is for a reason other than imaging results (PD).

Table 9.c Allowance range for protocol treatment and laboratory tests

Performed items	Protocol specification	Allowance range
Clinical Laboratory test values (During protocol treatment)	Course 1: Day 1, 8, 15, 22 (phase I part of the study) or Day 1, 15, 22 (phase II part of the study) Course 2: Day 1, 15	From Day -2 before scheduled day (However, Mg is tested once per course.)
Protocol treatment	From treatment day (Day 1) of previous course to 4 weeks later (Day 29)	Scheduled day ±3 days
Tumor markers and imaging tests (during protocol treatment)	Protocol treatment ≤ 1 year: 8 weeks (56 days)	Scheduled day ±1 week (7 days)
	Protocol treatment > 1 year: 12 weeks (84 days)	Scheduled day ±2 week (14 days)

9.2 Collection/test/observation items and procedures during the clinical study

The investigator or the subinvestigator will perform the following as scheduled in "9.1 Study calendar" or "Table 9.b Study calendar".

9.2.1 Informed consent procedure

Consent should be obtained from subject before initiation of study procedures.

A unique subject ID code to anonymize the subject will be assigned to each subject at the time of obtaining consent. The subject ID code will be used throughout the study period and not changed.

The method for obtaining consent is described in Section "15.3 Written information and subject's consent."

9.2.2 Enrollment and protocol treatment

For procedures and storage of enrollment and initiation of protocol treatment, see: "7.3 Procedures for Enrollment and Protocol Treatment."

9.2.3 Subject demographics

For demographic data of the subject, date of birth (or age at enrollment if date cannot be provided) and sex will be checked. Also, the following items concerning the primary disease of colorectal cancer will be examined.

(1) Information on primary organ

- Solitary/Multiple
- Primary tumor site (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectosigmoid, rectum)

(2) Information on metastasis

- Number of organs with metastasis (0, 1, ≥ 2)*

  *: Does not include primary tumor/regional lymph node, other lymph nodes in several sites will be counted as "1 organ". For example, even if it is observed in cervical lymph node and thoracic lymph node, it will be counted as 1 organ.

- Organs with metastasis (liver, lung, peritoneum, lymph node*, bone, adrenal gland, skin, and others**)

  *: Does not include regional lymph node, other lymph nodes in several sites will be counted as "1 organ". For example, even if it is observed in cervical lymph node and thoracic lymph node, it will be counted as 1 organ.

  **: Name of organ to be recorded in CRF

(3) History of treatment

- History of surgery in primary tumor site/palliative metastasis site and history of colostomy /bypass surgery
  - Subjects with history, the date of surgery
    However, endoscopic surgery, which is not considered a history of surgery, should not be entered into the CRF.
- History of radiotherapy (radical irradiation)
  - Subjects with history, the date of final dose
    However, irradiation for pain relief (palliative irradiation) in the bone metastasis site, which is not considered as radiotherapy, should not be entered into the CRF.
- Treatment history for subjects with unresectable lesions
  - Description of first-, second-, and third-line treatment (FOLFOX, FOLFOX + anti-angiogenic agent (e.g., bevacizumab); CapeOX, CapeOX + anti-angiogenic agent (e.g., bevacizumab); FOLFIRI, FOLFIRI + anti-angiogenic agent (e.g., bevacizumab); IRIS, IRIS + anti-angiogenic agent (e.g., bevacizumab); IRI, IRI + anti-angiogenic agent (e.g., bevacizumab); FOLFOXIRI, FOLFOXIRI + anti-angiogenic agent (e.g., bevacizumab); SOX, SOX + anti-angiogenic agent (e.g.,

bevacizumab); SOX, SOX + anti-angiogenic agent (e.g., bevacizumab); other), date of initiation of first-line treatment

- History of preoperative and/or postoperative adjuvant chemotherapy
  - Subjects with history, history of preoperative and/or postoperative adjuvant chemotherapy with OXA, date of final treatment

9.2.4 Concurrent medical condition

A concurrent medical condition is defined as any symptom or disease present at initiation of protocol treatment. Any notable concurrent medical condition will be entered into the CRF. Clinically problematic laboratory test data, ECG findings, and abnormal physical examination findings observed immediately before initiation of protocol treatment should be handled as a concurrent medical condition at the discretion of the investigator or the subinvestigator.

9.2.5 Clinical findings

Medical examination will be performed prior to protocol treatment. In particular, the following symptoms at the medical examination will be confirmed.

Allergic reaction, rash acneiform, cutaneous dryness, paronychia, infusion reaction (infusion related reaction), anorexia, diarrhoea, nausea, vomiting, oral mucositis, hypomagnesemia, blood neutrophil count decreased, febrile neutropenia, reduced blood platelet count, peripheral sensory neuropathy, thromboembolism, gastrointestinal perforation, interstitial pneumonia, fatigue.

The results of medical examinations after initiation of protocol treatment will be compared with the results of medical examinations before initiation of protocol treatment to evaluate the clinically problematic abnormalities.

See “10.0 Adverse event” for definition of adverse event.

9.2.6 Body weight, height

Body weight at enrollment should be measured within 2 weeks (14 days) before enrollment (including the same day of week as the day of enrollment) and recorded in the CRF. Height obtained after the diagnosis of colorectal cancer may be used.

9.2.7 Eastern Cooperative Oncology Group Performance Status (ECOG) Performance Status

ECOG Performance Status (P.S.) will be assessed according to Table 9.d. P.S. at enrollment will be determined within 2 weeks (14 days) prior to enrollment (including same day of the week as the day of enrollment). P.S. before initiation of each course will be determined before administration on treatment day. P.S. at discontinuation will be determined as much as possible within 4 weeks (28 days) after discontinuation or before the initiation of follow-up treatment whichever date is earlier.

Table 9.d Eastern Cooperative Oncology Group Performance Status (ECOG P.S.)

P.S.	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

9.2.8 Compliance

The investigator or the subinvestigator should record the compliance with protocol treatment in the CRF as follows:

- Doses and treatment days for panitumumab
- Doses, treatment initiation day, and number of doses of TAS-102

9.2.9 Clinical laboratory tests

In principle, laboratory tests should be conducted at each study site.

Laboratory tests at enrollment will be conducted within 2 weeks (14 days) prior to enrollment (including same day of the week as the day of enrollment).

Testing will be performed from 2 days before to the day of the visit during the protocol treatment period.

Tests at discontinuation will be conducted as much as possible within 4weeks (28 days) after discontinuation or before the initiation of follow-up treatment whichever date is earlier.

Test items and notes are listed in Table 9e to Table 9. g.

The investigator and the subinvestigator should evaluate and store the reported laboratory test results.

For laboratory test standard values, common standard values (common standard range list, Japan Clinical Oncology Group, hereinafter referred to as JCOG) will be used.

Table 9.e Laboratory tests performed at the time of enrollment

Hematology	Serum chemistry	Immunology
Neutrophil count	Total bilirubin	HBs antigen *
Platelet count	ALT	
Hemoglobin content	AST	
	Creatinine	
	Mg	
	Albumin	
	Na	
	K	
	Ca	

*: Test results measured up to 1 year before obtaining consent may be used. However, follow JSH Guidelines for the Management of Hepatitis B virus infection for the measurement of HBs antibody, HBc antibody and HBV-DNA.

