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

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

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

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

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

SAPPHIRE study

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

Sponsor	Takeda Pharmaceutical Company Limited
Protocol number	183/NRP-005
Version number	Version 3
Product name	Panitumumab
Creation date	October 20, 2016

1.0 STUDY ADMINISTRATIVE STRUCTURE AND PRINCIPLES

1.1 Study Administrative Structure

See Appendix for the contacts and study-related responsibilities.

1.2 Principles of the study

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
- International Conference on Harmonisation (ICH) Good Clinical Practice (GCP)
- All applicable laws and regulations, including, without limitation, data privacy laws, conflict of interest guidelines and Ethical Guideline for Clinical Research (the Ministry of Health, Labour and Welfare, revised in 2008)

TABLE OF CONTENTS

Figures and Tables List

2.0 STUDY SUMMARY

Sponsor: Takeda Pharmaceutical Company Limited

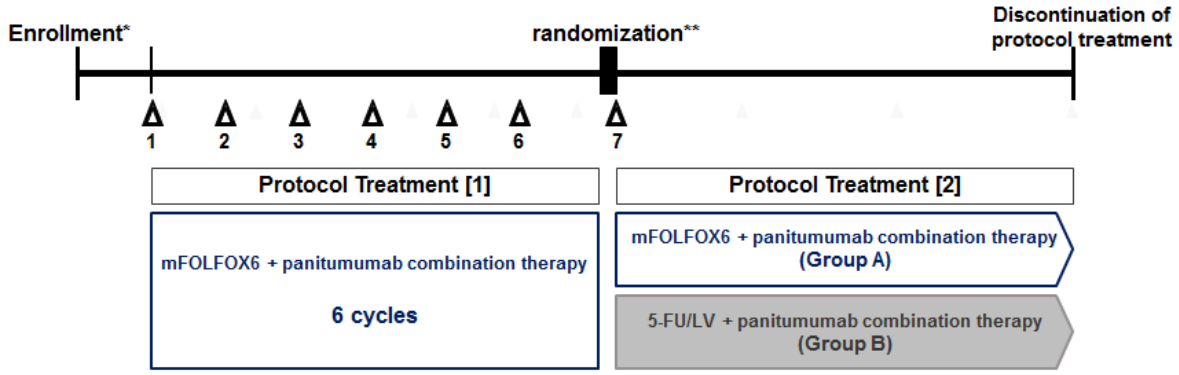
Investigational product: Panitumumab

Study title:
SAPPHIRE study (A phase II randomized study comparing the efficacy and safety of mFOLFOX6 + panitumumab combination therapy and 5-FU/LV + panitumumab combination therapy in the patients with chemotherapy-naïve unresectable advanced recurrent colorectal carcinoma of *KRAS* wild-type after 6 cycles of combination therapy with mFOLFOX6 + panitumumab)

Protocol number: 183/NRP-005

Study type: Exploratory study

Study design:



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

Patinets will be assigned to the Protocol Treatment through minimization using the following as stratification factors: study site, age at enrollment (≥ 20 and ≤ 69, or > 70), the number of metastasized organs (≤ 1, or ≥ 2) and response evaluated in accordance with the Response Evaluation Criteria in Solid Tumors version 1.1 (hereinafter referred to as "RECIST 1.1") criteria as Complete Response (CR), Partial Response (PR) or Stable Disease (SD).

Objective:
To exploratorily examine the efficacy and safety in patients with chemotherapy-naïve unresectable, advanced/recurrent colorectal carcinoma of *KRAS* wild-type who receive 6 cycles (2 weeks per cycle) of first-line mFOLFOX6 + panitumumab combination therapy and are to be assigned to either of the 2 groups, i.e., a group receiving 5-FU/LV + panitumumab combination therapy or a group receiving mFOLFOX6 + panitumumab combination therapy.

Study population:
The patients with chemotherapy-naïve unresectable, advanced/recurrent colorectal carcinoma of *KRAS* wild-type

Planned number of subjects:
100, as the allocated sample size

Group A: 50

Group B: 50

Number of study sites: 40 (planned)

Method of administration:
In both Protocol Treatment [1] and Protocol Treatment [2] (Group A and Group B), 1 cycle consists of 2 weeks, and the respective study drugs will be administered at the following doses according to the following schedule.

Protocol Treatment [1]
mFOLFOX6 + panitumumab combination therapy, once every 2 weeks, 6 cycles
Oxaliplatin (OXA): 85 mg/m^2/day 1
Levofolinate calcium (*l*-LV): 200 mg/m^2/day 1
Bolus 5-FU: 400 mg/m^2/day 1
Infusional 5-FU civ: 2400 mg/m^2/day 1-3
Panitumumab: 6 mg/kg

Protocol Treatment [2]

Group A: mFOLFOX6 + panitumumab combination therapy, once every 2 weeks
OXA: 85 mg/m^2/day 1
l-LV: 200 mg/m^2/day 1
Bolus 5-FU: 400 mg/m^2/day 1
Infusional 5-FU civ: 2400 mg/m^2/day 1-3
Panitumumab: 6 mg/kg
(same treatment as the Protocol Treatment [1])

Group B: 5-FU/LV + panitumumab combination therapy, once every 2 weeks
l-LV: 200 mg/m^2/day 1
Bolus 5-FU: 400 mg/m^2/day 1
Infusional 5-FU civ: 2400 mg/m^2/day 1-3
Panitumumab: 6 mg/kg

Duration of treatment (approximately):
12 months (assumed duration from the day of first administration in Protocol Treatment [1] until becoming Progressive Disease [PD] or intolerance)

Inclusion criteria

Inclusion criteria for enrollment:

(1) Patients with unresectable adenocarcinoma originating in the large intestine (excluding carcinoma of the appendix and anal canal cancer)

(2) Patients with measurable lesion(s) according to the RECIST 1.1criteria (refer to Appendix B)

(3) Chemotherapy-naïve patients. Patients who experience relapse more than 6 months after the final dose of perioperative adjuvant chemotherapy* with fluoropyrimidine agents may be enrolled.

*: Patients who received perioperative adjuvant chemotherapy using OXA may not be enrolled.

(4) Patients aged ≥20 years at enrollment

(5) Patients with confirmed *KRAS* wild-type* tumors
However, the criteria will be changed to all patients with confirmed *KRAS* or Neuroblastoma Rat Sarcoma (*NRAS*) wild-type tumors, when the *KRAS* and *NRAS* tests come to be covered by National Health Insurance, and the tests become feasible at medical institutions.

*: Patients with no mutation in any of the codons shown below are considered 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

**: To be considered when the test comes to be covered by insurance and becomes feasible at medical institutions.

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

1) Neutrophil count ≥ 1.5×10^3/μL

2) White blood cell count ≥ 3.0×10^3/μL

3) Platelet count ≥ $10.0 \times 10^4/\mu L$
4) Hemoglobin ≥ 9.0 g/dL
5) Total bilirubin ≤ 2.0 mg/dL
6) Aspartate aminotransferase (AST) ≤ 100 U/L (≤ 200 U/L if liver metastases are present)
7) Alanine aminotransferase (ALT) ≤ 100 U/L (≤ 200 U/L if liver metastases are present)
8) Serum creatinine ≤ 1.5 mg/dL

(7) Patients graded as 0 or 1in accordance with the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) scale
(8) Patients with life expectancy of ≥ 6 months after enrollment
(9) Patients who provide written informed consent after detailed explanation of the study prior to enrollment

Inclusion criteria for randomization:

(1) Patients who have received 6 cycles* of mFOLFOX6 + panitumumab combination therapy (Protocol Treatment [1])
*: Defined as the use of 5-FU/*l*-LV without dose interruption in all 6 cycles (2 weeks/cycle) of Protocol Treatment [1], in adherence to the specified Protocol Treatment [1] regimen. However, bolus 5-FU and panitumumab may be excluded.
(2) Patients graded as 0 or 1 in accordance with the ECOG-PS during the 6th cycle
(3) Patients whose imagings within 14 days (2 weeks) after the administration day in the 6th cycle are definitely evaluated as other than PD and Not Evaluable in accordance with the RECIST 1.1 criteria (refer to Appendix B)

Exclusion criteria

Exclusion criteria for enrollment:

(1) Patients who have received radiotherapy for a measurable lesion(s)
(2) Patients who received radiotherapy for a lesion(s) other than measurable lesions within 28 days (4 weeks) prior to enrollment. However, the treatment to relieve the pain of metastatic bone tumors is allowed.
(3) Patients with known or strongly suspected brain metastasis
(4) Patients with synchronous or metachronous cancers (other than colorectal cancer) with a disease-free period of ≤ 5 years, excluding mucosal cancers cured or 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, breast-feeding or pregnancy positive
(7) Patients with active hemorrhage requiring blood transfusion
(8) Patients with diseases requiring systemic steroids for treatment (excluding topical steroids)
(9) Patients who have undergone intestinal resection and colostomy within 14 days (2 weeks) prior to enrollment
(10) Patients with history of, or obvious and extensive computerized tomography (CT) findings of interstitial pulmonary disease (interstitial pneumonia, pulmonary fibrosis, etc.)
(11) Patients with serious drug hypersensitivity
(12) Patients with local or systemic active infection requiring treatment, or with a fever indicating infection
(13) Patients with intestinal paralysis, gastrointestinal obstruction, or uncontrollable diarrhoea (incapacitating symptoms despite adequate treatment)
(14) Patients with active hepatitis B and/or C
(15) Patients with known HIV infection
(16) Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study

Exclusion criteria for randomization:

(1) Patients in whom interstitial pneumonia has been newly diagnosed during the period from enrollment to randomization

(2) Patients who have received radiotherapy for a measurable lesion(s) during the period from enrollment to randomization. However, the treatment to relieve the pain of metastatic bone tumors is allowed

(3) Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study

Endpoints:

[Primary endpoint]

- Efficacy

  Progression-Free Survival (PFS) rate at 9 months after randomization

[Secondary endpoints]

- Efficacy
  - PFS duration
  - Overall survival (OS)
  - Response rate (RR)
  - Time to treatment failure (TTF)
- Safety
  - Incidence rate of adverse events (AEs) and the severity by incidence rate
  - Incidence rate of peripheral nerve disorders
  - Incidence rate of skin disorders
- Additional endpoint
  - Duration of Performance Status Maintenance (DPSM)
  - Duration of OXA continuation in mFOLFOX6 + panitumumab group (Group A)
  - Duration of panitumumab continuation in both groups

Statistical method:

The primary objective of this study is to explore the worthiness of a confirmatory study verifying the non-inferiority of the 5-FU/LV + panitumumab arm versus mFOLFOX6 + panitumumab arm, setting the PFS rate at 9 months after randomization as the primary endpoint.

The PFS rate at 9 months after randomization serves as a primary endpoint and is defined as the gross proportion of subjects who survive with no evidence of progression during from the day of randomization (Day 0) until at 9 months after the Day 0. For each treatment group, a binomial test will be performed for the null hypothesis that the PFS rate to determine invalidity will be equal to or less than 30%, based on the PFS rate observed at 9 months after randomization. The main analysis will be at the one-sided 10% significance level. A two-sided 80% confidence interval using Agresti-Coull Method will be applied to the interval estimation.

The PFS duration is defined as the time from the day of randomization (Day 0) until the first evidence of progression, or until death from any cause, whichever comes earlier. For each treatment group, the PFS duration will be illustrated with Kaplan-Meier curves, and the quartile of PFS and its 95% confidence interval (two-sided) will be culculated. At the same time, for the sake of reference, the hazard ratio of Group B versus Group A and its 95% confidence interval (two-sided) will be calculated on the basis of the stratified Cox regression model, and a log-rank test will be performed.

Rationale for planned number of subjects:

This study will be designed as a phase II randomized screening comparative study where direct comparisons are excluded from the primary analysis.

In the phase III study (PRIME Study) in which FOLFOX4 therapy was combined with bi-weekly administration of panitumumab 6 mg/kg as a first-line therapy, the median PFS duration in the patients of KRAS wild-type as the primary endpoint was reported as 9.6 months. Moreover, in the PEAK Study in which panitumumab and bevacizumab were compared as the drugs to be administered in combination with mFOLFOX6 therapy, the median PFS duration in the mFOLFOX6 therapy + panitumumab group was reported as 10.9 months. In these 2 studies, the incidence of events or study withdrawals within 3 months was approximately 10% of the total.

The subject population of this study is patients who can continue OXA administration following 3-month mFOLFOX6 + panitumumab combination therapy. Since the 45% point of PFS duration in the PRIME Study and PEAK Study was approximately 12 months, the median PFS duration in the Group A in this study is expected to be approximately 9 months, which is obtained by subtracting 3 months from the said point. The median PFS duration in the Group B is assumed to be comparable to that in the Group A. Therefore, the expected PFS rates at 9 months after randomization in the 2 groups are both set as 50%. In the meantime, a threshold to consider the worthiness of the study is set as 30%, based on the data previously reported.

In the primary analysis, a binominal test will be performed for the null hypothesis, "a true PFS rate at 9 months after randomization will be equal to or lower than the threshold PFS rate to determin invalidity," in the respective groups based on the PFS rates observed at 9 months after randomization. Given that the threshold PFS rate at 9 months after randomization is 30%, the expected PFS rate is 50%, one-sided significance level is 10% and the power of test is 90%, the required sample size for the both groups will be 44 subjects each. Considering dropouts and study withdrawals, the target sample size to be randomised shall be designed as 50 patients for each group (100 patients in total).

3.0 LIST OF ABBREVIATIONS

Abbreviation	Unabbreviated expression
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ALP	alkaline phosphatase
ASCO	American society of clinical oncology
BRAF	v–raf murine sarcoma viral oncogene homolog B1
BSC	best supportive care
CEA	carcinoembryonic antigen
COI	conflict of interest
CR	complete response
CRO	contract research organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	deepness of response
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
ETS	early tumor shrinkage
FAS	full analysis set
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FFPE	Formalin-Fixed Paraffin-Embedded
G-CSF	granulocyte colony stimulating factor
γ-GTP	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
ICH	International Conference on Harmonisation
INR	International normalized ratio
IRB	institutional review board
JCOG	Japan Clinical Oncology Group
KRAS	Kirsten rat Sarcoma-2 virus
LDH	lactate dehydrogenase
LLN	lower limit of normal
l-LV	Leucovorin
mCRC	metastatic colorectal cancer

Abbreviation	Unabbreviated expression
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
NE	Not Evaluable
NRAS	
OS	Overall survival
OXA	Oxaliplatin
PD	progressive disease
PFS	Progression free survival
PPS	per-protocol analysis set
PR	partial response
PS	performance status
PT	Preferred Term
PI3K	Phosphoinositide 3-kinase
RAS	rat sarcoma
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TTF	Time to Treatment Failure
ULN	upper limit of normal
UMIN-CTR	University Hospital Medical Information Network - Clinical Trials Registry
UPC	urine protein creatinine
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
WT	wild type
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

4.1.1 Etiology of target disease

According to "Cancer Statistics 2013,"[1)] and "Site-specific Cancer Prevalence" in 2008 in Japan, colon cancer was the third most prevalent cancer in men (15.0%) and the second in women (15.1%). According to "Site-specific Cancer Deaths (2012)," in men, lung cancer was the leading cause of cancer death (accounting for 23.9% of cancer deaths), followed by gastric cancer (15.0%) and hepatic cancer (9.3%); 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 (13.8%) was also the leading cause of cancer death, followed by gastric cancer (11.6%) and pancreatic cancer (9.9%); 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 target disease

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 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 chemotherapy regimens for the patients with unresectable, advanced/recurrent colorectal carcinoma necessitating powerful treatment that have been demonstrated to be useful in clinical studies and are currently covered by national health insurance in Japan are presented below. There is a consensus that cetuximab and panitumumab should be used only for *KRAS* wild-type (WT) colorectal cancer.