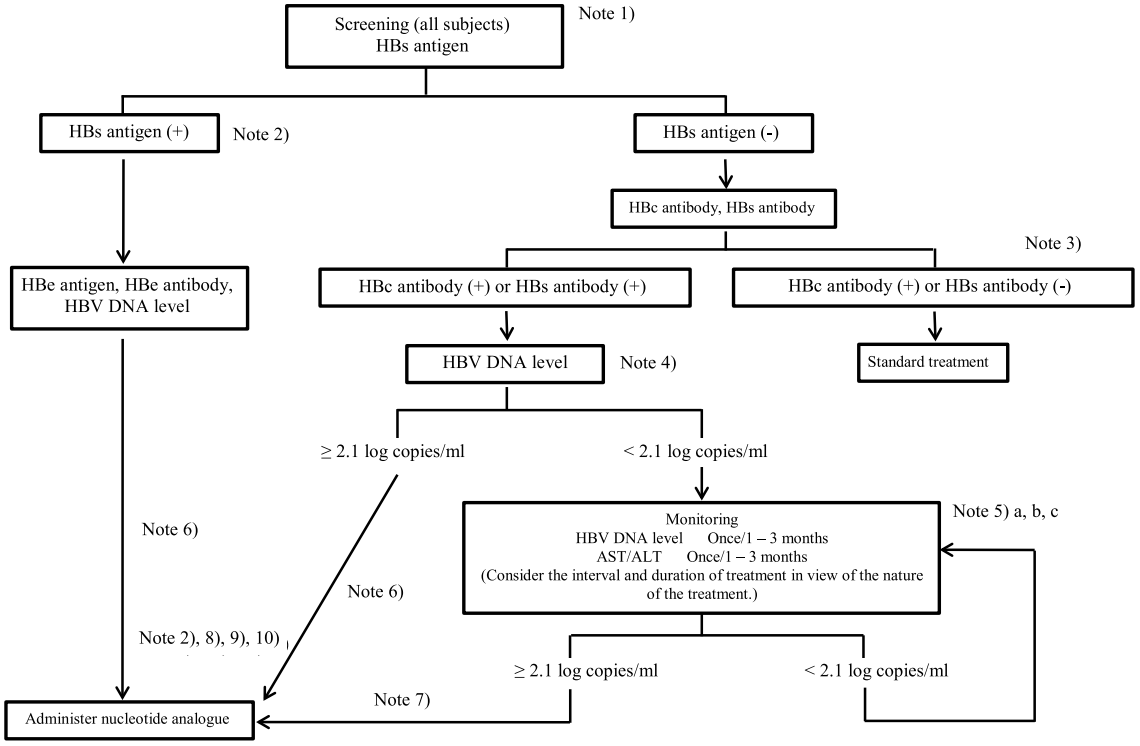


Figure 9.a JSH Guidelines for the Management of Hepatitis B virus infection

Supplementary note: During or after completion of potent chemotherapy for hematological malignancies, caution is required because hepatitis B occurs in a portion of HBs antigen-positive and -negative patients as a result of reactivation of the hepatitis B virus, and the disease becomes fulminant in portion of these patients. Action is also necessary with standard chemotherapy for hematological malignancies and solid tumors and

immunosuppressive therapy for autoimmune diseases such as rheumatological diseases in view of the risk of reactivation of HBV. The frequency of reactivation of HBV and the occurrence and progression to fulminant status of hepatitis with standard chemotherapy and immunosuppressive therapy is not known, and there is insufficient evidence related to guidelines. In addition, treatment with nucleotide analogues does not completely guarantee prevention of progression to a fulminant status.

Note 1) Screening will be conducted for HBV carriers and subjects with previous infections prior to immunosuppressive therapy or chemotherapy. First, HBs antigen will be measured to identify HBV carriers. In HBs antigen-negative subjects, HBc antibody and HBs antibody will be measured to identify subjects with previous infections. Highly sensitive techniques should be used to measure HBs antigen, HBc antibody, and HBs antibody. In subjects positive for HBs antibody only (HBs antigen-negative and HBc antibody-negative), HBV reactivation will be reported, and action should be taken according to guidelines, except when the subject is known to have been vaccinated.

Note 2) When a subject is HBs antigen-positive, consult with a hepatologist. A hepatologist should be consulted when administering nucleotide analogues to any subjects.

Note 3) Antibody titers may decrease when initially starting chemotherapy in subjects who are being retreated but have not been measured for HBc antibody and HBs antibody and subjects who have already been started on immunosuppressive therapy, and detailed examinations should be performed, e.g., measuring HBV DNA levels.

Note 4) Screening for HBV DNA will be performed by real time PCR in subjects with previous infections.

Note 5)

a. Caution is required with subjects receiving chemotherapy with rituximab, a steroid, and fludarabine and hematopoietic stem cell transplantation because they are at high risk of HBV reactivation from previously infected people. HBV DNA should be monitored once a month during and for a period of at least 12 months after completion of therapy. Subjects receiving hematopoietic stem cell transplantation require long-term monitoring after transplantation.
b. There is also a risk of HBV reactivation with combination therapy using standard chemotherapy and molecularly targeted drugs having an immunological effect, although the frequency of reactivation is low. As a general guideline, HBV DNA levels should be monitored every 1 to 3 months, but the frequency and time of monitoring should take the nature of the treatment into consideration. Action should be taken prudently in the case of hematological malignancies.
c. There is also a risk of HBV reactivation with immunosuppressive therapy using corticosteroids, immunosuppressives, and molecularly targeted drugs having an immunosuppressive or immunomodulating effect. With immunosuppressive therapy, HBV DNA levels should be monitored monthly for at least 6 months after staring or changing the therapy. After the first 6 months, the frequency and time of monitoring should take the nature of the treatment into consideration.

Note 6) Administration of nucleotide analogues should be started as early as possible before starting immunosuppressive therapy or chemotherapy. However, deaths from fulminant hepatitis during prophylactic nucleotide analogue therapy have been reported in HBs antigen-positive patients with a high viral load, and the viral load should therefore be reduced before starting immunosuppressive therapy or chemotherapy.

Note 7) Administration of nucleotide analogues should be started immediately when HBV DNA has reached 2.1 log copies/mL or higher during or after completion of immunosuppressive therapy or chemotherapy. During immunosuppressive therapy or chemotherapy, a hepatologist should be consulted about the action to be taken without immediately discontinuing the immunosuppressive agent or anti-neoplastic agent with an immunosuppressive action.

Note 8) The recommended nucleotide analogue is entecavir.

Note 9) Termination of nucleotide analogue treatment may be considered when the following conditions are satisfied. In subjects who are HBs antigen-positive at screening: when the criteria for terminating nucleotide analogue treatment in chronic hepatitis B are satisfied. In subjects who are HBc antibody-positive or HBs antibody-positive at screening: (1) Nucleotide analogue treatment should continue for at least 12 months after completing immunosuppressive therapy or chemotherapy. (2) Normalization of ALT (GPT) should be achieved during this period of continued treatment. (unless ALT is abnormal for a reason other than HBV). (3) Sustained negative HBV DNA should be maintained during this period of continued treatment.

Note 10) Subjects should be followed vigilantly, including HBV DNA monitoring, for at least 12 months after terminating nucleotide analogue treatment. The follow-up should be based on the Precautions for Use in the package insert of the nucleotide analogue used. Nucleotide analogue treatment should be resumed immediately when HBV DNA reaches 2.1 log copies/mL or higher in subjects being followed.

Table 9.f Clinical laboratory tests performed during the protocol treatment period

Hematology	Serum chemistry	Tumor markers
Neutrophil count *	Total bilirubin *	CEA**, †
Platelet count *	ALT*	
Hemoglobin content *	AST*	
	Creatinine *	
	Mg ***	
	Albumin *	
	Na*	
	K*	
	Ca*	

*: The test in Course 1 may be omitted when the pre-entry test had been performed within 2 days before treatment in Course 1. The test in Course 1 will be performed before administration in Course 1 when the pre-entry test had been performed more than 2 days before treatment in Course 1.

**: If it had been conducted within 28 days before treatment day, it may be omitted.

***: May be measured once during each course.

†: Measure every 8 weeks (56 days) with Day 1 of Course 1 as starting point. However, when 1 year has passed since initiation of protocol treatment, once every 12 weeks (84 days).

Table 9.g Laboratory tests performed at the time of discontinuation

Hematology	Serum chemistry	Tumor markers
Neutrophil count	Total bilirubin	CEA*
Platelet count	ALT	
Hemoglobin content	AST	
	Creatinine	
	Mg	
	Albumin	
	Na	
	K	
	Ca	

*: If ≥ 28days has not passed since the last measurement, the test can be omitted.

9.2.10 Imaging test (thoracoabdominal-pelvic CT/MRI)

Imaging test will be performed within 4 weeks (28 days) prior to enrollment (including the same day of week as the day of enrollment). The results of imaging diagnosis/test performed before obtaining consent may be used if it is performed within 4 weeks (28 days) prior to enrollment.

Furthermore, the data of measurable lesion should be evaluated with imaging test conducted within 2 weeks (14 days) prior to initiation of protocol treatment (including the same day of week as the day of enrollment) preferably. If another imaging test has been conducted newly after enrollment but before initial administration, this data should be recorded in CRF.

After initiation of protocol treatment, imaging test will be performed every 8 weeks (56 days) with protocol treatment initiation date (Day 1) of Course 1 as the starting point. However, when 1 year has passed since initiation of protocol treatment, imaging may be performed once every 12 weeks (84 days), counting from the point in time at which 1 year has passed. (For details, see "Table 9.a Study calendar (phase I part of the study)" or "Table 9.b Study calendar (phase II part of the study)."