(1) FOLFOX therapy or CapeOX therapy +bevacizumab[*1]
FOLFOX therapy: combination chemotherapy with fluorouracil (hereinafter referred to as 5-FU), Isovorin (hereinafter referred to as *l*-LV), and oxaliplatin (hereinafter referred to as OXA)
CapeOX therapy: combination chemotherapy with capecitabine and OXA

(2) FOLFIRI therapy + bevacizumab[*1]
FOLFIRI therapy: combination chemotherapy with irinotecan (hereinafter referred to as IRI), 5-FU, and *l*-LV

(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], CapeOX + bevacizumab[*1] or UFT + LV
UFT: combination preparation of tegafur and uracil

*1: Combination with molecular-targeted drugs such as bevacizumab and epidermal growth factor receptor (EGFR) antibody is recommended, but if this cannot be indicated, chemotherapy alone will be provided.
*2: Indicated only for *KRAS* wild-type.
*3: infusional 5-FU + *l*-LV

FOLFOX-based therapy is more frequently selected as first-line chemotherapy 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.

For third-line treatment, regorafenib, trifluridine/ tipiracil hydrochloride (TAS-102) or symptomatic therapy is recommended for cases on anti-EGFR antibodies as the first-line treatment.

4.1.3 Efficacy and safety of mFOLFOX6 in patients with unresectable, advanced/recurrent colorectal cancer

As therapy for unresectable, advanced/recurrent colorectal cancer, regimens mainly based on fluoropyrimidine anticancer agents are considered to be the standard for a long term[3)]. Based on the evidence showing that 5-FU combined with *l*-LV is superior to 5-FU monotherapy, the combination therapy with 5-FU and *l*-LV (hereinafter referred to as 5-FU/LV therapy) had been considered as standard chemotherapy for colorectal cancer for a long time. The type I topoisomerase inhibitor IRI and the third generation of platinum-based anticancer drug OXA were then developed, and have been shown to improve treatment outcome in a number of large scale controlled trials[4) to 9)]. At present, continuous infusion of 5-FU/LV in combination with OXA (FOLFOX therapy) or in combination with IRI (FOLFIRI therapy) is the standard chemotherapy regimen for advanced/recurrent colorectal cancer[3), 10)]. FOLFOX and FOLFIRI therapies were compared in the GERCOR V308 study[9),] in which the median final overall survival (hereinafter referred to as OS) was similar between the precedent FOLFIRI and the precedent FOLFOX arms (21.5 months vs. 20.6 months), and thereby both of the therapies are used as the standard for unresectable colorectal cancer. The development of these therapies provided improvement of the median survival time of unresectable advanced colorectal cancer from 12 months with 5-FU/LV therapy to 20 months or more with 5-FU/LV therapy in combination with IRI or OXA.

Among several FOLFOX regimens, FOLFOX4 therapy and modified FOLFOX6 (hereinafter referred to as mFOLOFX6) therapy, which include OXA at the approved dosage (85 mg/m^2) in Japan, are covered by national health insurance, and simpler and easier mFOLFOX6 therapy is more frequently used.

4.1.4 Efficacy and safety of panitumumab in patients with unresectable, advanced or recurrent colorectal cancer

4.1.4.1 Panitumumab

EGFR, 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 (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.

4.1.4.2 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 (BSC) vs. BSC + panitumumab therapy in patients with unresectable, recurrent or advanced, EGFR-positive colorectal cancer that became resistant to fluoropyrimidine agents, OXA, and IRI (BSC arm, 232 patients; BSC + panitumumab arm, 231 patients) [11]. The primary endpoint of median PFS duration was 8 weeks and significantly longer in the BSC + panitumumab therapy, showing the efficacy of panitumumab therapy as compared with 7.3 weeks in the BSC alone arm (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 arms (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 arm received follow-up therapy with panitumumab.

With regard to 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 1,180 patients (590 in each arm)[12]. The primary endpoint of median PFS in *KRAS* wild-type patients was 9.6 months and significantly longer in the FOLFOX4 + panitumumab arm as compared with 8.0 months in the FOLFOX4 alone arm (HR, 0.80; two-sided 95% CI, 0.66 to 0.97; p = 0.02). Of Grade 3/4 AEs, panitumumab-related adverse events such as dermatologic toxicities, diarrhoea, and hypomagnesaemia occurred more frequently in the FOLFOX4 + panitumumab arm, but there were no major differences in the incidence of other adverse events between the two arms. 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 [13]. The primary endpoints were PFS duration and OS in *KRAS* wild-type patients. In *KRAS* wild-type patients, the median PFS duration was 5.9 months and significantly longer in the FOLFIRI + panitumumab arm than 3.9 months in the FOLFIRI alone arm (HR, 0.73; two-sided 95% CI, 0.59 to 0.90; p = 0.004). On the other hand, OS in the same population was 14.5 months in the FOLFIRI + panitumumab arm and 12.5 months in the FOLFIRI alone arm, with no statistically significant difference between the two arms (HR, 0.85; two-sided 95% CI, 0.70 to 1.04; p = 0.12). The RR was 35% and higher in the FOLFIRI + panitumumab arm

as compared with 10% in the FOLFIRI alone arm. 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 arm; however, there were no major differences in the incidence of toxicities including hematologic toxicities between the two arms, and the incidence of infusion reaction was not more than 1%.

Both the PRIME Study[12)] and Study 20050181[13)] described above, in which *KRAS* mutation status 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.

4.1.4.3 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. Again, in this study, panitumumab showed a good tolerability profile.

In a Japanese phase II clinical study of panitumumab monotherapy[14)], 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 median PFS of 8.0 weeks (two-sided 95% CI: 7.4 to 11.4), and a median 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 incurable/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 Events	Panitumumab Monotherapy (n = 52)			
	All		≥ Grade 3	
	n	%	N	%
Any adverse drug reaction	51	98	6	12
Skin disorder	51	98	3	6
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	
Malaise	13	25	0	
Stomatitis	12	23	0	
Anorexia	11	21	1	2

4.1.4.4 Result of the post-marketing Surveillance (overall survey) in Japan

In a study conducted during a certain post-marketing period by enrolling all patients[15)], the median treatment duration (first day of administration to last day of administration) in 3,085 patients included in safety evaluation was 113 days (range: 1-559 days), and the incidence rate of adverse

drug reactions was 84.1% (≥Grade 3, 25.8%). The incidence rate in 1,254 patients in the group treated with panitumumab monotherapy was 80.1% (≥Grade 3, 19.7%) and that in 1,831 patients in the group treated with panitumumab + chemotherapy was 86.9% (≥Grade 3, 30.0%). The status of occurrence of adverse drug reactions of special interest is shown in Table 4.b.

Table 4.b Adverse Drug Reactions (ADRs) of special interest on Post-marketing survey in Japan

Overall incidence of Post-marketing survey	Panitumumab Monotherapy (n=1,254)				Combination therapy (n=1,831)			
	All		≥ Grade 3		All		≥ Grade 3	
ADRs of special interest	n	%	n	%	n	%	N	%
Skin and 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
Hypomagnesemia	257	20.5	61	4.9	263	14.4	62	3.4
Hypocalcemia	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

* : Based on the evaluation of the Interstitial Lung Disease (ILD) subcommittee

4.1.5 Adverse reactions to OXA

Major dose-limiting toxicities of OXA are neurological manifestations, which are peripheral sensory nerve disorders characterized by dysaesthesia or paraesthesia in four limbs. They may accompany convulsion and are induced by exposure to coldness. Hochster et al.[16] reported that these symptoms appeared in 85% to 95% of the patients who received FOLFOX therapy in combination with bevacizumab, that the duration became longer as the administration frequency increased, and that the incidence of functional disorders after administration of a cumulative dose of 800 mg/m^2 was approximately 15%. In many cases, these neurological manifestations remit or disappear after discontinuation of administration. Acute sensory neurological manifestations appear within several hours after administration, and are induced by exposure to coldness. They may appear as transient paraesthesia, dysaesthesia, hypoaesthesia or acute laryngopharyngeal dysaesthesia syndrome.

In addition to nerve disorders, acute laryngopharyngeal dysaesthesia syndrome is estimated to occur with an incidence of 1% to 2%. It is characterized by respiratory disorders without cyanosis and hypoxia, sensation of dyspnoea without direct effects on the respiratory functions such as dysphagia, decreased SaO_2, laryngospasm, and bronchospasm without wheezing in the upper and lower respiratory tracts. Convulsion in the jaw, abnormal feeling in the tongue, dysarthria, eye pain, and chest pressure sensation are also observed[17]. These symptoms improve reversely without treatment. The incidence of acute laryngopharyngeal dysaesthesia syndrome is suggested to decrease as the duration of administration becomes longer.

Among these adverse reactions, nerve disorders in particular make continuous administration of OXA difficult, and may lead to modification of the FOLFOX therapy regimen involving molecular-targeted drugs. For the patients responding to the therapy, they may miss the patients of important opportunities of treatment (internal data).

4.1.6 Examination of the method of administration of OXA in first-line therapy

Reduction of neurological manifestations associated with FOLFOX as standard chemotherapy for unresectable, advanced/recurrent colorectal carcinoma is urgently needed for improvement of the QOL of patients and for realization of long-term treatment. The reports of Tournigand et al[18]. presented that neurological manifestations was able to recover by setting a certain period of sLV5FU2 therapy without OXA after FOLFOX therapy in the OPTIMOX1 (Stop and Go method) Study. They also presented that hematological toxicity and non-hematological toxicity were highly likely to be reduced during this period. Concerning the treatment effect, the response rate was 59.2% and MST was 21.2 months. Furthermore, the final report of OPTIMOX2 by F Maindrault-Goebel et al.[19] showed that the OS in the administration schedule of OPTIMOX1 (Stop and Go method) was 26 months.

4.2 Rationale for the proposed study

In Japan, mFOLFOX6 therapy is conducted most frequently as the first-line therapy for unresectable, advanced/recurrent colorectal carcinoma. Peripheral nerve disorders induced by OXA contained in mFOLFOX6 therapy may cause a clinical problem because they become a cause of deterioration of the patients' QOL, thereby making continuous treatment impossible. When peripheral nerve disorders as mentioned above have occurred, mFOLFOX6 therapy as the baseline therapy is switched to FOLFIRI therapy in some cases in spite of favorable responses to the first-line therapy, instead of discontinuing OXA which is the cause of peripheral nerve disorders. This is deemed to lead to a loss of the opportunity of treatment for the patients. In the meantime, long-term administration of OXA may induce peripheral nerve disorders. For patients who discontinue administration of OXA after having received the drug for a certain period and who have experienced no peripheral nerve disorders during the treatment period, re-introduction of OXA in the later stage of treatment may remain as a treatment option. With regard to the discontinuaiton and resumption of OXA administration in FOLFOX therapy as the first line therapy at present, the evaluation for efficacy and safety of OPTIMOX study[18] have been presented. However, appropriate administration method of OXA in first-line therapy with mFOLFOX6 + panitumumab has not been revealed.

For these reasons, this study was planned on the basis of the judgment that efficacy and safety in the group in which OXA is discontinued after 6 cycles of the treatment and the group in which OXA is continued need to be examined in the patients responding to mFOLFOX6 + panitumumab combination therapy.

5.0 OBJECTIVE AND ENDPOINTS OF THE STUDY

5.1 Objective

To exploratorily examine efficacy and safety in the patients with chemotherapy-naïve unresectable, advanced/recurrent colorectal carcinoma of *KRAS* wild-type who have been treated with 6 cycles of first-line mFOLFOX6 + panitumumab combination therapy and then assigned to two groups, i.e., a group receiving 5-FU/LV + panitumumab combination therapy and a group receiving mFOLFOX6 + panitumumab combination therapy.

5.2 Endpoints

See Section 13.1.3 for Efficacy analysis.

5.2.1 Primary endpoint

- Efficacy
  - PFS rate at 9 months after randomization

5.2.2 Secondary endpoints

- Efficacy
  - PFS duration
  - OS
  - RR
  - TTF
- Safety
  - Incidence rate of AEs, and the severity by incidence rate
  - Incidence rate of peripheral nerve disorders
  - Incidence rate of skin disorders

5.2.3 Additional endpoint

- DPSM
- Duration of OXA continuation in mFOLFOX6 + panitumumab group (Group A)
- Duration of panitumumab continuation in both groups

5.3 Rationale for the endpoints

5.3.1 Primary endpoint

The PFS is known as a strong surrogate endpoint for predicting treatment effects in OS, as a true endpoint[20]. Accordingly, the PFS was selected as the best indicator for evaluation of efficacy of the regimen with and without OXA after 6 cycles (2 weeks/cycle) of mFOLFOX6 + panitumumab combination therapy without being affected by the after-treatment. In addition, possible reduction in evaluation bias by using the PFS rate with preset time points is known in open-label, phase II, randomized screening controlled studies[21]. Consequently, the PFS rate at 9 months after randomization was employed as the primary endpoint of this study. The time point of 9 months was designed based on the median PFS rate expected in this study population.

5.3.2 Secondary endpoints

As a help for interpretation of primary efficacy results, PFS duration, OS as a true endpoint, RR and TTF were selected as secondary endpoints.

Concerning safety, the appropriateness of continuing and discontinuing OXA and panitumumab was evaluated in an exploratory manner. The incidence rate of adverse events, the incidences of peripheral nerve disorders and skin disorders were selected as secondary endpoints because they are important factors for the choice of treatment.

6.0 STUDY DESIGN

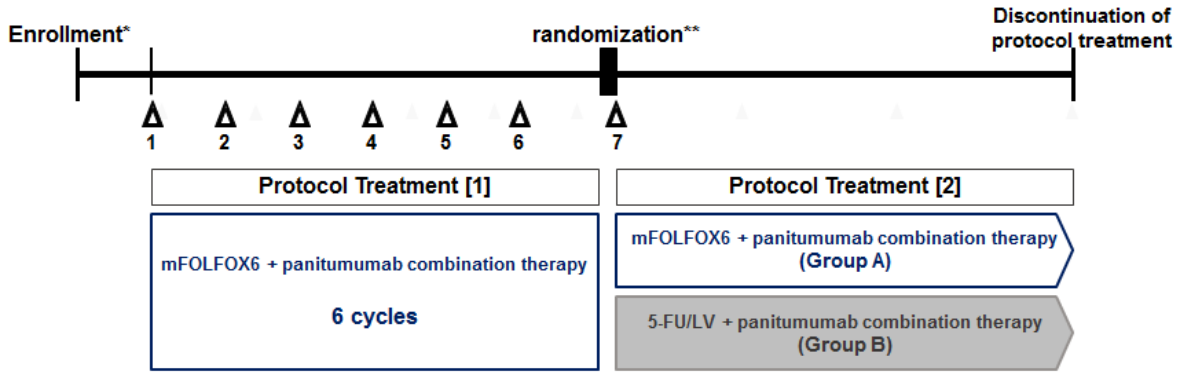
6.1 Study design

This is a phase II, multi-center joint, open-label, parallel-group randomized screening controlled study to exploratorily examine the efficacy and safety in the patients with chemotherapy-naïve unresectable, advanced/recurrent colorectal carcinoma of *KRAS* wild-type after treating them with 6 cycles of mFOLFOX6 + panitumumab combination therapy and subsequently assigning them to a group continuing mFOLFOX6 + panitumumab combination therapy (Group A) and a group in which OXA is discontinued and 5-FU/LV + panitumumab combination therapy is provided (Group B).

The investigator and staff involved in this study (hereinafter referred to as "subinvestigator") enroll patients considered eligible for the study based on the inclusion criteria at enrollment within 14 days (2 weeks) before the first administration (1st cycle), and treat them with 6 cycles of mFOLFOX6 + panitumumab combination therapy (Protocol Treatment [1]). The patients for whom continuation of mFOLFOX6 + panitumumab combination therapy is considered appropriate on the basis of the examination before administration of the 7th cycle and imagings within 14 days after administration of the 6th cycle, who satisfy the inclusion criteria for randomization, and who do not fall under any of the exclusion criteria for randomization will be randomly assigned to either the mFOLFOX6 + panitumumab combination group (Group A) or the 5-FU/LV + panitumumab combination group (Group B) at the ratio of 1:1 before administration of the 7th cycle. After randomization, treatment in Group A or Group B will be continued according to the administration standards for Protocol Treatment [2] until the "8.8. Criteria for discontinuation of protocol treatment" are met. The reasons for randomization criteria failure will be documented. The patients who fail to meet the administration standards for Protocol Treatment based on the examination before administration of the 7th cycle will be examined again after an appropriate interval. The patients who satisfy the subject inclusion criteria on the re-examination will receive the protocol treatment of the assigned group. Both inpatients and outpatients are eligible. Refer to "8.2 Treatment regimen" for details about the protocol treatment ([1] and [2]).

Patinets will be randomized through minimization using the following as stratification factors: study site, age at enrollment (≥ 20 and ≤ 69, or > 70), the number of metastasized organs (≤ 1, or ≥ 2) and response evaluated in accordance with the RECIST 1.1[22] criteria as CR, PR or SD.

See "13.3 Determination of the planned number of subjects" for the number of subjects.



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

Figure 6.a Outline of study design

6.2 Rationale for study design, dose and endpoints

6.2.1 Study population

The timing at which OXA-induced peripheral nerve disorders occurs most frequently has been reported to be the time point at which the accumulated amount of OXA administered reaches 780-850 mg/m^2 [20]. This amount is equivalent to 9 or 10 doses when converted using the dose of 85 mg/m^2 of OXA administered at a time in Protocol Treatment [1] and [2]. According to the report by Hochster et al[16]. who investigated the mean number of doses administered continuously in FOLFOX therapy in initial therapy in routine medical care, the number was 10 times in the FOLFOX + bevacizumab combination therapy in first-line therapy (TREE2). In the report by Giantonio et al.[21], the mean number of doses administered continuously in FOLFOX±bevacizumab combination therapy in the second-line therapy (ECOG3200) for the patients with a history of chemotherapy was 7 to 10 times. This study aims at comparing efficacy and safety in the group continuing OXA from the 7th cycle and the group discontinuing OXA in the patients receiving first-line mFOLFOX6 + panitumumab combination therapy before the occurrence of peripheral nerve disorders. Since the above-described status of the frequency of OXA administration also seems to suggest that discontinuation of OXA after 6th administration in Protocol Treatment [1] does not greatly deviate from the situation in routine medical care, the number of cycles of OXA administration given before randomization was set at 6.

Moreover, since no significant differences were seen in the duration of disease control and PFS duration in OPTIMOX study, the response duration of treatment is not expected to differ significantly between the two groups even when OXA is discontinued after 6 cycles of mFOLFOX6 + panitumumab therapy while 5-FU/LV + panitumumab combination therapy is continued. Furthermore, although concomitant administration of panitumumab does not cause differences in time to treatment failure and PFS duration, discontinuation of OXA before the occurrence of peripheral nerve disorders enables re-introduction of OXA. Therefore, differences larger than in OPTIMOX study may be expected for OS. In addition, it may become possible to propose, for combination therapy of mFOLFOX6 and panitumumab, an approach which enables long-term continuation of treatment through prevention of the occurrence of OXA-induced peripheral nerve disorders.

6.2.2 Treatment regimens and planned number of subjects

See "13.3 Determination of the planned number of subjects" for details.

6.3 Discontinuation of entire study or discontinuation at a study site

6.3.1 Criteria for discontinuation of entire study

The sponsor should immediately discontinue the study when it is notified by the DMC and/or the research steering committee that at least one of the following criteria is applicable.

- Occurrence of serious event/violation which endangers safety of subjects.
- 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.

6.3.2 Procedures of study suspension and discontinuation of entire study or study at a study site

When the sponsor or the Institutional Review Board (IRB) such as the Ethics Review Committee (ERC) determines suspension or discontinuation of the entire study or the study at a certain study site, the sponsor will instruct the procedures specified for the relevant study. The relevant study site should observe the procedures for study suspension or discontinuation.

6.4 Procedures for revision of the protocol

When a need arises to revise the protocol, the sponsor will consult with the research steering committee members to make a decision.

Details of the protocol revision will be notified to investigators of all study sites.

When the investigator of each study site receives the notification, he should arrange the revised protocol to be reviewed by the IRB such as the ERC again as necessary according to the stipulation at each study site and obtain approval of the head of the study site.

7.0 SELECTION OF STUDY SUBJECTS

7.1 Inclusion criteria

7.1.1 Inclusion criteria for enrollment

Patients who satisfy all the criteria below will be enrolled in this study.

(1) Patients with unresectable adenocarcinoma originating in the large intestine (excluding carcinoma of the appendix and anal canal cancer)

(2) Patients with measurable lesion(s) according to the RECIST 1.1criteria (refer to Appendix B)

(3) Chemotherapy-naïve patients. Patients who experience relapse more than 6 months after the final dose of perioperative adjuvant chemotherapy* with fluoropyrimidine agents may be enrolled.

*: Patients who received perioperative adjuvant chemotherapy using OXA may not be enrolled.

(4) Patients aged ≥20 years at enrollment

(5) Patients with confirmed KRAS wild-type* tumors

(6) However, the criteria will be changed to all patients with confirmed KRAS or Neuroblastoma Rat Sarcoma (NRAS) wild-type tumors, when the KRAS and NRAS tests come to be covered by National Health Insurance, and the tests become feasible at medical institutions.

*: Patients with no mutation in any of the codons shown below are considered 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

**: To be considered when the test comes to be covered by insurance and becomes feasible at medical institutions.

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

1) Neutrophil count ≥ $1.5 \times 10^3/\mu L$
2) White blood cell count ≥ $3.0\times 10^3/\mu L$
3) Platelet count ≥ $10.0 \times 10^4/\mu L$
4) Hemoglobin ≥ 9.0 g/dL
5) Total bilirubin ≤ 2.0 mg/dL
6) Aspartate aminotransferase (AST) ≤ 100 U/L (≤ 200 U/L if liver metastases are present)
7) Alanine aminotransferase (ALT) ≤ 100 U/L (≤ 200 U/L if liver metastases are present)
8) Serum creatinine ≤ 1.5 mg/dL

(8) Patients graded as 0 or 1in accordance with the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) scale

(9) Patients with life expectancy of ≥ 6 months after enrollment

(10) Patients who provide written informed consent after detailed explanation of the study prior to enrollment

7.1.2 Inclusion criteria for randomization

Patients who satisfy all the criteria below will be randomized. If possible, randomization will be conducted immediately before administration of the 7th cycle.

(1) Patients who have received 6 cycles* of mFOLFOX6 + panitumumab combination therapy (Protocol Treatment [1])
   *: Defined as the use of 5-FU/l-LV without dose interruption in all 6 cycles (2 weeks/cycle) of Protocol Treatment [1], in adherence to the specified Protocol Treatment [1] regimen. However, bolus 5-FU and panitumumab may be excluded.

(2) Patients graded as 0 or 1 in accordance with the ECOG-PS during the 6th cycle

(3) Patients whose imagings within 14 days (2 weeks) after the administration day in the 6th cycle are definitely evaluated as other than PD and Not Evaluable in accordance with the RECIST 1.1 criteria (refer to Appendix B)

7.2 Exclusion criteria

7.2.1 Exclusion criteria for enrollment

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

(1) Patients who have received radiotherapy for a measurable lesion(s)

(2) Patients who received radiotherapy for a lesion(s) other than measurable lesions within 28 days (4 weeks) prior to enrollment. However, the treatment to relieve the pain of metastatic bone tumors is allowed.

(3) Patients with known or strongly suspected brain metastasis

(4) Patients with synchronous or metachronous cancers (other than colorectal cancer) with a disease-free period of ≤5 years, excluding mucosal cancers cured or 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, breast-feeding or pregnancy positive

(7) Patients with active hemorrhage requiring blood transfusion

(8) Patients with diseases requiring systemic steroids for treatment (excluding topical steroids)

(9) Patients who have undergone intestinal resection and colostomy within 14 days (2 weeks) prior to enrollment

(10) Patients with history of, or obvious and extensive computerized tomography (CT) findings of interstitial pulmonary disease (interstitial pneumonia, pulmonary fibrosis, etc.)

(11) Patients with serious drug hypersensitivity

(12) Patients with local or systemic active infection requiring treatment, or with a fever indicating infection

(13) Patients with intestinal paralysis, gastrointestinal obstruction, or uncontrollable diarrhoea (incapacitating symptoms despite adequate treatment)

(14) Patients with active hepatitis B and/or C

(15) Patients with known HIV infection

(16) Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study

7.2.2 Exclusion criteria for randomization

Patients who meet any of the criteria below will not be randomized.

(1) Patients in whom interstitial pneumonia has been newly diagnosed during the period from enrollment to randomization

(2) Patients who have received radiotherapy for a measurable lesion(s) during the period from enrollment to randomization. However, the treatment to relieve the pain of metastatic bone tumors is allowed

(3) Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study

8.0 TREATMENT

The protocol treatment, contraindicated drugs/therapies, and recommended supportive care/combination therapies in this study are explained in this section. Commercially available drugs used at the study sites will be used in this study. See the latest package insert for details and handling of each drug.

8.1 Protocol treatment

The study period in this study is defined as the period consisting of Protocol Treatment [1] (from obtaining informed consent to Cycle 6) and Protocol Treatment [2] (after randomization).

8.1.1 Protocol Treatment [1]

mFOLFOX6 + panitumumab combination therapy

OXA and infusional 5-FU will be administered in all of the specified 6 cycles (2 weeks/cycle). The dose can be reduced.

Panitumumab will also be administered in all the possible 6 cycles; however dose interruption due to the occurrence of skin disorders will be allowed.

8.1.2 Protocol Treatment [2]

Group A: mFOLFOX6 + panitumumab combination therapy

Group B: 5-FU/LV + panitumumab combination therapy

Dose reduction, interruption and discontinuation of every study drugs are allowed in accordance with "8.5 Criteria for dose change." If the study drugs are partially withdrawn, treatment with the other drugs will be continued unless any of the criteria specified in "8.8 Criteria for discontinuation of protocol treatment" is met.

8.2 Treatment regimen

8.2.1 Protocol Treatment [1]

During the period of Protocol Treatment [1], mFOLFOX6 + panitumumab combination therapy will be given once in two weeks according to the following treatment regimen until any of the criteria specified in "8.8 Criteria for discontinuation of protocol treatment" is met (one administration will be regarded as one cycle). For administration of each drug, see "8.4 Criteria for initiation of protocol treatment (common for Protocol Treatment [1] and [2])" and "8.5 Criteria for dose change".

For the patients aged 80 years or older at the time of enrollment, the drug can be administered at a dose one level lower than the designated dose from Cycle 1.

Table 8.a Treatment regimen of mFOLFOX6 + panitumumab combination therapy

Drug	Dose	Method of administration (recommended)	Date of administration
Panitumumab	6 mg/kg	div 60 min*	Day 1
OXA	85 mg/m^2	div 120 min	Day 1
***l*-LV**	200 mg/m^2	div 120 min	Day 1
5-FU (iv)	400 mg/m^2	iv <15 min	Day 1

5-FU (civ)	2400 mg/m^2	civ 46 hrs	Day 1-2

div: intravenous drip infusion, iv: intravenous infusion, civ: continuous intravenous infusion
*: When the dose at one time exceeds 1000 mg, intravenously administer it over 90 min or longer after dilution with JP physiological saline to make approximately 150 mL.

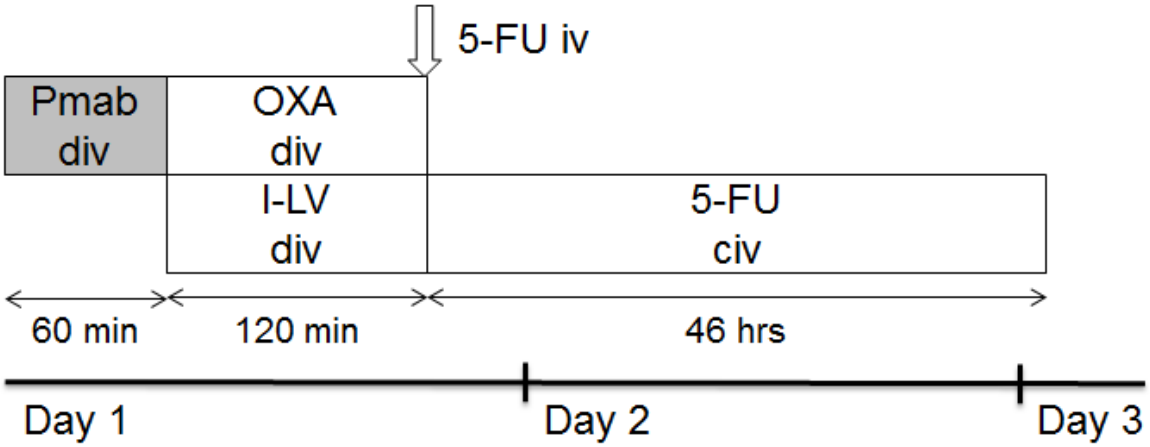


Figure 8.a mFOLFOX6 + panitumumab combination therapy

8.2.2 Protocol Treatment [2]

If the dose of the drug has been reduced during the period of Protocol Treatment [1], the drug will be administered at the reduced dose from Cycle 7.