Thoracoabdominal-pelvic CT (in principle, contrast CT; a slice width of 5 mm or less is recommended, but MRI is also acceptable) will be used for imaging test, and the modality and the date of imaging test will be entered into the CRF. If necessary, brain MRI / CT and a neck CT will be performed.

In principal, the same modality should be used for imaging test during protocol treatment throughout the study period.

The investigator or the subinvestigator should evaluate the test results according to the RECIST v1.1 (see Appendix A) and enter the determined results into the CRF.

Furthermore, for subjects withdrawn from the study for any reason other than imaging test results such as clinical PD, imaging test specified at the time of discontinuation should be performed within 4 weeks (28 days) including the day of decision (including the same day of week as the day of decision).

If the subject is not determined to have PD on imaging up to the time of withdrawal, the following information should be collected until the subject dies or the sponsor terminates the study, even after follow-up treatment has been started.

- Day of decision on clinical PD (only when the subject is not determined to have clinical PD by the time of discontinuation)
  - It will not be necessary to collect information if the subject is determined to have radiological PD before the subject is determined to have clinical PD.
- Day of decision on radiological PD
  - The day of decision on radiological PD will be collected, regardless of the state of clinical PD. The final imaging test date will be collected in subjects not determined to have radiological PD during the follow-up period as well.
- Date of last confirmed progression-free survival
  - The date of last confirmed progression-free survival will be collected in subjects not determined to have either clinical PD or radiological PD during the follow-up period as well.

However, when follow-up is not possible due to withdrawal of consent, loss to follow-up, etc., the date of the last visit will be entered in the CRF as the date of last confirmed progression-free survival.

9.2.11 Follow-up treatment

The following information will be collected when follow-up treatment is performed after discontinuation of protocol treatment. If several types of follow-up treatment are performed, information will only be collected on the follow-up treatment immediately following discontinuation of protocol treatment.

- Name of drugs used (regorafenib, other)
- Initiation date

9.2.12 Survival survey

After discontinuation of protocol treatment, every subject will be followed-up to confirm survival of subjects every 6 months in principle after discontinuation of protocol treatment. The following information on survival should be collected. The survey should be continued until the subject dies or the sponsor terminates the study.

- Survival survey date
- Date of death or last confirmed date of survival
  - If deceased, the reason of death (death from primary disease/others)

9.2.13 Pregnancy

When it becomes apparent that a female subject is pregnant, with consent from female subject, the investigator or the subinvestigator should notify the primary care physician (obstetrician and gynecologist, etc.) that the female subject was participating in a clinical study at the time she became pregnant and provide details of protocol treatment.

For every female subject reported to have become pregnant, the investigator or subinvestigator should follow-up to delivery including result of premature delivery with consent from the female subject and report to the sponsor using the specified follow-up form. Evaluation after delivery will also be conducted.

9.3 Records of subjects who discontinued before enrollment

Every subject who has signed the ICF and dropped-out before enrollment should be registered in the Web registration center and a CRF should be prepared.

The following items are to be entered in the CRF.

- Date of consent obtained

- Date of birth (the age at enrollment)
- Sex
- Eligibility
- Reason for discontinuation

For subjects who drop-out from the study before enrollment, the main reason for dropping-out should be entered into the CRF according to the following categories.

- Not satisfying at least one of the inclusion criteria or meeting any of the exclusion criteria
- Serious deviation from the protocol
- Lost to follow-up
- Voluntary discontinuation <specify the reason>
- Discontinuation of the entire study
- Others <specify the reason>

The subject ID code of a subject withdrawn from the study before enrollment should not be reused.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse events

Adverse events are any unfavorable medical events encountered in a subject treated with a drug. They are not limited to the events with clear causal relationship with treatment with the concerned drug.

In other words, adverse events are any unfavorable or unintended sign (including clinically problematic abnormalities of laboratory test data), symptoms or diseases that develop after administration of a drug irrespective of a causal relationship with the relevant drug.

10.1.2 Items to be considered concerning adverse events

Generally unfavorable findings are shown below:

- Newly diagnosed disease or unexpected aggravation of existing symptom (intermittent event of the existing symptom is not considered an adverse event)
- Requiring action or medical practice
- Requiring invasive diagnostic treatment
- Requiring discontinuation of protocol treatment (panitumumab + TAS-102 combination therapy) or of combination therapy or change in dose
- Considered unfavorable by the investigator or the subinvestigator

Diagnosis name and signs/symptoms:
Adverse events should be recorded by a diagnosis name. Accompanying signs (including abnormal laboratory values, abnormal ECG findings) and symptoms should not be recorded as adverse events. If an adverse event could not be expressed by a diagnosis name, sign or symptom will be the adverse event.

Laboratory test values and ECG findings:
Abnormal laboratory values and ECG findings are recorded as adverse events when the investigator or the subinvestigator judges the course to be clinically problematic (in other words, when certain action or medical practice is required, or the investigator or the subinvestigator judges the change to have exceeded the normal physiological variation range of the subject). Retest and/or continued monitoring of abnormality are not considered medical practice. Also, repeated or additional conduct

of non-invasive test for verification, evaluation and monitoring of abnormality are not considered medical practice.

However, when abnormal laboratory values and ECG findings are the accompanying symptoms of the disease diagnosed as an adverse event (e.g., increased creatinine due to renal dysfunction, etc.), the diagnosis name is handled as an adverse event.

Existing symptoms (diseases and/or symptoms that have been present from before initiation of protocol treatment): Diseases and/or symptoms that have been present from before initiation of protocol treatment should be recorded as concurrent medical conditions and not as adverse events. When a concurrent medical condition is aggravated, the aggravation will be determined as an adverse event and the investigator or the subinvestigator should record in CRF that the adverse event is an aggravation of the concurrent disease (e.g., "aggravation of hypertension", etc.).

When a subject has an existing symptom that is transient (e.g., asthma, epilepsy) and incidence of the symptom is increased, or the symptom becomes serious or severe, it should be recorded as an adverse event. When a subject has a chronic disease (e.g., cataract, rheumatoid arthritis) and the symptom is aggravated more than anticipated, it should be recorded as an adverse event. The investigator or the subinvestigator should record in a way that will make the reported adverse event name be recognized as a change from baseline (e.g., aggravation of XX).

Change of severity of adverse events:
When the severity of an adverse event has changed, the event should be recorded once at the highest degree of severity (grade based on the CTCAE [Japanese edition JCOG version 4.03]), and should be recorded in each protocol treatment course.

Previously planned surgery or treatment:
Surgery or treatment planned before initiation of protocol treatment is not considered an adverse event. However, when the existing symptom is aggravated to require emergency surgery or treatment, the condition or the event is considered an adverse event. A complication which resulted from previously planned surgery is reported as an adverse event.

Non-urgent surgery or treatment:
Non-urgent surgery or treatment that does not induce a change in the condition of a subject (cosmetic surgery, etc.) is not considered an adverse event. However it should be recorded in the source documents. Complications due to a non-urgent surgery should be reported as an adverse event.

Progressive Disease (PD):
PD should be considered lack of efficacy, not an adverse event. In addition, the single fact of PD does not necessarily constitute a serious adverse event. However, if a clinical or on imaging progression of pre-existing cancer (including new metastasis) is confirmed, it will be determined as a serious adverse event if the severity satisfies any of the criteria specified in Section 10.1.3.

Panitumumab overdose:
When overdose of panitumumab becomes apparent, it should be recorded in the CRF. If adverse event occurs with overdose, it should be recorded as an adverse event in the adverse event column of the CRF.

Furthermore, the overdose of panitumumab is defined as follows.

1) Received administration exceeding approved dosage (6 mg/kg) of panitumumab
2) Received next administration within 10 days of previous administration

10.1.3 Serious adverse events

Of all the unfavorable medical events that developed with administration of drugs (irrespective of dose), serious adverse event is an event that:

1. Results in death during protocol treatment* and all deaths irrespective of a causal relationship with protocol treatment.

   *: Period from initiation of protocol treatment up to 4 weeks (28 days) after discontinuation of protocol treatment or initiation of follow-up treatment.

2. Results in death after discontinuation** of protocol treatment for which a causal relationship with protocol treatment cannot be denied. However, death obviously due to the underlying disease is not applicable.

   **: from 29 days after discontinuation of protocol treatment or from initiation of follow-up treatment

3. Is life-threatening. The term “life-threatening” refers to an event in which the subject was at risk of death during onset of the adverse event; it does not refer to an event which hypothetically might have caused death if it were severer.