8.2.2.1 mFOLFOX6 + panitumumab combination therapy (Group A)

See Section 8.2.1 for Protocol Treatment [1]. The term of Protocol Treatment [1] is regarded as Protocol Treatment [2].

8.2.2.2 5-FU/LV + panitumumab combination therapy (Group B)

During the period of Protocol Treatment [2], 5-FU/LV + panitumumab combination therapy will be given once in two weeks according to the following treatment regimen until any of the criteria specified in "8.8 Criteria for discontinuation of protocol treatment" is met (one administration will be regarded as one cycle). For administration of each drug, see "8.4 Criteria for initiation of protocol treatment (common for Protocol Treatment [1] and [2])" and "8.5 Criteria for dose change".

Table 8.b Treatment regimen of 5-FU/LV + panitumumab combination therapy

Drug	Dose	Method of administration (recommended)	Date of administration
Panitumumab	6 mg/kg	div 60 min*	Day 1
***l*-LV**	200 mg/m^2	div 120 min	Day 1
5-FU (iv)	400 mg/m^2	iv < 15 min	Day 1
5-FU (civ)	2400 mg/m^2	civ 46 hrs	Day 1-2

div: intravenous drip infusion, iv: intravenous infusion, civ: continuous intravenous infusion
*: When the dose at one time exceeds 1000 mg, intravenously administer it over 90 min or longer after dilution with JP physiological saline to make approximately 150 mL.

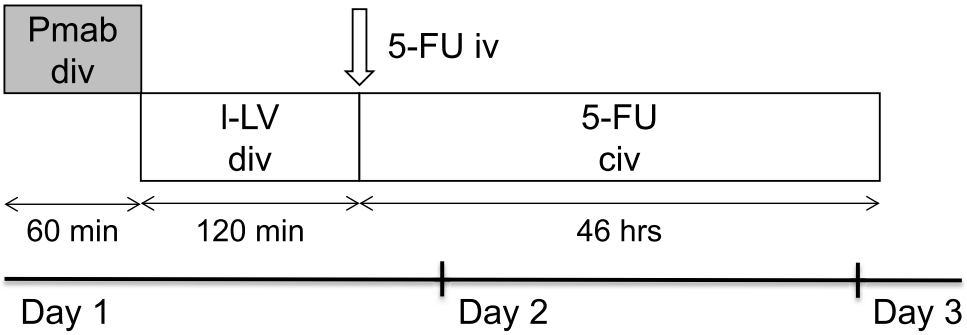


Figure 8.b 5-FU/LV + panitumumab combination therapy

8.3 Recommended dose of protocol treatment

The dose will be calculated based on the body surface area and body weight at the time of study entry. At the time of study entry, the enrollment center will announce the body surface area, which is calculated using the DuBois & DuBois formula, as well as the dose, which is calculated according to the criteria for truncation described below and will serve as the reference value. The dose should be recalculated and confirmed at the study site. The calculated dose of each drug at one time may be adjusted according to the description below. The dose should be recalculated for 10% change in body weight, in principle, but at the discretion of the study site.

Panitumumab : round down in unit of 10 mg

OXA : round down in unit of 10 mg

l-LV : round down in unit of 25 mg

Bolus 5-FU : round down in unit of 50 mg

Infusional 5-FU: round down in unit of 50 mg

8.4 Criteria for initiation of protocol treatment (common for Protocol Treatment [1] and [2])

In principle, the day (Day 13 to 18) 2 weeks after the day of treatment (Day 1) in the previous cycle will be Day 1 of the subsequent cycle. Postponement due to holidays is allowed. It should be confirmed that all of the criteria for initiation of protocol treatment (Table 8.c to Table 8.e) are satisfied on the day of treatment. However, the latest data obtained from 2 days before treatment to the day of treatment may be used for blood tests.

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.

When treatment is postponed, the date of starting treatment after postponement will be designated as Day 1 of the cycle and serve as the reference point for the subsequent schedule.

Protocol treatment should be discontinued when the subsequent cycle of treatment has not been started 28 days later than scheduled (on Day 43 with the date of starting the previous cycle as Day 1). Postponement due to holidays is allowed.

Table 8.c Criteria for initiation of treatment cycle

Item	Criteria for initiation
White blood cell count	≥ 2,500/mm^3
Neutrophil count	≥ 1,200/mm^3
Platelet count	≥ 7.5 x 10^4/mm^3
Total bilirubin	≤ 2.0 mg/dL
Infection	Absence of fever (≥ 38°C) indicating infection
Nausea, vomiting, diarrhoea, stomatitis	≤ Grade 1
Initiation of treatment may be postponed at the discretion of the investigator or subinvestigator due to adverse events not listed above.	

8.5 Criteria for dose change

8.5.1 Protocol Treatment [1]

8.5.1.1 Criteria for dose reduction/suspension of mFOLFOX6

The criteria for dose reduction/suspension and the doses of OXA and 5-FU (bolus/infusional) during the period of Protocol Treatment [1] are shown in Table 8.d and Table 8.e, respectively. The dose of *l*-LV should not be changed.

Table 8.d Criteria for dose reduction/suspension of OXA and 5-FU (Protocol Treatment [1])

Adverse events in previous cycle	Grade	Dose adjustment of OXA and 5-FU
Neutropenia, thrombopenia	4	Dose reduction of both OXA and 5-FU (bolus/infusional) by 1 level
Grade 3 neutropenia or thrombopenia that persists for more than 7 days	3	
Febrile neutropenia, infection, nausea, vomiting, diarrhoea, fatigue	3	
Sensory nerve disorder*	3	Discontinuation of protocol treatment*
	2	Discontinuation of protocol treatment* Or dose reduction of OXA by 1 level
Allergic reaction	3	Discontinuation of protocol treatment*
Dose reduction is allowed as necessary at the discretion of the investigator or subinvestigator due to stipulations/reasons other than above. However, protocol treatment will be discontinued at the time point of suspension of OXA and infusional 5-FU.		

*: When allergic reaction occurs during treatment with OXA, the treatment should be stopped immediately. The decision of restarting this cycle will be entrusted to the study site. If the allergic reaction is Grade 2 or less, protocol treatment with care is allowed under actions such as providing appropriate supportive care or slowing the infusion speed for the treatment after the next course.

Table 8.e Doses of OXA and 5-FU (Protocol Treatment [1])

Dose reduction level	OXA	5-FU iv	5-FU civ
Initial dose	85 mg/m^2	400 mg/m^2	2400 mg/m^2
-1	65 mg/m^2	200 mg/m^2	2000 mg/m^2
-2	50 mg/m^2	0 mg/m^2 (discontinuation**)	1600 mg/m^2
-3	Discontinuation of protocol treatment*	0 mg/m^2 (discontinuation**)	Discontinuation of protocol treatment*

iv: intravenous infusion, civ: continuous intravenous infusion

*: See "8.8 Criteria for discontinuation of protocol treatment" for details.
**: The drug will be withdrawn; however, the Protocol Treatment [1] will be continued.

8.5.1.2 Criteria for dose reduction/suspension of panitumumab

The criteria for dose reduction/suspension and the dose of panitumumab during the period of Protocol Treatment [1] are shown in Table 8.f and Table 8.g, respectively.

Table 8.f Criteria for dose reduction/suspension of panitumumab (Protocol Treatement [1])

Adverse events in previous cycle	Grade	Dose adjustment of panitumumab
Skin disorder	3	Dose reduction by 1 level after a certain washout period. However, treatment at a dose of 6 mg/kg is allowed without dose reduction when it recovers to Grade 2 or milder within 6 weeks.
	2	Dose suspension is allowed. (Suspension is not mandatory.) If the severity after the washout period recovers to the same or milder level than that at onset, the drug will be administered at the same dose before suspension.
	1	
Hypomagnesaemia*	3	Dose reduction by 1 level after a certain washout period. However, treatment at a dose of 6 mg/kg is allowed without dose reduction when it recovers to Grade 2 or milder within 6 weeks.
Infusion reaction, ***	3	Discontinuation of protocol treatment
Dose reduction/suspension is allowed as necessary at the discretion of the investigator or subinvestigator due to stipulations/reasons other than 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
***: The protocol treatment should be stopped immediately upon infusion reactions observed during infusion. The applicability of restarting this cycle should be considered at the study site's discretion. If the infusion reactions are Grade 2 or milder, the cautiously managed protocol treatment may be provided in and after the next cycle, such as providing appropriate supportive care or reducing the infusion rate by 50%.

Table 8.g Dose of panitumumab (Protocol Treatement [1])

Dose reduction level	Panitumumab
Initial dose	6 mg/kg
-1	4.8 mg/kg
-2	3.6 mg/kg
-3	0 mg/kg (discontinuation of protocol treatment)

8.5.2 Protocol Treatment [2]

8.5.2.1 Criteria for dose reduction/suspension of mFOLFOX6

The criteria for dose reduction of OXA and 5-FU (bolus/infusional) during the period of Protocol Treatment [2] is shown in Table 8.h. Refer to Table 8.i for the doses of OXA and 5-FU (bolus/infusional), respectively.

Table 8.h Criteria for dose reduction of OXA and 5-FU (Protocol Treatment [2])

Adverse events in previous cycle	Grade	Dose adjustment of OXA and 5-FU
Neutropenia, thrombopenia	4	Dose reduction of both OXA and 5-FU (bolus/infusional) by 1 level
Grade 3 neutropenia or thrombopenia that persists for more than 7 days	3	
Febrile neutropenia, infection, nausea, vomiting, diarrhoea, fatigue	3	
Sensory nerve disorder	3	Discontinuation of OXA* (no resumption)
	2	Discontinuation* of OXA (no resumption)
Allergic reaction**	3	Discontinuation of OXA* (no resumption)
Dose reduction/suspension is allowed as necessary at the discretion of the investigator or subinvestigator due to stipulations/reasons other than above.		

*: The protocol treatment will be continued until any criterion specified in "8.8 Criteria for discontinuation of protocol treatment" is met.

**: The protocol treatment should be stopped immediately upon allergic reactions observed during administration. The applicability of restarting this cycle should be considered at the study site's discretion. If the allergic reactions are Grade 2 or milder, the cautiously managed protocol treatment may be provided in and after the next cycle, such as providing appropriate supportive care or reducing the dosing speed by 50%.

Table 8.i Doses of OXA and 5-FU (Protocol Treatment [2])

Dose reduction level	OXA	5-FU iv	5-FU civ
Initial dose	85 mg/m^2	400 mg/m^2	2400 mg/m^2
-1	65 mg/m^2	200 mg/m^2	2000 mg/m^2
-2	50 mg/m^2	0 mg/m^2 (discontinuation*)	1600 mg/m^2
-3	0 mg/m^2 (discontinuation)	0 mg/m^2 (discontinuation*)	0 mg/m^2 (discontinuation)

iv: intravenous infusion, civ: continuous intravenous infusion

*: The drug will be withdrawn; however, the Protocol Treatment [2] will be continued.

8.5.2.2 Criteria for dose reduction/suspension of panitumumab

The criteria for dose reduction/suspension and the dose of panitumumab during the period of Protocol Treatment [2] are shown in Table 8.j and Table 8.k, respectively.

Table 8.j Criteria for dose reduction/suspension of panitumumab (Protocol Treatement [2])

Adverse events in previous cycle	Grade	Dose adjustment of panitumumab
Skin disorder	3	Dose reduction by 1 level after a certain washout period. However, treatment at a dose of 6 mg/kg is allowed without dose reduction when it recovers to Grade 2 or milder within 6 weeks.
	2	Dose suspension is allowed. (Suspension is not mandatory.) If the severity after the washout period recovers to the same or milder level than that at onset, the drug will be administered at the same dose before suspension.
	1	
Hypomagnesaemia*	3	Dose reduction by 1 level after a certain washout period. However, treatment at a dose of 6 mg/kg is allowed without dose reduction when it recovers to Grade 2 or milder within 6 weeks.
Infusion reaction** , *****	3	Discontinuation of protocol treatment***
Dose reduction/suspension is allowed as necessary at the discretion of the investigator or subinvestigator due to stipulations/reasons other than 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

***: The protocol treatment will be continued until any criterion specified in "8.8 Criteria for discontinuation of protocol treatment" is met.

****: The protocol treatment should be stopped immediately upon infusion reactions observed during infusion. The applicability of restarting this cycle should be considered at the study site's discretion. If the infusion reactions are Grade 2 or milder, the cautiously managed protocol treatment may be provided in and after the next cycle, such as providing appropriate supportive care or reducing the infusion rate by 50%.

Table 8.k Dose of panitumumab (Protocol Treatement [2])

Dose reduction level	Panitumumab
Initial dose	6 mg/kg
-1	4.8 mg/kg
-2	3.6 mg/kg
-3	0 mg/kg (discontinuation*)

*: The drug will be withdrawn; however, the Protocol Treatment [2] will be continued.

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 Overdose of panitumumab

Overdose of panitumumab is defined as below regardless of whether or not adverse events have occurred.

(1) Administration at doses higher than the approved dose of panitumumab (6 mg/kg)

(2) The next dose is administered within 10 days after the date of previous administration.

Aiming at consistent entry of significant safety information regarding overdose in the database, the investigator or subinvestigator will record all cases of overdose (irrespective of the presence or absence of adverse events) in the page of overdose of the Case Report Forms (CRFs). Adverse events associated with overdose will be recorded in the page of "Adverse Events" in the CRFs according to "10.0 ADVERSE EVENTS".

Serious adverse events (SAEs) associated with overdose will be reported according to the procedure described in "10.2.2. Collection and reporting of serious adverse events."

In the cases of overdose of panitumumab, the investigator or subinvestigator will provide treatment appropriate for the symptoms.

8.8 Criteria for discontinuation of protocol treatment

The protocol treatment specified below 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 decides on discontinuation of protocol treatment. The investigator should record the main reason for discontinuation of protocol treatment in the CRF according to the classification described below. See "9.3 Records of subjects who discontinued before enrollment"for subjects withdrawn from the study before enrollment.

<Common for Protocol Treatment [1] and [2]>

1. AE
   When the protocol treatment is discontinued due to AEs, or when the next protocol treatment cannot be resumed due to AEs for 44 days at longest after Day 1 of the last cycle of the protocol treatment. However, treatment delays due to holidays are allowed.

2. 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 randomization of protocol treatment has not been observed.

3. Lost to follow-up
When a subject fail to make visits and cannot be contacted. That attempts were made to contact the subject should be recorded in the source documents.

4. Voluntary discontinuation
When a subject wishes to discontinue study participation. Reasons for discontinuation should be documented in theCRF as long as they are recognizable.
Note: Efforts to clarify the reasons for voluntary discontinuation should be made as possible. (A discontinuation due to AEs or lack of efficacy is not to be classified as "voluntary discontinuation.")

5. Discontinuation of entire study
When study discontinuation is decided by the sponsor, or IRB such as the ERC.

6. Pregnancy
When a female subject is found out to be pregnant.
Note: Study participation should be immediately discontinued when pregnancy is known.

7. Lack of efficacy
When PD is evident in the clinical or imaging evaluation. The date of PD diagnosis should be documented in the CRF.
In the case of a study withdrawal due to clinical PD, his/her CRF should include the dates of clinical PD diagnosis and subsequent imaging PD diagnosis.

8. Death during protocol treatment
Death before the consideration of protocol treatment discontinuation.

9. When surgery aimed at curative resection (complete resection: R0 resection) of colorectal cancer is scheduledNote that PFS evaluation data (as described below) of a subject withdrawn from this study during the period of Protocol Treatment [2] should be collected to the extent possible.
Data to be collected: all imaging tests after curative resection (dates, methods and results of tests)

10. Other
When the investigator or subinvestigator consider that the protocol treatment should be discontinued. Details should be documented in the CRF.

<Protocol Treatment [1] >

11. When any of the inclusion criteria for randomization fails to be met or any of the exclusion criteria is met.<specify the applicable inclusion/exclusion criteria>

8.9 Contraindicated drugs/therapies

The drugs and therapies shown below are contraindicated from informed consent until 28 days (4 weeks) after discontinuation of protocol treatment. The investigator and/or subinvestigator should instruct the patients not to use any drugs including over-the counter drugs other than the prescribed drugs without prior consultation. The following therapies are allowed to be started without waiting for the specified period only when the scheduled tests are performed until the next treatment upon starting it within 28 days (4weeks) after discontinuation of protocol treatment.

- ✓ Chemotherapy other than protocol treatment
- ✓ Hormone therapy
- ✓ Immunotherapy
  - ➢ Cellular immunotherapy

- ➢ Vaccine therapy
- ➢ Cytokine therapy
- ➢ Biological response modifiers (BRM)
- ➢ Antibody therapy
- ➢ Gene therapy

✓ Other antibody therapy

✓ Radiotherapy

However, the treatment to relieve the pain of metastatic bone tumor is allowed.

✓ Hyperthermia therapy

✓ Denosumab*

*: Use of bisphosphonates is allowed.

✓ Study drug and unapproved drug

8.10 Allowed supportive care and combination medications

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

- Neutropenia
  Administration of G-CSF products is recommended. G-CSF products should be administered according to the NHI indications and should not be prophylactically used.

- Nausea, vomiting
  Premedication including prophylactic administration of antiemetics is allowed. Premedication with 5-HT_3 (serotonin) receptor antagonists, NK1 (neurokinin 1) receptor antagonists, steroids, and antihistamines may be carried out using the method employed at each study site.

- Allergic reaction
  Treatment with adrenal corticosteroids, antihistamines, etc. may be considered at the time of onset or for premedication at the start of protocol treatment. Careful administration of panitumumab by slowing the infusion speed may be considered.

- Interstitial pneumonia
  Interstitial pneumonia should be treated according to the severity (e.g., steroid pulse therapy).

- Other
  Drugs for treatment of adverse events may be coadministered at the discretion of the investigator. 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 when any of panitumumab-related adverse events shown below is observed. The absence of supporting therapy does not constitute a protocol deviation.

- It is recommended that oral minocycline, etc. be administered when skin disorder is observed.

- At the time of onset of skin disorder
  External salicylic acid petrolatum (10%)
  External steroid therapy (example)
  Face: hydrocortisone butyrate (0.1%)
  Trunk: difluprednate (0.05%)

It is recommended the following skin care prophylactically against the skin disorder from the start of protocol treatment [1].
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).

- At the time of onset of 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

8.11 Handling of surgery aimed at curative resection (complete resection: R0 resection) of colorectal cancer

Surgery is recommended for patients who can tolerate curative resection (complete resection: R0 resection) thanks to the antitumor effect after initiation of protocol treatment.

Protocol treatment should be discontinued when surgery aimed at curative resection (complete resection: R0 resection) of colorectal cancer is scheduled, and all tests and observation scheduled at discontinuation of protocol treatment should be conducted (see “9.1 Study calendar”).

8.12 Recommended follow-up therapy

8.12.1 Recommended second-line treatment

- Group A: Administration of bevacizumab in combination with IRI-based chemotherapy is recommended.
- Group B: Readministration of bevacizumab in combination with OXA-based chemotherapy is recommended.

8.12.2 Recommended third-line or subsequent treatment

- Group A: All approved drugs (regorafenib, etc.) should be administered appropriately as best as possible.
- Group B: Administration of bevacizumab in combination with the IRI-based chemotherapy is recommended. After that, all approved drugs (regorafenib, etc.) should be administered appropriately as best as possible.

9.0 PROTOCOL, EVALUATION ITEMS AND PROCEDURES FOR OBSERVATIONS

9.1 Study calendar

The investigator should collect data according to the following procedures. The same investigator should perform tests/observation/evaluation of subjects in principle.

Table 9.a Study calendar (Protocol Treatment [1])

Item	Enrollment	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Discontinuation of protocol treatment*7
Informed consent	●*							
Eligibility	●							
Subject background	●							
Clinical findings (physical examination) *1	●	●	●	●	●	●	●	●
Vital signs*1		●	●	●	●	●	●	●
Height, body weight*1,*2	●		○	○	○	○	○	
ECOG P.S. *1	●	●	●	●	●	●	●	●
Treatment compliance		●	●	●	●	●	●	
Laboratory tests								
Hematology*1	●*3	●	●	●	●	●	●	●
Serum chemistry*1	●*3	●	●	●	●	●	●	●
Tumor markers*1	●*3	●						○*4
Imaging test *1 (thoracoabdominal-pelvic CT/MRI)	●*5	●		●				○*6
NRAS test	●*8							
Adverse Event	—	←			●		→	

●: Mandatory, ○: Perform as necessary

*1: Consent should be obtained before enrollment

*2: Perform before initiation of each cycle of protocol treatment.

*3: The test in Cycle 1 may be skipped if laboratory tests at enrollmentare performed within 2 days before the treatment in Cycle 1. The tests in Cycle 1 should be performed before the treatment in Cycle 1 when the tests at enrollment are performed more than 3 days before the treatment in Cycle 1.

*4: Measure body weight for dose-change.

*5: Measure only when more than 56 days (8 weeks) have passed after the previous measurement.

*6: If the imaging test before enrollment is performed within 14 days prior to Cycle 1, the test of first cycle can be omitted, but an imaging test should be preferably conducted immediately before administration of Cycle 1.

*7: Perform the imaging test within 28 days (4 weeks) after decision on discontinuation for subjects withdrawn from the study for any reason other than PD.

*8: Perform within 28 days (4 weeks) after discontinuation. Perform until the next treatment when it will be startied within 28 days (4weeks) after discontinuation.

*9: Perform the test in the patients who agree to participate in the study before *NRAS* test comes to be covered by insurance, and the patients who agree to participate in the study after *NRAS* test comes to be covered by insurance but before the test becomes feasible at the study site and who give consents to the conduct of the test. The timing of submission of samples does not need to be upon registration.

Table 9.b Study calendar (Protocol Treatment [2])

Item	Randomization	Cycle 7§	Cycle 8	Cycle 9	Cycle 10	Cycle 11~§	9 months after randomization	Discontinuation of protocol treatment*7	Follow-up period *10
Eligibility	●								
Clinical findings (physical examination)*1	●	●	●	●	●	●	●	●	
Vital signs *1		●	●	●	●	●	●	●	
Height, body weight *3		○	○	○	○	○	○		
ECOG P.S.*1		●	●	●	●	●	●	●	
Treatment compliance (incluing the test at discontinuation)		●	●	●	●	●	●	●	
Laboratory tests									
Hematology *1		●*2	●	●	●	●	●	●	
Serum chemistry *1		●*2	●	●	●	●	●	●	
Tumor markers§, *1		●*2				●	○§	○*8	
Imaging test (thoracoabdominal-pelvic CT/MRI)§	●*4					●*5	●*6	○*9	○
Follow-up therapy									●
Survival survey									●
Adverse Event	←				●		→		–

●: Mandatory, ○: Perform as necessary

§: As a rule, tests of tumor markers and imaging tests will be conducted in the (4n + 3)th administration cycle. However, when the administration interval becomes longer because of the criteria for extension of administration period, the tests will be conducted at appropriate timings.

*1: Perform before the initiation of each cycle of protocol treatment.

*2: The test in Cycle 7 may be skipped when the tests in Cycle 7 are performed within 2 days before treatment in Cycle 7.

*3: Measure body weight for dose-change.

*4: Masure between the day within 14 days (2 weeks) after administration in Cycle 6 and randomization.

*5: Two years after the initiation of protocol treatment, the frequency of imaging test will be reduced to once every 112 ± 14 days (16 ± 2 weeks).

*6: Perform the imaging test at 9 months after randomization in addition to the cycles scheduled as the § rule above.

*7: Perform within 28 days (4 weeks) after discontinuation , and also before the initiation of next treatment course if the next course starts within 28 days (4 weeks) after discontinuation.

*8: Perform only when 56 days (8 weeks) or more have passed after the previous measurement.

*9: Perform within 28 days (4 weeks) after discontinuation in only withdrawals for any reason other than PD.

*10: Perform every 6 months (approximately) after discontinuation of protocol treatment.

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

The investigator will perform the following as scheduled in “9.1 Study calendar.”

9.2.1 Informed consent procedure

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

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

A unique subject ID code will be assigned to each subject when explanation is given to obtain consent. The subject ID code will be used throughout the study period.

9.2.2 Procedures for registration and allocation of drugs

9.2.2.1 Procedures for registration and initiation of protocol treatment

The investigator will register subjects according to the following procedures.

1) The investigator or study collaborator should record the necessary items in subject screening list for a subject who was selected to receive explanation for obtaining consent for study enrollment.

2) The investigator or study collaborator should input the necessary items into the Web case registration system* for a subject who has given consent**.

   * : The case registration is temporarily processed on facsimiles using case registration forms until the Web case registration system release. The investigator, subinvestigator or study collaborator provides required descriptions in the case registration forms. The Case Registration Center determines the eligibility based on the provided case registration forms. The results are to be sent from the Case Registration Center to the investigator, subinvestigator or study collaborator by e-mail.

   ** : The study collaborator may input into the Web case registration system by instruction of the investigator.

3) Eligibility of a prospective subject is judged by the Web case registration system and a protocol study group will be assigned when the subject is eligible.

4) The investigator and study collaborator will check the registration result and assigned protocol study group on the Web case registration system. The registration result and assigned protocol study group will be sent via e-mail from the Web case registration system to the investigator and study collaborator.

5) The investigator should start the allocated protocol treatment within 15 days of formal registration (including the same day of week as the day of enrollment).

6) The investigator or study collaborator should immediately contact the sponsor and input necessary items in the Web subject registration system when the study drug is not administered for reasons such as withdrawal of consent after allocation, or when a change related to allocation is made to the data of the registered subject.

9.2.2.2 Preparation of allocation and storage procedures

The statistical analysis manager (or its designees) should prepare the allocation procedures and manage allocation information of subjects. Dynamic allocation by minimization will be applied to protocol treatment allocaion, using the following as stratification factors: study site, age at enrollment (≥ 20 and ≤ 69, or > 70), the number of metastasized organs (≤ 1, or ≥ 2) and response evaluated in accordance with the RECIST 1.1 criteria (CR, PR or SD). The allocation information should be accessible only by personnel with independent authorization from the statistical analysis manager or its designees.

9.2.3 Subject demographics

The following demographic data will be collected: date of birth and sex at the time of enrollment.

The following data concerning the target disease of colorectal cancer will be collected.

1) Tissue type
The tissue type will be assessed based on the histological findings in the "Japanese Classification of Colorectal Carcinoma" and recorded in the CRF with the date and site of sampling for diagnosis.

   - Date of initial diagnosis
   - Date of diagnosis of Stage 4 (no need for CRF data entry when it is the day of the initial diagnosis)

2) History of treatment

   - History of surgery
     - For subjects with a history of surgery, the date of surgery, surgery site (primary/metastatic lesion), and the number of lymph nodes resected. Endoscopic surgery, which is not considered a history of surgery, should not be entered into the CRF.
   - History of radiotherapy
     - For subjects with a history of radiotherapy, the final irradiated date.
   - History of preoperative and/or postoperative adjuvant chemotherapy
     - For subjects with a history of adjuvant chemotherapy, the type of preoperative and/or postoperative adjuvant chemotherapy, date of final treatment.

3) Information on metastatic organ

   - Number of metastatic organs (0, 1, 2 or more)*
     *: The primary lesion/regional lymph node is not included, and the distant lymph node is counted as "one organ" even if there is more than one.
   - Metastatic organs (liver, lung, peritoneum, lymph node*, bone, adrenal gland, skin, other**)
     *: distant lymph node is counted as "one organ" even if there is more than one.
     **: The name of the organ will be recorded in the CRF.

4) Information on primary organ

   - Single/multiple
   - Primary lesion site [ascending colon, transverse colon, descending colon, sigmoid colon, rectosigmoid or rectum (further information as follows will be required for the case of transverse colon: proximal two thirds or distal one third of the transverse colon, or unknown)]

9.2.4 Medical history

A medical history is defined as any clinically problematic disease or symptom that has resolved within one year prior to initiation of protocol treatment. Any notable medical history will be recorded in the CRF.

9.2.5 Current medical condition

A current medical condition is defined as any symptom or disease present at initiation of protocol treatment. Any notable current medical condition will be recorded in 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 current medical condition at the discretion of the investigator.

9.2.6 Clinical findings (physical examination)

The following locations and parts of the body will be examined:
(1) eyes, (2) ears, nose, and throat, (3) cardiovascular system, (4) respiratory system, (5) gastrointestinal system, (6) dermatologic system, (7) extremities, (8) musculoskeletal system, (9) nervous system, (10) lymph nodes, (11) other.

In particular, subjects will be checked for the following symptoms at the physical examination: allergic reaction, fatigue, rash acneiform, dry skin, paronychia, infusion related reaction, palmar-plantar erythrodysaesthesia syndrome, anorexia, diarrhoea, nausea, vomiting, oral mucositis, febrile neutropenia, infection, hemorrhage, pain, peripheral motor neuropathy, peripheral sensory neuropathy, alopecia, thromboembolism, gastrointestinal perforation, pneumonitis, and pulmonary fibrosis.

For diagnosis after initiation of protocol treatment, evaluate the clinically problematic abnormality compared with the result of diagnosis before initiation of protocol treatment.

9.2.7 Body weight and height

Body weight and height will be measured at enrollment. Body weight (kg) will be measured to the first decimal place and rounded off to the first decimal place when the second decimal place is known. Height (cm) determined will be expressed in integer value (rounded off to integer).
In principle, measurement is unnecessary during the treatment period. However, body weight should be measured for dose-change, although CRF recording is unnecessary. In the case of weight loss, which the investigator or subinvestigator considers as a clinical problem, should be classified as an AE and documented in the CRF.