4. Requiring hospitalization or prolongation of hospitalization
   However, hospitalization or prolongation of hospitalization for the following reasons will not be handled as a serious adverse event.

   (1) Preplanned inpatient hospitalization or prolongation of existing hospitalization

(2) Inpatient hospitalization or prolongation of existing hospitalization unrelated to an adverse event

5. Results in persistent or significant disability/incapacity.
6. Leads to a congenital anomaly/birth defect.
7. Other medically significant condition: medically important event which causes a risk to a subject even if it is not immediately life-threatening, nor does it result in death or hospitalization, or requires an action or treatment to prevent the results shown in 1 to 6 above.

10.1.4 Special interest adverse event for sponsor

Adverse events listed in Table 10.a "Takeda Medically Significant AE List" will be handled as "special interest adverse event" for sponsor irrespective of severity determined by the investigator or the subinvestigator. Further, any adverse events listed in Table 10.a that has been determined as serious by the investigator or the subinvestigator will be handled as serious adverse event.

Table 10.a Takeda Medically Significant AE List

Acute respiratory failure/acute respiratory distress syndrome (ARDS)	Hepatic necrosis
Torsades de pointes/ ventricular fibrillation/ventricular tachycardia	Acute hepatic failure
Malignant hypertension	Anaphylactic shock
Convulsive seizure (including convulsion and epilepsy)	Acute renal failure
Agranulocytosis	Pulmonary hypertension
Aplastic anemia	Pulmonary fibrosis (including interstitial pneumonia)
Toxic epidermal necrolysis/ oculomucocutaneous syndrome (Stevens-Johnson syndrome)	Neuroleptic malignant syndrome/ malignant hyperpyrexia
	Spontaneous abortion/ stillbirth and fetal death
	Confirmed or suspected transmission of infection by a medicinal product
	Confirmed or suspected endotoxin shock

10.1.5 Severity of adverse events

The severity of adverse event is classified into 5 grades (Grade 1-5) as follows based on the Common Terminology Criteria for Adverse Events (hereafter referred to as CTCAE, Japanese edition JCOG version 4.03), of the National Cancer Institute, USA. Furthermore, the grade for adverse events not listed in CTCAE will be classified according to the following criteria.

Table 10.b CTCAE (Japanese edition JCOG version 4.03) Grade

Grade 1	Mild; asymptomatic or slightly symptomatic; only clinical or test findings; or requiring no treatment
Grade 2	Moderate; requiring the least treatment or local or non-invasive treatment; or interfering with age-appropriate activities of daily living except for self-care activities*
Grade 3	Severe or medically critical, but not immediately life-threatening; requiring hospitalization or prolongation of existing hospitalization; disabling/incapacitating; or interfering with self-care activities of daily living**
Grade 4	Life-threatening; or requiring emergent treatment
Grade 5	Death due to an adverse event

AE: Adverse Event, ";" stands for "or"
*: Activities of daily living except for self-care activities include meal preparation, shopping for daily necessities and clothings, phone call, and financial management.
**: Self-care activities of daily living include bathing, dressing, eating, toilet, and oral drug intake, and indicate that a person is not confined to bed.

10.1.6 Causality of adverse events

Causal relationship between protocol treatment (panitumumab + TAS-102 combination therapy) and adverse events, and causal relationship between panitumumab and adverse events (information on causal relationship with panitumumab will be collected only when causal relationship is "related" with protocol treatment) is classified and defined as described below. Information on causal relationship with adverse event is not collected for any drugs other than protocol treatment.

Related	An adverse event with apparent temporal relation (including clinical course after discontinuation). Possibly due to protocol treatment or panitumumab although other factors such as underlying disease, complications, concomitant drugs/treatment are also presumed.
Not related	An adverse event with no chronological correlationship with protocol treatment (chemotherapy, panitumumab, or bevacizumab). Very likely due to other factors such as underlying disease, complications, and concomitant drugs/treatment.

10.1.7 Date of onset of adverse events

The date of onset of adverse events will be determined according to the following criteria.

Adverse event, etc.	Date of onset
Signs, symptoms, and diseases (diagnoses)	The subject, investigator, or subinvestigator will record the date on which the sign or symptom of an adverse event is first noticed.
Asymptomatic diseases	The date on which diagnosis is confirmed by testing will be recorded. Even if testing reveals old findings or if the time of occurrence can generally be estimated, the date on which diagnosis is confirmed will be recorded.
Aggravation of concurrent medical conditions	The subject, investigator, or subinvestigator will record the date on which a disease or aggravation of a disease is first noticed.
Test results that became abnormal after initiation of protocol treatment	The test date on which abnormal test results determined to be clinically problematic were observed will be recorded.
Test results that are abnormal at initiation of protocol treatment and aggravated in later testing	The date on which the time profile of a laboratory value shows a clear increase or decrease, based on medical judgment, will be recorded.

10.1.8 Action taken for protocol treatment

As for action concerning protocol treatment, when protocol treatment is discontinued as an action against the concerned adverse event, it will be defined as “discontinuation”.

10.1.9 Outcome

Outcome of adverse events is classified as follows.

Category	Criteria for judgment
Recovered	• disappearance or recovery of symptoms and findings • laboratory values returned to normal or baseline
Improved	• severity was improved by one or more grades • symptoms or findings mostly disappeared • laboratory values improved but has not returned to normal or baseline • when the subject died from a cause other than the adverse event concerned while the event was resolving
Not recovered	• no change in symptoms, findings, or laboratory data • the symptoms, findings, or laboratory data on the final day of observable period aggravated compared with the date of onset • irreversible congenital anomaly • when a subject died where the concerned adverse event is not a direct cause of death and the concerned adverse event remained not recovered
Recovered with sequelae	• disability which disturbs daily life
Death	• direct relationship between death and the concerned adverse event • "Direct relationship" means that the concerned adverse event was the cause of death, or the concerned adverse event was clearly responsible for death. • Outcome of an adverse event which was not determined (judged, presumed) a direct cause of death observed in the same subject is not considered as death.
Unknown	• follow-up specified in the protocol after the date of onset was not possible due to change of hospitals or relocation, etc.

10.2 Procedures

10.2.1 Collection and reporting of adverse events

10.2.1.1 Period for collection of adverse events

Adverse events should be continuously collected from initiation of protocol treatment up to 4 weeks (28 days) after discontinuation of protocol treatment or initiation of follow-up treatment, whichever date is earlier. In addition, adverse event causal relationship cannot be ruled out of protocol treatment collected later 4 weeks (28 days) after discontinuation of protocol treatment or initiation of follow-up treatment.

10.2.1.2 Reporting of adverse events

At each visit of subject, the investigator or the subinvestigator should confirm whether the onset of subjective symptoms is present or not. Onset of any adverse event that developed after the previous visit should be checked by asking a question such as "how has your condition been since the last visit?" to a subject.

The investigator or the subinvestigator should follow up all subjects who developed adverse events irrespective of a causal relationship with protocol treatment until disappearance of symptoms or abnormal laboratory values, return of clinically problematic abnormal laboratory values to the value before administration of study drug, or if not, until observed changes can be sufficiently explained for other events (persistent/irreversible adverse event, etc.).

All adverse events should be entered into the CRF. The name of the adverse event, date of onset, severity, seriousness, causal relationship with protocol treatment (unrelated or related), further if event has causal relationship "related" to protocol treatment, causal relationship with panitumumab (unrelated or related) should be recorded. Also, for the last course, action taken and outcome concerning protocol treatment as well as date of resolution should be recorded.

Follow-up period of adverse events is until recovery of an adverse event, or the investigator or the subinvestigator judges that further follow-up would be unnecessary.

10.2.2 Collection and reporting of serious adverse events

When a serious adverse event develops during the period of collecting adverse events, it should be reported according to the following procedures.

When the investigator or the subinvestigator judges that a serious adverse event has occurred based on the reporting by a subject, etc., or results of various tests, imaging findings or definitive diagnosis, etc., it should be reported immediately to the director of the study site.

Also, the investigator or the subinvestigator should report to the sponsor (see attached sheet for contact information) within 72 hours of recognition of onset of event. Further, the investigator should submit a formal report within 10 calendar days to the sponsor.

Furthermore, the content below which is to be reported to the sponsor within 72 hours is mandatory, and other items should be reported as much as possible.

- Brief description of adverse event and the reason for why it was determined as serious
- Study title

- Subject ID code
- Name of study site
- Name of investigator or the subinvestigator
- Name of protocol treatment being conducted
- Determined causal relationship

10.2.3 Follow-up of serious adverse events

The investigator or the subinvestigator should follow-up all serious adverse events, etc., until recovery is confirmed, or the final outcome is determined.

When a change such as alteration of outcome was made to the report of a serious adverse event, the investigator or the subinvestigator should submit a report specifying details of the change to the director of study site and the sponsor. When requested by the sponsor or the study site committee such as the ethics review committee, related data of the study site (e.g., ECG, laboratory test values, summary of discharge report, result of autopsy, etc.) should be provided.

10.2.4 Reporting of additional information concerning adverse events

If the sponsor requests provision of additional information concerning adverse events for reporting to regulatory authorities, the investigator or the subinvestigator should confirm the necessary additional information and enter in the EDC system or submit a report within the period specified by the sponsor.

10.2.5 Dissemination of unknown serious adverse event to joint research institutions

If the director of the study site receives a report of an unexpected serious adverse event, for which a direct causal relationship with protocol treatment cannot be denied, from the investigator or subinvestigator, the director should ask the opinion of a study site committee such as the ethics review committee and add the items below to the report submitted by the investigator, and disseminate it to the monitoring committee and research institutions that are jointly conducting clinical study through the sponsor.

- Date of review, summery of review, result, necessary action, etc., related to the study site committee such as ethics review committee.

10.2.6 Reporting of serious adverse events, etc., to ethics review committee, etc., and regulatory authorities

If the director of the study site receives report of serious adverse event from the investigator, the director should ask opinion of the ethics review committee, etc., and disseminate the study sites that are conducting clinical study through the sponsor or the CRO (research secretariat office) consigned by the sponsor.

If the director of the study site receives report of unexpected serious adverse event, the director should add the items below to the report submitted by the investigator, and prepare unexpected serious adverse event report and report to the Minister of Health, Labour and Welfare, and disseminate the study sites that are conducting clinical study (report to the Minister of Health, Labour and Welfare, and dissemination to study sites through sponsor is also possible).

- Action taken for serious adverse event
  (discontinuation of new enrollment, revision of ICF, re-consent from other subjects, etc.)
- Date of review, summery of review, result, necessary action, etc., related to ethics review committee, etc.
- Dissemination to joint research institutions.

The sponsor should report according to regulations, unexpected serious adverse drug reactions and other serious adverse events that are subject to emergency reporting to regulatory authorities, the investigator and director of study site.

From the time point of first acknowledging the event or receiving additional information, the sponsor or the CRO (research secretariat office) consigned by the sponsor should comply with regulatory required time frame for reporting, and make emergency report concerning unexpected serious adverse drug reactions and expected serious adverse drug reactions to regulatory authorities. Also, the sponsor should in the same way make an emergency report of other critical safety information that may have a major effect on the study drug risk-benefit, continuation of study drug administration, and continuation of clinical study. The study site should submit copies of emergency report documents to the ethics review committee, etc.

11.0 COMMIITTEES ESTABLISHED FOR THIS STUDY

11.1 Research steering committee

The research steering committee will be established to effectively promote this study.

The research steering committee will consist of the sponsor, research steering committee chairman, research steering committee members and statistics representative, and the sponsor or its designee will act as the secretariat.

Details of management of the research steering committee will be specified in a separately prepared procedure manual. Research steering committee members are listed in Section 1.2.

11.2 Data monitoring committee

The Data Monitoring Committee (hereinafter referred to as DMC) will be established according to the ICH E6 (1.25), and the sponsor or its designee will serve as the secretariat of the DMC.

The purpose of the DMC is to evaluate safety report data (including DLT occurring during the DLT evaluation period of the phase I part of the study) independent of the research steering committee concerning the appropriateness of continuing the study, or changing, discontinuing, suspending, or other measures regarding the study, and to submit the results to the sponsor. The sponsor will determine whether to continue, discontinue, or change the study based on the results.

The sponsor will prepare the DMC procedures (DMC charter) specifying the details such as the objective, roles, and responsibilities of the DMC, and management procedure. DMC members are listed in Section 1.2.

12.0 DATA MANAGEMENT AND STORAGE OF RECORDS

The sponsor's Data Management Group will perform data management activities independent of the Medical Affairs Division in accordance with standard operating procedures. Adverse events and concurrent conditions should be coded using MedDRA.

12.1 Case report form

The investigator or the subinvestigator should prepare the case report form (CRF) for all subjects who have given consent.

The sponsor or its designee should provide study sites with access authorization to the electronic data capture (hereinafter referred to as EDC). The sponsor should provide the investigator, subinvestigators, and study collaborators with training for utilization of EDC. The CRF will be used to report the information collected during the study period to the sponsor. The CRF will be prepared in Japanese. Data will be directly entered in preparing the CRF.

A change or correction of the CRF will be recorded as an audit trail that records the information before and after the change or correction, the person who made the change or correction, date of change or correction, and its reason.

The investigator or its designee should ensure the accuracy and completeness of the CRF, and provide an electronic signature on the relevant page of the case report form. The investigator bear full responsibility for the accuracy and reliability of all the data entered into the CRF.

The data below will be directly recorded into the CRF.

- Seriousness, severity and causal relationship of adverse event with protocol treatment and “panitumumab”

When the investigator or the subinvestigator makes a change or correction in the data entered into the CRF after fixation of clinical data base, a record (Data Clarification Form) of change or correction in the CRF provided by the sponsor should be used. The investigator should confirm that the record of change or correction in the CRF is accurate and complete, and sign or write name/ affix a seal, and date it.

The sponsor or its designee should confirm CRF has been prepared appropriately. The sponsor or its designee should have access to the medical records of study subjects and in-house records to ensure the accuracy of the CRF as necessary. The completed CRF is the property of the sponsor, and the investigator or the subinvestigator should not disclose the information to a third party without a written permission from the sponsor.

12.2 Time limit for data input into the EDC

The sponsor or its designee should request the investigator or the subinvestigator to promptly enter EDC during the period from enrollment of subject to the end of follow-up.

It is recommended that after consent has been obtained from subject, the EDC should be entered within the time frame described below, in principle. A failure to enter the data within the time frame does not constitute a deviation, but it is recommended that it should be entered as much as possible.

1. At enrollment: within 2 weeks (14 days) after enrollment (within 1 week (7 days) of course 1 of the phase I part of the study (the DLT evaluation period))
2. During protocol treatment: within 2 weeks (14 days) after the final day of each course (the starting day of the next course) (within 1 week (7 days) of course 1 of the phase I part of the study (the DLT evaluation period))
3. At discontinuation of protocol treatment: within 4 weeks (28 days) after the day of discontinuing protocol treatment (within 2 weeks (14 days) of course 1 of the phase I part of the study (the DLT evaluation period))
4. Imaging test results: within two weeks (14 days) after evaluation of efficacy
5. Follow-up period: within two weeks (14 days) after request for follow-up
6. Inquiry about data input items: within two weeks (14 days) from inquiry

12.3 Storage of records

The investigator or the director of study site should store the following materials including those specified in Section 14.1 and study specific documents to be used by the sponsor or its designee for investigation and audit. The materials include a list of subject screening, medical records, signed and dated original consent form, and a record of change and correction of the CRF (copy)/electronic copy of electronic CRF containing audit trail. Also, the investigator and the director of study site should store the essential documents until the date that passes five years after discontinuation or completion of the study. However, when the sponsor requires a longer storage period, the director of the study site will discuss the period and methods of storage with the sponsor.

Further, the investigator and the director of the study site will store the essential documents until the sponsor notifies that storage is no longer necessary.

13.0 STATISTICAL ANALYSIS METHODS

The statistics representative or his/her designee (a personnel belonging to an institution independent from sponsor, analysis personnel) will conduct analysis. Sponsor will not be involved in analysis.

13.1 Statistical and analytical plans

The statistics representative or analysis personnel should start preparing the statistical analysis plan (SAP) (first version) and establish the SAP (first version) before conducting the final analysis. The SAP (first version) should be finalized before data fixation. Detailed definition of endpoints and analysis methods should be specified in the SAP to deal with all the purposes of the study.

Data review should be performed before data fixation. Data review is performed to evaluate the accuracy and completeness of the study data, subject evaluability, and appropriateness of the planned analysis methods.

13.2 Statistical analysis of the phase I part of the study

13.2.1 Analysis set

Two analysis sets will be created for the phase I part of the study: "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 definition subjects included in the DLT evaluation in Section 8.9.2.

13.2.2 Analysis of demographic and other baseline characteristics

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

Demographic factors will be tabulated for each subject. Frequency will be tabulated for discrete data, and summary statistics will be calculated for continuous data.