9.2.8 Vital signs

The following vital signs will be measured: body temperature, blood pressure at sitting position (after rest for 5 min or longer) and pulse rate (bpm).

9.2.9 ECOG-PS

ECOG-PS will be assessed according to Table 9.c.

Table 9.c Eastern Cooperative Oncology Group Performance Status (ECOG-PS)

Grade	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

Grade	Definition
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

9.2.10 Treatment compliance (Protocol Treatment [1] and [2] implementation status)

The investigator should record the compliance with protocol treatment in the CRFs as follows:

- When protocol treatment is administered: The dose and the date of treatment should be recorded. The reason for dose reduction should also be recorded when appropriate.
- When any drug used in protocol treatment is suspended: The date of suspension should be recorded.
- When any drug used in protocol treatment is discontinued: The date and reason for discontinuation should be recorded.

9.2.11 Laboratory tests

The laboratory tests performed at each time point during the study are shown in Table 9.d to Table 9.g. The laboratory tests will be performed at each study site.

The investigator or subinvestigator should evaluate the reported laboratory test results. The standard values of laboratory tests are consistent to the "List of Common Reference Ranges" issued by the JCOG.

Table 9.d Laboratory tests performed at enrollment

Hematology	Serum chemistry	Tumor marker
WBC	Total bilirubin	CEA
Neutrophil count	ALT	CA19-9
Platelet count	AST	
Hemoglobin content	Creatinine	

Immunology
HBs antigen
Hepatitis tests including anti-HCV

Table 9.e Laboratory tests performed before the initiationof each cycle(Protocol Treatment [1])

Hematology	Serum chemistry	Tumor marker
WBC*	Total bilirubin*	CEA*, †
Neutrophil count*	ALT*	CA19-9*, †
Platelet count*	AST*	
Hemoglobin content*	Creatinine*	
	Mg	
	ALP	
	LDH	
	Albumin	
	Na	
	K	
	Ca	
	Cl	

*: The tests in Cycle 1 may be skipped when the tests at enrollment are performed within 2 days before the treatment in Cycle 1. The tests in Cycle 1 should be performed before the treatment in Cycle 1 when the tests at enrollment are performed more than 3 days before the treatment in Cycle 1.
†: Measure before the initiation of Cycle 1 only.

Table 9.f Laboratory tests performed before the initiation of each cycle(Protocol Treatment [2])

Hematology	Serum chemistry	Tumor marker
WBC	Total bilirubin	CEA*
Neutrophil count	ALT	CA19-9*
Platelet count	AST	
Hemoglobin content	Creatinine	
	Mg	
	ALP	
	LDH	
	Albumin	
	Na	
	K	
	Ca	
	Cl	

*: Perform every 8 weeks.

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

Hematology	Serum chemistry	Tumor marker
WBC	Total bilirubin	CEA*
Neutrophil count	ALT	CA19-9*
Platelet count	AST	
Hemoglobin content	Creatinine	
	Mg	
	ALP	
	LDH	
	Albumin	
	Na	
	K	
	Ca	
	Cl	

*: Measure only when more than 56 days (8 weeks) have passed after the previous measurement.

9.2.12 Imaging test (thoracoabdominal-pelvic CT/MRI)

An imaging test at enrollment will be performed within 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 28 days prior to enrollment.

During the period of Protocol Treatment [1], the imaging test will be performed before administration in Cycle 1 and Cycle 3. The results of imaging tests before administration in Cycle 1 will be handled as the image data for measurable lesion, and the test will be performed within 14 days prior to initiation of Protocol Treatment [1] (including the same day of week as the day of enrollment). If the imaging test before enrollment is performed within 14 days prior to initiation of Protocol Treatment [1], the imaging test can be omitted, but an imaging test should be preferably conducted immediately before administration in Cycle 1.

The imaging test before administration in Cycle 3 will be performed 14 ± 3 days after administration in Cycle 2.

The imaging test before initiation of Protocol Treatment [2] will be perfoemed within 2 weeks after administration in Cycle 6. It will be performed every 56 ± 14 days (8 ± 2 weeks) after initiation of Protocol Treatment [2], and at 9 months (252 ± 14 days, i.e., 36 ± 2 weeks) after randomization. Two years after the initiation of protocol treatment, the frequency of imaging test will be reduced to once every 112 ± 14 days (16 ± 2 weeks). (See "Table 9.b Study calendar (Protocol Treatment [2])" for details.)

Thoracoabdominal-pelvic CT (in principle, contrast CT with a slice width of 5 mm or less, but MRI is also acceptable) will be used for imaging test, and the modality and the date of imaging test will be recorded in the CRF.

The same modality should be used during protocol treatment throughout the study period.

The investigator should evaluate the test results according to the RECIST 1.1 criteria and record the evaluation results in the CRF.

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

The following data of subjects who shift into the Protocol Treatment [2] and are not associated with imaging evidence of PD shall be collected until death of the relevant subjects or the entire study termination by the Sponsor, even after the initiation of the next treatment course.

- Date of clinical PD diagnosis (for cases without clinical PD diagnosis until discontinuation)
  - Cases with imaging PD diagnosis before clinical PD diagnosis are out of the scope of data collection.
- Date of imaging PD diagnosis
  - The date of imaging PD diagnosis should be documented, regardless of presence/absence of clinical PD evidence.
    The date of last imaging test should be documented for cases without imaging PD diagnosis throughout the follow-up period.
- Last confirmation date of PFS
  - The last confirmation date of PFS should be documented for cases with neither clinical or imaging PD diagnosis throughout the follow-up period.
- Imaging findings
  - All the imaging findings during from the imaging test at discontinuation until imaging PD diagnosis should be documented.

The last confirmation date of PFS should be documented if follow-up is unavailable, due to such as consent withdrawals and losses to follow-up.

9.2.13 *NRAS* test

9.2.13.1 Subjects

The subjects will be the patients who agree to participate in the study before *NRAS* test comes to be covered by insurance, and the patients who agree to participate in the study after *NRAS* test comes to be covered by insurance but before the test becomes feasible at the study site and who give consents to the conduct of the test.

9.2.13.2 Samples and submission

For the patients who have given consent to the test, the tumor tissue samples which have been collected in surgery or biopsy performed prior to informed consent, and which are used for evaluation of *KRAS* will be used for the test. From paraffin-embedded samples, 5-μm slices will be obtained, and 5 pathological samples fixed on slide glasses will be submitted to [redacted]. It is also acceptable to submit samples in the form of paraffin-embedded samples. When paraffin-embedded samples are submitted, [redacted] will prepare a necessary number of slide glass samples, and will return the remaining sample to the study site.

Investigators will use the materials prepared by [redacted] in advance at the beginning of the study and send the samples to [redacted]. Details are described in the written procedure prepared separately. [redacted] will send in advance the materials necessary for storing and sending samples to the study sites where enrollment of study subjects has become possible.

Details regarding submission of tumor tissues will be described in the written procedure prepared separately.

9.2.13.3 Data

Among the subjects specified in "9.2.13.1 Subjects", the investigators will enter the following issues regarding the submitted tumor tissues in the CRFs for the subjects for whom the samples required for the test have been submitted to [redacted]. However, recording of the results of *NRAS* measurement in the CRFs will be unnecessary.

1) Informed consent date

2) Samples submission(Done/Not yet)

3) Are the samples identical to the samples used for the KRAS test (KRAS exon 2)? (Yes/No)

Table 9.h EXON and codon verified on *NRAS* test

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

9.2.14 Surgery aimed at curative resection (complete resection: R0 resection) of colorectal cancer

When surgery is performed for patients who are expected to tolerate curative resection of colorectal cancer during protocol treatment, the operative procedure, date of surgery, and postoperative assessment of residual tumor should be recorded in the CRF. The residual tumor is assessed according to the table shown below, and the histological results of resection specimens should be recorded in the CRF wherever possible. The date when surgery aimed at curative resection (complete resection: R0 resection) of colorectal cancer is scheduled is considered as the date of discontinuation of protocol treatment

When surgery aimed at curative resection is performed in more than one session, the number of sessions should be recorded in the CRF. As for the postoperative assessment of residual tumor, data obtained by the time of initiation of subsequent treatment should be recorded in the CRF. Data generated after initiation of subsequent treatment will be collected through monitoring and assessed by the steering committee for the validity.

Table 9.i Residual tumor after surgical treatment

Classification	Criteria
RX	The presence of residual tumor cannot be assessed.
R0	No residual tumor
R1	Resected, but tumor on the margins of a surgical resection specimen or the radial margin
R2	Macroscopic residual tumor

9.2.15 Survival survey

All subjects will be followed up after discontinuation of protocol treatment to confirm survival of subjects. Survival survey should be continued until a subject dies or the sponsor terminates the study.

- Date of death or date of last confirmation of survival

9.2.16 Follow-up therapy

When follow-up therapy is performed after discontinuation of Protocol Treatment [2], the following information on follow-up therapy should be collected until a subject dies or the sponsor terminates the study.

- Name of regimen (name of drugs used)

9.3 Records of subjects who discontinued before enrollment

For subjects withdrawn from the study before enrollment of protocol treatment, the main reason for discontinuation should be recorded in the CRF according to the following categories.

- Not satisfying at least one of the inclusion criteria or meeting any of the exclusion criteria <specify the applicable inclusion/exclusion criteria>
- Serious deviation from the protocol
- Lost to follow-up
- Voluntary discontinuation <specify the reason>
- Discontinuation of the entire study
- Other <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 all untoward 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 treatment
- Requiring invasive diagnostic treatment
- Requiring discontinuation or change in the dose of protocol treatment (chemotherapy, panitumumab and bevacizumab) or concomitant drugs under use
- Considered unfavorable by the investigator

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. Any adverse events that could not be expressed in medical terminology (name of diagnosis) should be recorded with signs or symptoms observed.

Laboratory test findings:

Abnormal laboratory values and ECG findings are recorded as adverse events when the investigator judges the course to be clinically problematic (in other words, when certain action or treatment is required, or the investigator judges the change to have exceeded the normal physiological variation range of the subject).

Retest and continued monitoring of abnormality are not considered treatment. Also, repeated or additional conduct of non-invasive test for verification, evaluation and monitoring of abnormality are not considered treatment.

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 is recorded as an adverse event and the investigator should record in the CRF that the adverse event as aggravation of the complication (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 should record it so that a reported adverse event name is a change from the baseline (e.g., aggravation of XX).

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. Complications due to a non-urgent surgery should be reported as an adverse event.

PD:

PD should be considered lack of efficacy, not an adverse event. In addition, the single fact of PD does not necessarily constitute an SAE. However, clinical or imaging progression of the preexisting cancer (including new metastasis) is considered an SAE when the severity satisfies any of the criteria for seriousness specified in Section 10.1.3.

Overdose of panitumumab:

Overdose of panitumumab which does not accompany the occurrence of events will not be regarded as adverse events, but the overdose of panitumumab will be recorded in the page of overdose in the CRF. If any events have occurred, they will be recorded as adverse events in the page of adverse events in the CRF.

10.1.3 Serious adverse events

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

1. Results in death during protocol treatment and all deaths irrespective of a causal relationship with protocol 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.

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. Requires inpatient hospitalization or prolongation of existing hospitalization.
   Hospitalization described below is not considered an SAE:
   (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 Noteworthy adverse events for the sponsor

The events listed in "Takeda Medically Significant AE List" in Table 10.a will be handled as noteworthy adverse events by the sponsor irrespective of the severity determined by the principal investigator or investigator. Of the events listed in Table 10.a, the adverse event that the principal investigator or investigator determines to be serious should be handled as an SAE.

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 and defined as follows based on the CTCAE (Japanese edition JCOG version 4.03):

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

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

*: 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 (OXA, 5-FU, or panitumumab) and adverse events 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 with treatment discontinuation (including clinical course after discontinuation). Possibly due to protocol treatment (chemotherapy 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 or panitumumab). Very likely due to other factors such as underlying disease, complications, and concomitant drugs/treatment.

10.1.7 Date of onset

Judge the date of onset of adverse event according to the following criteria:

Adverse event, etc.	Date of onset
Signs, symptoms, diseases (diagnosis name)	Record the date when the subject or the investigator noticed the first signs and symptoms of adverse event.
Asymptomatic disease	Record the date of obtaining a definite diagnosis after conducting a test for diagnosis. Record the date of obtaining a definite diagnosis even when the test findings show old findings or suggest approximate timing of onset.
Aggravation of complications	Record the date when the subject or the investigator noticed the signs and symptoms of adverse event for the first time.
Abnormal laboratory findings after initiation of protocol treatment	Record the date of test where abnormal laboratory values considered clinically problematic were observed.
Abnormality was observed on the test at initiation of protocol treatment, and aggravation was shown on subsequent tests.	Record the date of tests when values were medically judged to be obviously increased and decreased based on the changes in test values.

10.1.8 Date of resolution

The date when the adverse event resolved (or resolved with sequelae). Date of death when a subject died of the concerned adverse event. When recovery cannot be confirmed at study completion, it is considered ongoing.

10.1.9 Incidence

When the investigator considers the first occurrence up to the final remission of a series of adverse events which repeatedly appear to be resolved or recurred as one event (e.g., constipation, diarrhoea, vomiting, etc.), it is considered to be “intermittent”. Other events are considered “ongoing”.

10.1.10 Action taken for protocol treatment

The withdrawal of OXA, 5-FU, or panitumumab in protocol treatment should be documented in the CRF. The treatment discontinuation is defined as follows:

Treatment discontinued	Treatment with OXA, 5-FU, or panitumumab in protocol treatment was discontinued due to the adverse event.
Not applicable	Treatment with OXA, 5-FU, or panitumumab in protocol treatment had already been completed or discontinued by the time of the onset of the adverse event.

10.1.11 Outcome

Outcomes of adverse events are classified as follows:

Category	Criteria for judgment
Recovered	• Disappearance or recovery of symptoms and findings • Laboratory values returned to normal or baseline
Improved	• Severity is improved by one or more grades • Symptoms or findings mostly disappeared
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 • Death not directly caused by the adverse event (AE) but the AE remains unrecovered (no need for recording the date of death in this case)
Recovered with sequelae	• Disability which disturbs daily life
Death	• Direct relationship between death and the AE "Direct relationship" means that the AE is the cause of death, or death is clearly associated with the event. • The outcome of an AE which is not determined (considered or presumed) as a direct cause of death observed within the same subject is not considered as death. • The date of death should be documented when the outcome is death.
Unknown	• Losses to follow-up specified in the protocol after the date of onset, due to change of hospitals, 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 four weeks after discontinuation of protocol treatment.

10.2.1.2 Reporting of adverse events

At each visit, the investigator should assess the onset of subjective symptoms are present. 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 should follow up all subjects who developed adverse events irrespective of a causal relationship with protocol treatment until disappearance of symptoms or return of abnormal laboratory values to the value at initiation/dose reduction of protocol treatment, or until observed changes can be sufficiently explained for other events (persistent/irreversible adverse event, etc.).