13.2.3 Safety analysis

13.2.3.1 Primary endpoint and analysis method

[Primary endpoint]
Incidence of DLT with panitumumab + TAS-102 combination therapy

[Analysis method]

The incidence of DLT will evaluated in the DLT evaluation set according to Section 6.1 Study Design (Figure 6.a Outline of study design). In addition, a table listing each DLT event that occurs will be prepared.

13.3 Statistical analysis of the phase II part of the study

13.3.1 Analysis sets

In the phase II part of the study, statistical analysis will be performed in a "full analysis set" and "safety analysis set". The "full analysis set" is the main efficacy analysis set, and is defined as "subjects enrolled in phase I and 2 who received at least one dose of protocol treatment (RD) and satisfied all of the enrollment criteria". Detailed definitions of analysis sets are separately specified in the SAP.

The analysis personnel should finalize the definition of analysis sets and appropriateness of analytical handling rules of the subject data in the analysis sets before data fixation in discussion with the statistics representative.

13.3.2 Analysis of demographic and other baseline characteristics

Perform the following analysis in the "full analysis set".

In the analysis of the main subject demographic factors, frequency will be tabulated for discrete data, and summary statistics will be calculated for continuous data.

13.3.3 Efficacy analysis

13.3.3.1 Primary endpoint and analysis method

[Primary endpoint]
PFS rate 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.

The criteria for determining progression are described in "13.3.3.2 Secondary Endpoints and Analytical Methods for Them".

[Main analysis]
The following analysis will be performed in the "full analysis set".

TBased on the observed PSF rate at 6 months from the day of enrollment, binomial test will be conducted on the null hypothesis "value will be determined invalid at PSF rate ≤ 29%". Significant level will be 2.5% (one-sided) in main analysis. For interval estimation, accurate 90% confidence interval (two-sided) based on binomial distribution will be used.

13.3.3.2 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 all causes whichever comes earlier.

  Progression will include both PD based on diagnostic imaging assessed according to RECIST ver 1.1 (see Appendix A) and primary disease progression that cannot be confirmed by diagnostic imaging (clinical progression). When progression is documented by diagnostic imaging, the day that 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 where, 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 confirming progression-free survival). 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.

[Analysis method]

Show the Kaplan-Meier survival curve until the onset of event in the "full analysis set" and calculate the quartiles for PFS and their 95% confidence intervals (two-sided). The Log-Log conversion of Brookmeyer and Crowley[23)] 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 all causes. For surviving subjects, the period is terminated on the final day of confirming survival 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 (see Appendix A) is either CR or PR. Overall response will be graded by favorability in the order of CR, PR, SD, PD, and 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 all causes, 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 confirming progression-free survival). 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 confirming progression-free survival).

  [Analysis method] Show the Kaplan-Meier survival curve until the onset of event for the subjects who showed response among the "full analysis set" and calculate the point estimation value of survival rate and its 95% confidence interval (two-sided) at the quantile 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 (see Appendix A) 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 all causes whichever comes earlier.

  [Analysis method]

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

13.3.3.3 Data conversion method and handling of missing data

Details are separately determined in the SAP.

13.3.3.4 Level of significance, confidence coefficient

- Significance level: Main analysis only, 10% (two-sided); other analyses, 5% (two-sided)
- Confidence coefficient: Main analysis only, 90% (two-sided); other analyses, 95% (two-sided)

13.3.4 Safety analysis

The following analysis will be performed in the "full analysis set" and "safety analysis set".

13.3.4.1 Treatment-Emergent Adverse Events

Treatment-Emergent Adverse Events (TEAE) are adverse events which develop after initiation of protocol treatment.

Perform the following analysis for TEAE. Code TEAE using MedDRA and summarize by Preferred Term (PT) and System Organ Class (SOC).

- Frequency tabulation of all TEAE
- Frequency tabulation of TEAE for which the causal relationship with protocol treatment was "related"
- Frequency tabulation of all TEAE by severity
- Frequency tabulation of TEAE by severity for which the causal relationship with protocol treatment was "related"
- Frequency tabulation of TEAE for action taken for protocol treatment was "discontinuation"
- Frequency tabulation of serious TEAE

13.4 Criteria for interim analysis and premature discontinuation

No interim analyses are scheduled.

13.5 Determination of the planned number of subjects

See "6.2.2.2 Rationale for planned number of subjects".

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring of study sites

The sponsor or its designee will perform periodic monitoring of study sites during the study to confirm that the study is carried out in accordance with all specifications in the protocol. Central monitoring and site visit monitoring, when necessary, will be performed in this study.

Details of procedures for monitoring will be determined in the separately prepared procedures.

14.1.1 Central monitoring

Central monitoring will be performed to check that the study is safely conducted in accordance with the protocol and that data are accurately collected, based on the data collected by EDC. Central monitoring will be conducted twice a year in principle, and periodic monitoring report will be prepared. Periodic monitoring report will be evaluated by research steering committee and feedback will be given to study sites when necessary.
Detailed procedures for central monitoring will be determined in the separately prepared procedures.

14.1.2 Site visit monitoring

Site visit monitoring is conducted to confirm that the study is carried out safely and in compliance with the protocol and the data are accurately collected by checking the data entered into the EDC against source documents. Source documents are the original documents, data and records. The investigator and the director of study site will ensure that the sponsor or its designee and the ethics review committee, etc., have access to the source documents.

The sponsor or its designee will access the records including the list of subject screening, medical records, signed and dated original consent forms to confirm that the study is appropriately conducted in compliance with the protocol. Also, confirm the consistency between CRF and the related source documents. The investigator and the subinvestigator and other personnel involved in the study will spare sufficient time to facilitate monitoring procedures during visits to the study site.

Prior to site visit monitoring, study sites will be randomly selected to perform Source Documents Verification (SDV) for the enrolled subjects.

The frequency and procedures of study site visit monitoring should follow separately prepared procedure manual.

14.1.3 Deviations from Ethical Guideline for Clinical Research, ICH-GCP, and Protocol

The investigator or the subinvestigator should record all deviations from Ethical Guideline for Clinical Research, ICH-GCP, and protocol.

The investigator or the subinvestigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from ethics review committee, etc. In the event of a deviation or change, the investigator should notify the sponsor and the director of the site of the deviation or change as well as its reason in a written form, and retain a copy of the written form. When necessary, the investigator may consult and agree with the sponsor on a protocol amendment. If the protocol is to be amended, the amendment proposal should be submitted to the director of the site as soon as possible and an approval should be obtained from site committee such as ethics review committee.

14.2 Quality assurance

The sponsor or its designee and site committee such as ethics review committee will perform audit at the study site when necessary. In such a case, the auditor designated by the sponsor should contact the study site in advance to determine the date of audit. The auditor may request a visit to other sites that will be used during the study. The investigator and the director of the study site should ensure that the auditor has access to study-related source documents.

15.0 ETHICAL CONDUCT OF CLINICAL STUDY

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, Ethical Guideline for Clinical Research and the ICH-GCP. Each investigator will conduct the study according to regulatory requirements and in accordance with Appendix B "Responsibilities of the Investigator".

15.1 Approval by the study site committee such as the ethics review committee

The study site committee such as the ethics review committee is constituted according to regulations.

The sponsor or its designee should obtain the document listing the name and title of each committee member.

The sponsor or its designee should provide related documents to the study site committee such as the ethics review committee for review and approval of the protocol. In addition to the protocol, a copy of informed consent form, written materials related to subject recruitment, advertisement, and other documents required by regulation, when necessary, should be submitted to the central committee or the study site committee such as the ethics review committee to obtain approval. The sponsor should notify the study site, the investigator and the subinvestigator after confirming the appropriateness of the regulatory documents of the study site. Protocol procedures such as obtaining consent should not be started until the study site, the investigator and the subinvestigator receive the notification.

The study site should comply with all the requirements specified by the study site committee such as the ethics review committee. The requirements include notifications to committees such as the ethics review committee, for instance, revision of the protocol, revision of the informed consent form, revision of materials related to subject recruitment, report on safety in accordance with the regulatory requirement, report on study implementation state at intervals determined by the study site committee such as the ethics review committee, and study completion report. The sponsor or its designee should obtain written approval from the study site committee such as the ethics review committee related to the above mentioned items and all related materials.

15.2 Conflict of interests

This study will be conducted with support from sponsor. Prior to conduct of the study, the investigator should appropriately manage according to the study site regulation, that this study has no conflict of interests (hereinafter referred to as COI). [24)~28)]

The study site should comply with all the requirements specified by the ethics review committee, etc. The requirements include the COI self-declaration, protocol, and informed consent form.