All adverse events should be recorded in the CRF. The name of an adverse event, date of onset, date of disappearance, frequency, severity, causal relationship with protocol treatment (unrelated or related), action taken for protocol treatment (chemotherapy and panitumumab), outcome, and seriousness should be recorded.

Follow-up period of adverse events is until recovery of an adverse event, or the investigator judges that further follow-up would not be necessary.

When requested by the representative researcher, the investigator should check the additional necessary information and data and complete recording them in the CRF within the designated period.

10.2.2 Collection and reporting of serious adverse events

When an SAE develops during the period of collecting adverse events, it should be reported according to the following procedures.

When the investigator judges that an SAE has occurred based on the reporting by a subject, etc. and the result of various tests, imaging findings or definitive diagnosis, a report should be submitted to the head of the study site and the representative researcher (see attached sheet for contact information) within one working day and a report should be made via the sponsor to the investigators of other sites jointly performing the clinical study. In addition, the investigator should submit a formal detailed report within 10 calendar days.

The following items are the requisite for reporting within one working day, and other items should be reported as best as possible.

- Study title
- Subject ID code
- Name of study site
- Name of investigator
- Name of the SAE, course (date of onset, reason for the judgment of "serious", protocol treatment given, causal relationship with protocol treatment, course, and outcome)
- Action taken for the SAE (suspension of new enrollment, revision of the written informed consent, newly obtaining consent from other subjects)

10.2.3 Notification of unexpected serious adverse event to joint study sites

Upon receiving a report of an unexpected SAE from the investigator, the head of the study site should ask for opinions from the IRB such as the ERC, add the following information to the report from the investigator, and notify the DMC and the joint study sites of the event-relevant information through the sponsor.

- Date of review by the IRB such as the ERC, summary of review, results, necessary actions, etc.

10.3 Follow-up of serious adverse events

The investigator should follow-up each SAE, etc. until the recovery is confirmed, or the final outcome is determined.

When a change such as alteration of an outcome was made to the report of an SAE, the investigator should submit a report specifying details of the change to the head of the study site and the sponsor. When requested by the sponsor or the IRB such as the ERC, related data owned by the study site (e.g., ECG, laboratory test values, discharge report summary, autopsy findings, etc.) should be provided.

10.4 Reporting of additional information on adverse events

When the sponsor requests the principal investigator or investigator to provide additional information on an adverse event for reporting to regulatory authorities and other agencies, the principal investigator or investigator, after verifying the required additional information, must enter it in an electronic CRF system or submit a written report within the period determined by the sponsor.

10.5 Notification of serious adverse events to IRB such as an ethics review committee and regulatory authorities

Upon receiving a report of an SAE from the investigator, the head of the study site should ask for opinions from the IRB such as the ERC, and notify other joint study sites of the event-relevant information through the sponsor or theCRO.

In the case of an unexpected SAE, the head of the study site shall prepare a written report of the unexpected SAE containing the information reported from the investigator plus the following information, submit the report to the Minister of Health, Labour and Welfare, and notify other joint study sites of the event-relevant information. (The head of the study site may, through the sponsor, make the report to the Minister of Health, Labour and Welfare and the notification to other joint study sites.)

- Actions taken for the SAE
  (e.g., any interruption of enrollment of new subjects, revision of the informed consent form and re-consent from other subjects currently in the study)
- Date reviewed by the IRB such as the ERC, review summary, review results, and necessary actions to be taken, etc.
- Notification to other joint study sites

The sponsor must report unexpected serious side effects and other SAEs applicable to expedited reporting to regulatory authorities, the investigators, and the heads of the study sites, according to the regulations.

The sponsor or the CRO outsourced by the sponsor must submit the expedited report of the unexpected or expected serious side effect to regulatory authorities in compliance with the reporting time frames determined by the regulations after first knowledge of the event or acquisition of the additional information. In addition, the sponsor must submit the expedited report of other important safety information which is expected to greatly affect the risk-benefit of the study drug, continuation of the treatment with the study drug, or continuation of the clinical study, in the same way. The study site will submit the copy of the document of expedited report to the IRB such as the ERC.

11.0 COMMIITTEES ESTABLISHED FOR ADMINISTRATIVE STRUCTURE AND 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 steering committee members and biostatistician, and the sponsor or the person designated by the sponsor will act as the secretariat.

See the supplement for the research steering committee members.
The research steering committee will not be informed of the treatment allocation throughout the study period.

Details of the research steering committee will be specified in a separately prepared SOP.

11.2 Data Monitoring Committee

The Data Monitoring Committee (DMC) will be established according to the ICH E6 (1.25), and the person designated by the sponsor will act as the secretariat. See the supplement for the DMC member.

The DMC will notify a DMC advisory report on continuation/discontinuation of the study and change of the study plan according to the safety analysis results for evaluation 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.

12.0 DATA MANAGEMENT AND STORAGE OF RECORDS

Detailed procedures concerning data management will be specified in the data management plan. Adverse events, medical history, and concurrent conditions should be substituted with the MedDRA terms.

12.1 Case report form

The investigator should prepare CRFs for all subjects who have provided informed consent.

The sponsor or its designee should provide study sites with access authorization to the electronic data capture (EDC). The sponsor should provide the investigator 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 CRFs will be prepared in Japanese. Data will be directly entered into the CRFs.

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, a person who made the change or correction, date of change or correction, and the reason.

The investigator should ensure the accuracy and completeness of the CRFs, and provide an electronic signature on the relevant page of the CRFs. The investigator assumes full responsibility for the accuracy and reliability of all the data entered into the CRFs.

The data below will be directly recorded into the CRFs.

- Severity and causal relationship of adverse event with “OXA”, “5-FU”, or “panitumumab” in protocol treatment

When the investigator makes a change or correction in the data entered into a CRF after clinical database lock, a record of change or correction in the CRF provided by the sponsor (Data Clarification Form) 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 the accuracy and completeness of the CRF during a visit to a study site. The sponsor or its designee should access to the medical records of study subjects and in-house records to ensure the accuracy of the CRFs. The completed CRFs are the property of the sponsor, and the investigator should not divulge the information to a third party other than the regulatory authority without a written permission of the sponsor.

12.2 Time limit for data input into the EDC

It is recommended that data obtained after informed consent be entered into the EDC within the time frame described below, in principle. A failure to enter the data within the time frame does not constitute a deviation, but efforts shall be made to adhere to the time frame.

1) At enrollment: within two weeks after enrollment

2) During protocol treatment: within two weeks after discontinuation of each cycle of protocol treatment

3) At discontinuation of protocol treatment: within four weeks after discontinuation of protocol treatment

4) Imaging findings: within two weeks after evaluation of efficacy

5) Follow-up period: within two weeks after request for follow-up

6) Inquiries about data to be input into the EDC: within two weeks after inquiry

12.3 Storage of records

The investigator or the head of the study site should store the following materials including those specified in Section 12.1 and study specific documents for use by the investigation or audit by the regulatory authority and the sponsor or their designee. 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. The investigator and the head of the study site should store the essential documents to be stored until five years after discontinuation or completion of the study. However, when the sponsor requires a longer storage period, the head of the study site will discuss the period and methods of storage with the sponsor.

The investigator and the head of the study site will store the essential documents to be stored until the sponsor notifies that storage is no longer necessary.

13.0 STATISTICAL ANALYSIS METHODS

The statistical analysis manager and its designees (personnel who belong to a CRO independent from the sponsor; hereinafter refeered to as "statisticians") perform the analyses. The sponsor should not be involved in the analyses.

13.1 Statistical and analytical plans

The statistical analysis manager and statisticians should prepare and finalize the statistical analysis plan (SAP) before data lock. Detailed definition of endpoints and analysis methods should be specified in the SAP to cover all purposes of the study.

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

13.1.1 Analysis set

Two analysis sets, "full analysis set" and "safety population," are used in this study. "Full analysis set" is defined as "randomized subjects," and the "safety population" is defined as "the subjects who received at least one dose of protocol treatment after randomization."

The sponsor should confirm the definition of analysis sets and appropriateness of analytical handling rules of the subject data in the analysis sets before data lock, add handling of problematic issues which have not been prescribed in the planning stage, and finalize the SAP.

13.1.2 Analysis of demographic and other baseline characteristics

The following analysis should be conducted in "full analysis set."

Concerning major subject background factors, frequency analysis should be conducted for numerical data and summary statistics should be calculated for quantitative data for each treatment group and collectively for all treatment groups.

13.1.3 Efficacy analysis

13.1.3.1 Primary endpoint and analysis method

[Primary endpoint]

PFS rate at 9 months after randomization

The PFS rate at 9 months after randomization serves as a primary endpoint and is defined as the gross proportion of subjects who survive with no evidence of progression during from the day of randomization (Day 0) until at 9 months after the Day 0. The presence/absence of PD will be determined based on imaging, consideration as clinical PD or survival research results at 9 months after randomization. The absence of progression includes a case unassociated with image data at 9 months after randomization, as far as the absence of progression is diagnosed by imaging at the latest time point and PFS is subsequently confirmed by imaging at the time point exceeding 9 months.

A subject who does not remain in the study for 9 months after randomization, and then withdraws his/her consent or becomes lost to follow-up will be excluded from the population without progression, although the denominator will include such subject. A diagnosis of progression will comply with the criteria described in "13.1.3.2 Secondary endpoints and analysis method."

[Main analysis]

Perform the following analysis for the “full analysis set.”

For each treatment group, a binomial test will be performed for the null hypothesis that the PFS rate to determine invalidity will be equal to or less than 30%, based on the PFS rate observed at 9 months after randomization. The main analysis will be at the one-sided 10% significance level. A two-sided 95% confidence interval using Agresti-Coull Method will be applied to the interval estimation.

13.1.3.2 Secondary endpoints and analysis method

[Secondary endpoints]

- **PFS** duration

The PFS duration is defined as the time from the day of randomization (Day 0) until the first evidence of progression, or until death from any cause, whichever comes earlier.

Progression includes both PD based on diagnostic imaging according to RECIST 1.1 and progression of the underlying disease which cannot be confirmed on diagnostic imaging (clinical progression). If progression is diagnosed on the basis of diagnostic imaging, the date of the imaging test will be regarded as the date of progression, and the date of clinical judgment will be regarded as the date of progression in the case of clinical progression. Even when a condition is regarded as PD according to the criteria for efficacy evaluation, such as in the cases of extreme shrinkage of the tumor size, but "progression is obviously ruled out" from a clinical point of view, PD according to the efficacy evaluation criteria will be given priority and the condition will be regarded as progression (in this case, clinical judgment will be prioritized with respect to whether or not protocol treatment should be continued). When the condition is not regarded as PD according to the efficacy evaluation criteria but it is obviously deemed as progression from a clinical point of view, the clinical judgment will be prioritized and the condition will be regarded as progression. The study will be cut off for the surviving patients without a diagnosis of progression on the last day of clinical confirmation of the absence of progression (date of last confirmation of progression-free survival; Confirmation of the absence of progression on imaging test and sample test is not essential. Clinical confirmation of the absence of progression at outpatient clinic will suffice. Reporting by telephone only will not be accepted). Even in the cases of protocol treatment discontinuation for such reasons as toxicity and patients' withdrawal in which other treatment has been given in the after-care, events and cutoff will be handled in the same manner. In other words, the timing of discontinuation of treatment or the date of the start of after care will not be regarded as the cut-off dates.

[Analysis method]

In the "full analysis set," the PFS duration will be illustrated with Kaplan-Meier curves, and the quartile of PFS and its 95% confidence interval (two-sided) will be culculated. The 95% confidence interval of the quartile of PFS will be calculated using log-log transformation in accordance with Brookmeyer and Crowley method[25]. At the same time, for the sake of reference, the hazard ratio of Group B versus Group A and its 95% confidence interval (two-sided) will be calculated on the basis of the stratified Cox regression model, and a log-rank test will be performed.

- **OS**

OS is defined as the time from the day of randomization (Day 0) until death by all causes.

[Analysis method]

The same analysis as that for the PFS duration will be performed for OS in the "full analysis set."

- **RR**

RR is defined as the percentage of subjects who have shown CR or PR as the best overall response in accordance with the RECIST 1.1 criteria after randomization. The best overall response will be CR, followed by PR, SD, progression, and nonevaluable.

[Analysis method]

In the "full analysis set," RR and two-sided 95% confidence interval will be calculated for each group. At the same time, for the sake of reference, the difference of RR between the groups (Group B - Group A) and the two-sided 95% confidence interval will be calculated. Agresti-Coull and Agresti-Caffo[26)] methods will be applied to the confidence interval calculations for RR and the difference of RR between the groups, respectively.

- TTF

TTF is defined as the time from the day of randomization (Day 0) until the day of protocol treatment discontinuation determination, the day of PD diagnosis during protocol treatment or death from any cause, whichever comes the earliest.

[Analysis method]

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

13.1.3.3 Other efficacy endpoints

- DPSM

DPSM is defined as the time from the day of randomization (Day 0) until the first evidence of aggravation by 1 or more points in accordance with the PS scale, the day of protocol treatment discontinuation determination or death from any cause, whichever comes the earliest.

[Analysis method]

The same analysis as that for the PFS duration will be performed in the "full analysis set."

- Duration of OXA continuation in mFOLFOX6 + panitumumab group (Group A)

Duration of OXA continuation is defined as the time from the day of randomization (Day 0) until the day of OXA discontinuation determination in the Group A protocol treatment, the day of PD diagnosis or death from any cause, whichever comes the earliest.

[Analysis method]

The same analysis as that for the PFS duration (other than group comparisons) will be performed in the "full analysis set."

- Duration of panitumumab continuation in both groups

Duration of panitumumab continuation is defined as the time from the day of randomization (Day 0) until the day of panitumumab discontinuation determination in the protocol treatment, the day of PD diagnosis or death from any cause, whichever comes the earliest.

[Analysis method]

The same analysis as that for the PFS duration will be performed in the "full analysis set."

13.1.3.4 Data conversion method and handling of missing data

The subjects who without any event experienceat the end of entire study will be classified as cencored cases in the analyses of PFS, OS and TTF.

The cencored day will be the last confirmation day of PFS in the PFS duration analysis, the last confirmation day of survival in the OS analysis, and the initiation day of the last protocol treatment. In DPSM analysis, the cencored day will be the last PS evaluation day for cases without PS aggravation.

Details about the method of conversion of other data and handling of missing data will be specified separately in the SAP.

13.1.3.5 Level of significance, confidence coefficient

- Level of significance: 5%
- Confidence coefficient: 95% (two-sided estimation)

13.1.4 Safety analysis

Perform the following analyses in the “safety population.”

13.1.4.1 Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are the adverse events which developed after initiation of protocol treatment after randomization.

For TEAEs, perform the following analyses for each treatment group. TEAEs should be substituted withthe MedDRA terms to summarize them by Preferred Term (PT) and System Organ Class (SOC).