15.3 Written information and subject's consent

The informed consent form contains specific requirements of the Declaration of Helsinki, Ethical Guideline for Clinical Research and the ICH-GCP and all applicable laws and regulations. The informed consent form specifies the use of personal information and medical information of subjects in this study (both in and outside Japan: supply to a third party), and disclosure. Written explanation explains in detail the general idea and purpose of the study, and its possible risks and benefits. The informed consent form also clarifies the conditions for study participation and states the fact that subjects can discontinue study participation at any time without giving reasons and without loss of benefits in treatment. In principal, the items below are described.

1) Clinical study and informed consent form
2) Disease and condition
3) Method of treatment for disease
4) Name of study and explanation that approval has been obtained from the director of study site for conducting the study
5) Name of research steering committee chairman, study site, and investigator
6) Objective of study and meaning
7) Method of study (including purpose of use of samples/information collected from subject) and study duration
8) The estimated number of patients participating in the study
9) The reason for being selected as subject
10) Burden for the patient and foreseeable risk and benefits
11) Consent for participation
12) Even if consent for carrying out or continuing the study has been given, this can be withdrawn at any time
13) Explanation that the patient can disagree on or withdraw consent for carrying out or continuing the study without loss of benefits
14) Method of information disclosure
15) Explanation that upon request, the patient can obtain and have access to material concerning protocol and method of study, and on the method of obtainment and access within the scope where protection of personal information of other patients and the assurance of originality of the study is not hindered.
16) Handling of personal information (including method of anonymity)
17) Method of storage and destruction of sample/information

18) Status related to funding of study, etc., study site related conflict of interest and personal benefits upon study, etc., study staff related conflict of interest upon study
19) Intellectual property rights
20) Possibility that the data is used for future studies
21) Correspondence to inquiries from patients and persons concerned
22) Expenses
23) Items on other methods of treatment
24) Correspondence to health care provided after study has been conducted
25) Compensation for injuries related to the study and what they consist
26) Issues to be followed
27) Notification of new information and study discontinuation
28) Explanation that on the premises of patients privacy being preserved, monitoring personnel, audit personnel and ethic review committee will have access to sample/information of subjects in the study within the scope of necessity.
29) Explanation that informed consent cannot be obtained from anyone but the patient him or herself.

The investigator is responsible for preparation, content, and the site committee such as ethics review committee approval of the informed consent form. The informed consent form should be approved by the site committee such as ethics review committee before use.

The informed consent form should be written in a language easily understood by subjects. The investigator or the subinvestigator is responsible for providing detailed explanation of the informed consent form to subjects. Information should be provided orally and in writing as much as possible by the method deemed appropriate by the site committee such as ethics review committee.

The investigator or the subinvestigator should ensure that the subjects have (1) an opportunity to inquire about the study and (2) sufficient time to determine study participation. When a subject decides to participate in the study, the subject should sign or write name/affix seal, and date the consent form prior to study participation. The investigator and the subinvestigator should request the subject to sign or write name/affix seal using a legal name and not a popular name with black or blue ballpoint pen. The investigator or the subinvestigator should also sign or write name/affix seal, and date the consent form prior to subject participation. Further, if study collaborator has made complementary explanations, the collaborator should also sign or write name/affix seal, and date the consent form.

The investigator or the subinvestigator should store the original consent form which was signed or contains name/ affixed seal. The investigator or the subinvestigator should document in the subject's medical record the date when the subject signed or wrote name/ affixed seal on the consent form. A

copy of the consent form with signature or name typed with seal affixed should be provided to the subject.

The investigator or the subinvestigator should take the same procedures taken for obtaining the initial consent for newly obtaining consent from the concerned subject when the informed consent form is revised. The date of obtaining new consent should be recorded in the subject's medical record, and a copy of the revised consent form should be provided to the subject.

15.4 Subject confidentiality

The sponsor and its designee should comply with the principles of protection of the subject's right against invasion of privacy. The subject ID code in this study is used to connect the clinical study database and related study documents of the sponsor with the source data of subjects. The limited information of subjects such as sex, age, and date of birth may be used within the scope of all applicable laws and regulations for identification of subjects and confirmation of accuracy of subject ID code.

In compliance with Ethical Guideline for Clinical Research and the ICH-GCP, the sponsor should request the investigator for the access to the original laboratory test data, ECG, record of hospitalization/discharge during study period, and the original medical records such as autopsy report (source data or materials) by a monitor or the person designated by the sponsor, auditor designated by the sponsor, and the ethical committee, etc. The investigator or the subinvestigator should obtain approval from subject concerning access to the original medical records by a monitor when obtaining consent from a subject (see Section 15.3).

When providing a copy of source documents to the sponsor, the investigator or the subinvestigator should delete the information leading to identification of an individual (name and address of subject, other personal information not recorded in CRF of subject).

15.5 Contacts for inquiries from subjects and concerned people

The investigator should establish a contact service to respond to inquiries concerning this study from subjects or concerned people. Details of the contacts for inquiries will be described in the ICF.

15.6 Advantages and disadvantages to subjects

15.6.1 Advantage to subjects

This study is performed as part of normal medical practice, and no advantage is expected by participating in this study.

15.6.2 Disadvantage to subjects

This study is performed as part of normal medical practice, and no disadvantage is expected by participating in this study.

15.7 Attribution of study results and access rights

15.7.1 Attribution of study results

The study results and data obtained from this study belong to the sponsor. The intellectual property rights regarding the pharmaceutical products manufactured and/or distributed by Takeda Pharmaceutical Company Limited also belong to Takeda Pharmaceutical Company Limited. Data generated from this study may be made available for secondary use (e.g., meta-analysis) without any link to personally identifying information only with approval from the research steering committee chairman and the research steering committee.

15.7.2 Data access rights

Access rights for all data and information generated from this study will be given to personnel approved by the sponsor.

15.8 Reporting of results, Publication, disclosure, and clinical study registration policy

15.8.1 Reporting of results, publication and disclosure

The investigator should report to the director of the study site written summary of results of the study and provide the sponsor with all the results and data obtained from the study. Only the sponsor may disclose the study information to other investigators or subinvestigators during the study period except for a case required by laws and regulations. The sponsor will be responsible for publication of

the protocol and study-related results (including the public web site) except for other cases permitted in the study contract.

During study period and after the end of study, the sponsor or its designee should promptly summarize the results and present it to medical journals and academic conferences, etc.

The sponsor may publish the data and information obtained from the study (including the data and information provided by the investigator) based on the agreement with the research steering committee chairman.

The investigator or the subinvestigator should obtain the prior written approval from the sponsor when publishing the information obtained in this study at an academic conference, etc.

The sponsor should report to the director of the study site that final publication of the study result has been made.

15.8.2 Clinical study registration

Takeda Pharmaceutical Company Limited will ensure timely publication of the information of a clinical study and registration of all clinical researches in patients under way all over the world, prior to study initiation, with ClinicalTrials.gov, JAPIC, and UMIN to comply with the applicable laws/regulations and guidelines. The city and country where a study is performed, and the subject recruitment status should be registered as well as the contact information of Takeda Pharmaceutical Company Limited to enable general access.

15.8.3 Clinical trial results disclosure

Takeda Pharmaceutical Company Limited will post the results of a clinical study on ClinicalTrials.gov, JAPIC, and UMIN as specified by the applicable laws and/or regulations irrespective of results.

15.8.4 Method of storage and destruction of material/information concerning clinical study

The director of the study site should appropriately retain the material/information related to this study for at least to the date passing 5 years from the date of reporting of the ending of the study from the investigator or to the date passing 3 years from the date of reporting of final publication of the study result, whichever date is later.

15.9 Insurance and compensation for injury

The subjects participating in this study will be compensated for any injury resulting from participation in the study according to local regulations applicable to the study site. It should be noted that any treatment provided will be covered by health insurance, and no monetary compensation will be provided.

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Appendix A Evaluation according to RECIST ver 1.1

Evaluation will be conducted according to RECIST ver 1.1 as follows.

1. Definition of measurable lesion

   Lesion that fulfills any of the conditions below will be considered as a measurable lesion.

   (1) Lesions other than malignant lymph node (non-nodal lesion) that meet either of the below
      1) CT scan slice thickness no greater than 5 mm or MRI largest diameter at least10 mm
      2) CT scan slice thickness greater than 5 mm or MRI largest diameter is 2 folds or more the slice thickness

   (2) Malignant lymph node CT scan slice thickness 5 mm or less and short diameter at least 15 mm
   (Malignant lymph node with short diameter at least 10 mm and less than 15 mm will be a non-target lesion, lymph node with short diameter of less than 10 mm will not be considered as a lesion)

   Any other lesion besides the above will be considered as non-measurable lesions.

   Note that lesions below will be considered as non-measurable lesions irrespective of test method or size of lesion:

   - Bone lesions
   - Cystic lesions
   - Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy
   - Leptomeningeal disease lesion
   - Ascites, pleural effusion, pericardial effusion
   - Lymphangitic involvement of skin or lung
   - Abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques

2. Baseline documentation of target lesions

   From measurable lesions observed before initiation of protocol treatment, select 5 lesions highest in diameter (long diameter for non-nodal lesion and short diameter for malignant lymph node), 2 lesions at most for 1 organ and determine them as target lesions. Upon selection, organs with measurable lesions should be included evenly, and select in consideration of those that lend themselves to reproducible repeated measurements (lesions with large diameter but difficult to measure should be avoided).

   For chosen target lesion, in order from head to tail, record site, lesion diameters (long diameter for non-nodal target lesions, short axis for nodal target lesion) and a sum of diameters (hereinafter referred to as SoD) of all target lesions should be recorded.

3. Baseline documentation of non-target lesions

   Lesions not selected for target lesion should be recorded as present or absent non-target lesion irrespective of whether measurement is possible or not. Multiple non-target lesions in the same

organ can be recorded as 1 lesion (e.g. multiple enlarged pelvic lymph nodes, multiple liver metastases)

4. Tumor response criteria

   Evaluate target lesion and non-target lesion using the same method as at enrollment according to "9.2.10 Imaging test (thoracoabdominal-pelvic CT/MRI)", and record diameter of target lesion, presence or absence of non-target lesion or onset of new lesion.

5. Response criteria of target lesion

   - CR (Complete Response):

     Disappearance of all non-nodal target lesions and all lymph node target lesions short axis <10mm If nodal target lesion is selected at baseline, response criteria may be CR even though SoD is not 0 mm.

   - PR (Partial Response):

     At least a 30% decrease in the SoD of target lesions, taking as reference the baseline SoD.

   - PD (Progressive Disease):

     Taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), at least a 20% increase in the SoD of target lesions, and the sum must also demonstrate an absolute increase of at least 5 mm.

   - SD (Stable Disease):

     Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest SoD while on study.

   - Not all Evaluated:

     When test cannot be conducted for some reason, or cannot be determined as CR, PR, PD or SD.

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

$$\text{Increase ratio of SoD} = \frac{\text{SoD at evaluation} - \text{Smallest SoD}}{\text{Smallest SoD}} \times 100\%$$

* Diameter of target lesion is recorded with actual measurements (e.g., even if under 5 mm) as much as possible, but when target lesion is determined as "too small to measure", irrespective of CT slice thickness, if it is determined that tumor lesion no longer exists and the diameter will be recorded as 0 mm, whereas if it is determined to exist the diameter will be 5 mm.

* If reduction ratio meets the PR criteria and increase ratio meets the PD criteria at the same time, criteria will be determined as PD.
* If one lesion is divided during treatment, each diameter should be added to the SoD.
* If multiple lesions agglutinate and the border cannot be distinguished, the diameter of the agglutinated lesion should be added to the SoD.
* Whenever lesions are in contact, if the borders of the lesions are distinguishable, the diameter of each lesion should be added to the SoD.

6. Response criteria of non-target lesion
   - CR (Complete Response):
     Disappearance of all non-nodal non-target lesions and all lymph nodes short axis <10mm
   - Non-CR/non-PD:
     Persistence of one or more non-target lesion(s) including lymph nodes short axis ≥ 10 mm and/or maintenance of tumor marker either of which the level is above the common normal limits.
   - PD (Progressive Disease):
     "Unequivocal progression" of existing non-target lesions (including recurrence).
     When the patient has measurable lesion: In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. When response criteria for target lesion is SD or PR, an increase of non-target lesion that will overwhelm the tumor burden decrease will be determined as "unequivocal progression", and if not it will be Non-CR/non-PD.
     When the patient has only non-measurable lesion: a 20% increase diameter in a non-measurable lesion, an increase in tumor burden representing an additional 73% increase in 'volume' will be determined as "unequivocal progression".
   - Not all Evaluated:
     When test cannot be conducted for some reason, or cannot be determined as CR, Non-CR/non-PD, or PD.

7. Appearance of new lesions
   When a lesion that was not present at baseline has been observed after initiation of treatment, this will be determined as appearance of "new lesion". However, "new lesion" should not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. For example, necrosis of a liver lesion may be

reported as a "new" cystic lesion, which it is not. A newly identified lesion in a location by test that was not mandatory at baseline (evaluation before enrollment) is considered a new lesion

If a lesion disappears and reappears later, measurement will be continued. However, the response at the time of reappearance of the lesion will be different depending on other lesions. If lesion has reappeared after CR, it will be determined as PD at the time of reappearance. On the other hand, if it was PR or SD, when the once disappeared lesion reappears, in order to calculate the response, the diameter of the lesion will be added to the rest of the lesions. Thus, when there are a number of lesions still existing, if one lesion apparently "disappears" and reappears later, from that alone, it will not be determined as PD but if the SoD of all the lesions meet the PD criteria, it will be determined as PD. The reason for this is that there is an understanding that most of the lesions do not truly "disappear" and yet it cannot be extracted due to the limit to resolution of imaging modality.

If there is a possibility of new lesion but cannot be confirmed, it should not be determined as a new lesion but re-examination by imaging test should be conducted after clinically appropriate interval. If new lesion is confirmed by imaging test re-examination, the date of the imaging test that confirmed the new lesion will be the time point for appearance of new legion.

8. Overall Response

Overall Response will be determined with combination of target lesion response, non-target lesion response, appearance of new lesion according to Tables A.1 and A.2 below.

Table A.1 Overall response at each time point: When patient has target lesion (with or without non-target lesion)

Target lesion	Non-target lesion	New lesion	Overall response
CR	CR	Absent	CR
CR	Non-CR/non-PD	Absent	PR
CR	Not determined	Absent	PR
PR	Non-PD or defect in evaluation	Absent	PR
SD	Non-PD or defect in evaluation	Absent	SD
Defect in evaluation	Non-PD	Absent	NE
PD	Any	Present or absent	PD
Any	PD	Present or absent	PD
Any	Any	Yes	PD

9. Best Overall Response

   Response will be more favorable in the following order: CR>PR>SD>PD>NE. The most favorable overall response through the entire course will be the best overall response.

   When response could not be determined by imaging due to an obvious aggression of disease or death before the first response determination, it will be determined as PD. When response could not be determined by imaging due to discontinuation from toxicity or rejection by subject before the first response determination, it will be determined as NE.

Appendix B Responsibilities of the investigator

1. To appropriately conduct the study in accordance with the protocol, Ethical Guideline for Clinical Research and the ICH-GCP considering the human rights, safety, and wellbeing of human subjects.
2. When assigning a part of important duties related to this study to subinvestigators or study collaborators, prepare a list of subinvestigators or study collaborators, which will be submitted to the director of study site as necessary.
3. To prepare the informed consent form and revise it as necessary.
4. To check the contents of the study contract.
5. To provide sufficient information on the protocol, drug and duties of each personnel to subinvestigators and study collaborators, and give guidance and supervision.
6. To select subjects who satisfy the protocol, give explanation using written information, and obtain consent in writing.
7. To be responsible for all medical judgments related to the study.
8. Corresponding to request from the director of the study site, report the latest progress status at least once a year to the director of the study site.
9. To request COI committee of each study site to review and approve that there is no COI issues in conducting this study.
10. To ensure together with the director of study site that sufficient medical care is provided to subjects for all study-related clinically problematic adverse events throughout the period of subject's study participation and thereafter.
11. When a subject is treated at another medical institution or department, inform a physician of the medical institution or department in writing of the subject's study participation and study completion/discontinuation after obtaining the subject's consent, and prepare the record.
12. When emergency report of serious adverse events, etc. is required, immediately report it in writing to the director of the study site and the sponsor.
13. To prepare accurate and complete CRF and submit it to the sponsor with an electronic signature.
14. To inspect and check the contents of CRF prepared by subinvestigators, or transcribed by study collaborators from the source data, and submit it to the sponsor with an electronic signature.
15. To discuss a revision of the protocol, etc., when proposed by the sponsor.
16. To report the study completion in writing to the director of study site.