- Frequency tabulation of all TEAE
- Frequency tabulation of TEAE for which the causal relationship with any of the protocol treatments was judged as “related”
- Frequency tabulation of all TEAE by severity
- Frequency tabulation of TEAE by severity for which the causal relationship with any of protocol treatment was judged as “related”
- Table of TEAE by frequency with the action taken for any of protocol treatment was handled as “discontinuation”
- Frequency tabulation of serious TEAE
- Frequency tabulation of TEAE of peripheral nerve disorders (secondary endpoint)

Peripheral nerve disorders will be defined as the events classified with the preferred term of "peripheral neuropathy" according to the Standardised MedDRA Queries, and skin disorders will be defined as the events classified with the System Organ Class of "Skin and subcutaneous tissue disorders" or the events classified as with the Preferred Term of "paronychia." The interstitial pneumonia will be the events of the Preferred Terms of the MedDRA Standard Search Formula.

13.1.5 Predetermined subgroup analysis

In this study, the following subgroup analysis will be conducted.

- Subgroup analysis based on *NRAS* test

- Subgroup analyses based on the following stratification factors other than study sites: age at enrollment (≥ 20 and ≤ 69, or > 70), the number of metastasized organs (≤ 1, or ≥ 2) and response evaluated in accordance with the RECIST 1.1 criteria (CR/PR/SD).

13.2 Criteria for interim analysis and premature discontinuation

Interim analysis will not be conducted.

13.3 Determination of the planned number of subjects

This study will be designed as a phase II randomized screening comparison study which does not use direct comparison for primary analysis[22].

In the phase III study (PRIME Study) in which FOLFOX4 therapy was combined with bi-weekly administration of panitumumab 6 mg/kg as a first-line therapy, the median PFS in the patients of *KRAS* wild-type as the primary endpoint was reported as 9.6 months[12]. Moreover, in PEAK study[23] in which panitumumab and bevacizumab were compared as the drugs to be administered in combination with mFOLFOX6 therapy, the median PFS in the mFOLFOX6 therapy + panitumumab group was reported as 10.9 months. The percentage of the cases in which any events occurred or the study was cut off within 3 months in PRIME Study and PEAK Study was approximately 10% of all cases.

The subjects of this study will be the patients who receive mFOLFOX6 + panitumumab combination therapy for 3 months, and can continue OXA administration. Since the PFS 40% point in PRIME Study and PEAK Study was approximately 13 months, the median PFS in Group A in this study is expected to be approximately 10 months, which is obtained by subtracting 3 months from the 40% point. The median PFS in Group B is assumed to be comparable to that in Group A.

In the primary analysis, a test based on the method of Brookmeyer-Crowley[24] will be conducted for the null hypothesis, "true median PFS will be lower than the threshold median PFS for judgment as ineffective", separately in Group A and Group B on the basis of the observed median PFS. When the threshold median PFS is regarded as 6 months, true median PFS as 10 months, enrollment period as 12 months, follow-up period as 12 months, one-sided significance level as 5%, and power of test as 80%, the number of subjects required in Group A and Group B will become 54 subjects each. Considering the cases of discontinuation, the target number of subjects to be randomised was set at 60 patients for each group (120 patients in total).

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. During site visit monitoring, the data recorded in EDC are checked against source documents. Source documents are the original documents, data and records. The investigator and the head of study site will ensure that the sponsor or its designee and the IRB such as the ERC have access to the source documents.

The sponsor or its designee will access the records including the subject code list, medical records, signed and dated original consent forms to confirm that the study is appropriately conducted in compliance with the protocol. The investigator and other persons involved in the study will spare sufficient time to facilitate monitoring procedures during visits to the study site.

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.

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

See separately prepared monitoring plan for the frequency and procedures of site visit monitoring.

14.2 Protocol deviations

The investigator should record all deviations from the protocol. When a deviation is disclosed, the investigator will immediately notify the head of study site and the sponsor in writing. Revision of the protocol should be discussed with the sponsor when necessary, and when the protocol is revised, the revised protocol should be submitted to the head of study site and approved by the IRB such as the ERC.

14.3 Quality assurance and regulatory agency inspections

The sponsor or its designee 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 the site of collecting laboratory test samples and other sites to be used during the study. This study may also be audited by overseas regulatory authorities (e.g., Food and Drug Administration [FDA], Medicines and Healthcare Products Regulatory Agency [MHRA]). The study site will immediately notify the sponsor when the study site is contacted by the regulatory authority concerning an audit. The investigator and the head of study site should ensure that the auditor has access to all the source documents listed in Section 14.1.

15.0 ETHICAL CONDUCT OF A STUDY

This study will be conducted in compliance with the protocol, ethical principles based on the Declaration of Helsinki, ICH-GCP and "Ethical Guidelines for Clinical Research" to preserve the interest of study participants (subjects). Each investigator should conduct a study based on the regulatory requirements and in compliance with the “Responsibilities of the investigator” in Attachment A.

15.1 Conflict of interests

Prior to the study, the investigator should obtain the review/approval by the IRB such as the COI committee that this study has no conflict of interests (COI)[25)-29)].

The study site should comply with all the requirements specified by the IRB such as the ERC. The requirements include the COI self-declaration, protocol, and informed consent form.

15.2 Approval by the institutional review board including the ERC

The IRB including the ERC is constituted according to local regulations applicable to the study site. The sponsor or its designee should obtain the document listing the name and title of each IRB member. When the IRB members are directly participating in this study, a document should be obtained that they are not taking part in deliberation and voting.

The sponsor or its designee should provide related documents to the IRB such as the ERC 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 IRB or the IRB of each study site such as the ERC to obtain approval. The sponsor or its designee should obtain written approval of the protocol and the informed consent form from the IRB such as the ERC prior to initiation of protocol treatment. The IRB’s approval document should contain the study title, protocol number, and date of preparation/revision of the concerned study, as well as version numbers and approval dates of other reviewed documents (e.g., informed consent form). The sponsor should notify the study site and the investigator 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 and the investigator receive the notification.

The study site should comply with all the requirements specified by the IRB such as the ERC. The requirements include notifications to the IRB such as the ERC, 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 IRB such as the ERC, and study completion report. The sponsor or its designee should obtain written approval of the abovementioned items and all related materials from the IRB such as the ERC.

15.3 Written information and subject’s consent

The informed consent from contains specific requirements of the Declaration of Helsinki and all applicable laws and regulations. The informed consent from 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 from 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.

The investigator is responsible for preparation, content, and IRB approval of the informed consent form. The informed consent form should be approved by IRB before use.

The informed consent from should be written in a language easily understood by subjects. The investigator is responsible for providing detailed explanation of the informed consent from to subjects. Information should be provided orally and in writing as best as possible by the method deemed appropriate by the IRB.

The investigator 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 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 should also sign or write name/affix seal, and date the consent form prior to subject participation.

The investigator should store the original consent form which was signed or contains name/affixed seal. The investigator 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 name seal affixed should be provided to the subject.

The investigator should take the same procedures as those for obtaining the initial consent to newly obtain consent from the concerned subject when the informed consent from 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.

To confirm that this study is performed in compliance with the protocol, 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, representative regulatory authority, auditor designated by the sponsor, and the IRB. The investigator should obtain approval of subjects concerning access to the original medical records by a monitor and the representative regulatory authority, etc. when obtaining consent from a subject (see Section 15.3).

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

15.5 Advantages and disadvantages to subjects

15.5.1 Advantage to subjects

This study is performed as part of routine clinical practice, and no advantage is expected by participation in this study.

15.5.2 Disadvantage to subjects

This study is performed in the scope of ordinary medical examination, and no disadvantage is expected by participation in this study.

15.6 Publication, disclosure, and clinical trial registration policy

15.6.1 Publication and disclosure

The investigator should 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 regulatory authorities 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.

The sponsor may make public the data and information obtained from the study (including the data and information provided by the investigator) based on the agreement with the representative researcher.

The investigator should obtain the prior written consent of the sponsor when making public the information obtained in this study at a specialized academic meeting, etc.

15.6.2 Clinical trial 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 at least to the Clinical Trials.gov and public web site (UMIN-CTR) to comply with the applicable laws/regulations and guidelines. The city and country where a study is performed, and the subject recruitment state should be registered as well as the contact information of Takeda Pharmaceutical Company Limited. to enable general access.

15.6.3 Clinical trial results disclosure

Takeda Pharmaceutical Company Limited. will post the results of a clinical study at the Clinical Trials.gov and public web site (UMIN-CTR) as specified by the applicable laws and regulations irrespective of results.

15.7 Attribution of study results and intellectual property rights

The study results generated in this study belong to Takeda Pharmaceutical Company Limited. 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 permission from the representative researcher and the research steering committee.

15.8 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.

16.0 REFERENCES

1 The Editorial Board of Cancer Statistics in Japan. Cancer Statistics in Japan 2013. Foundation for Promotion of Cancer Research: 2013.

2 Japanese Society for Cancer of the Colon and Rectum (JSCCR). JSCCR Guidelines 2014 for the Treatment of Colorectal Cancer.

3 Moertel CG. Chemotherapy for colorectal cancer. N Engl J Med. 1994;330(16):1136-42.

4 Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med. 2000;343(13):905-14.

5 Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet. 2000;355(9209):1041-7.

6 de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000;18(16):2938-47.

7 Rothenberg ML, Oza AM, Bigelow RH, Berlin JD, Marshall JL, Ramanathan RK, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. J Clin Oncol. 2003;21(11):2059-69.

8 Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol. 2004;22(1):23-30.

9 Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004;22(2):229-37.

10 National Comprehensive CancerNetwork. Clinical Practice Guidelines in Oncology. Colon Cancer verslon 3, 2013

11 Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007;25(13):1658-64.

12 Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol. 2010;28(31):4697-705.

13 Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol. 2010;28(31):4706-13.

14 Muro K, Yoshino T, Doi T, Shirao K, Takiuchi H, Hamamoto Y, et al. A phase 2 clinical trial of panitumumab monotherapy in Japanese patients with metastatic colorectal cancer. Jpn J Clin Oncol. 2009;39(5):321-6.

15 Boku N, Sugihara K, Kitagawa Y, Hatake K, Gemma A, Yamazaki N, et al. Panitumumab in Japanese Patients with Unresectable Colorectal Cancer: A Post-marketing Surveillance Study of 3085 Patients. Jpn J Clin Oncol. 2014;44(3):214-223.

16 Hochster HS, Hart LL, Ramanathan RK, Hainsworth JD, Hedrick EE, Childs BH. Safety and efficacy of oxaliplatin/fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer (mCRC): Final analysis of the TREE-Study. J Clin Oncol 2006;24(18S) 3510.

17 Summary of product characteristics, December 2003: Sanofi-Synthelabo.

18 Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, et al. OPTIMOX1:A Randomized Study of FOLFOX4 or FOLFOX7 With Oxaliplatin in a Stop-and-Go Fashion in Advanced Colorectal Cancer—A GERCOR Study. J Clin Oncol 2006;24(3):394-400.

19 Maindrault-Goebel F, et al. Final results of OPTIMOX2, a large randomized phase Ⅱ study of maintenance herapy or chemotherapy–free intervals(CFI) after FOLFOX in patients with metastatic colorectal cancer(MRC) : A GERCOR study. ASCO Meeting Abstructs, Jun 2007;25:4013.

20 Saif MW, Reardon J. Management of oxaliplatin-induced peripheral neuropathy. Therapeutics and Clinical Risk Management 2005;1(4):249–258.

21 Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007;25(12):1539-44.

22 Buyse M. Randomized designs for early trials of new cancer treatments - an overview. Drug Inf J 2000; 34: 387-396.

23 Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, et al. PEAK: A Randomized, Multicenter Phase II Study of Panitumumab Plus Modified Fluorouracil, Leucovorin, and Oxaliplatin (mFOLFOX6) or Bevacizumab Plus mFOLFOX6 in Patients With Previously Untreated, Unresectable, Wild-Type KRAS Exon 2 Metastatic Colorectal Cancer. J Clin Oncol. 2014.

24 Brookmeyer R and Crowley, JJ. A confidence interval for the median survival time. Biometrics 1982; 38: 29-41.

25 Report of the Working Group on Conflict of Interest (Ministry of Education, Culture, Sports, Science and Technology dated November 1, 2002)

26 Guidelines for determining the conflict of interest polity for clinical researches (Review group for ethical aspects of clinical researches and conflict of interest, March 2006)

27 Guidelines on the Management of Conflict of Interest (COI) in Health and Labour Sciences Research (March 31, 2008)

28 Guidelines for management of COI in medical reserach (COI Committee of Japan Association of Medical Sciences, February 2011)

29 Common guidelines for conflict of interest (COI) in clinical research (Japanese Society of Internal Medicine, Japan Society of Hepatology, Japanese Circulation Society, Japan Endocrine Society, Japan Diabetes Society, Japanese Respiratory Society, Japanese Society of Hematology, Japanese Society of Allergology, Japanese Association for Infectious Diseases, August 2011)

Appendix A Responsibilities of the investigator

1 To appropriately conduct the clinical study in compliance with the protocol and in consideration of the human rights, safety and welfare of subjects.

2 To request COI committee of each study site to review and approve that there is no COI issues with this study.

3 When assigning a part of important duties related to this study to subinvestigators or study collaborators, prepare a list of assigned duties and persons, submit it in advance to the head of study site, and to obtain approval.

4 To prepare the informed consent form and revise it as necessary.

5 To check the contents of the study contract.

6 To provide sufficient information on the protocol, drug and duties of each person to subinvestigators and study collaborators, and to provide them with guidance and supervision.

7 To select subjects who satisfy the protocol, give explanation using written information, and obtain consent in writing.

8 To be responsible for all medical judgments related to the study.

9 To ensure together with the head 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.

10 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 then prepare the record.

11 When an emergency report of SAEs, etc. is required, immediately report it in writing to the head of the study site and the sponsor.

12 To prepare accurate and complete EDC and submit it to the sponsor with an electronic signature.

13 To inspect and check the contents of EDC prepared by subinvestigators, or transcribed by study collaborators from the source data, and submit it to the sponsor with an electronic signature.

14 To discuss a revision of the protocol, etc. when proposed by the sponsor.

15 To report the study completion in writing to the head of study site.

SAPPHIRE study

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

Sponsor	Takeda Pharmaceutical Company Limited
Protocol number	183/NRP-005
Product name	Panitumumab
Creation date	March 19, 2015

1.0 STUDY ADMINISTRATIVE STRUCTURE AND PRINCIPLES

1.1 Study Administrative Structure

See Appendix for the contacts and study-related responsibilities.

1.2 Principles of the study

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.
- International Conference on Harmonisation E6 Good Clinical Practice (hereinafter referred to as "GCP").
- All applicable laws and regulations, including, without limitation, data privacy laws, conflict of interest guidelines, Ethical Guideline for Clinical Research (the Ministry of Health, Labour and Welfare, revised in 2008).

TABLE OF CONTENTS

Figures and Tables List

2.0 STUDY SUMMARY

Sponsor: Takeda Pharmaceutical Company Limited

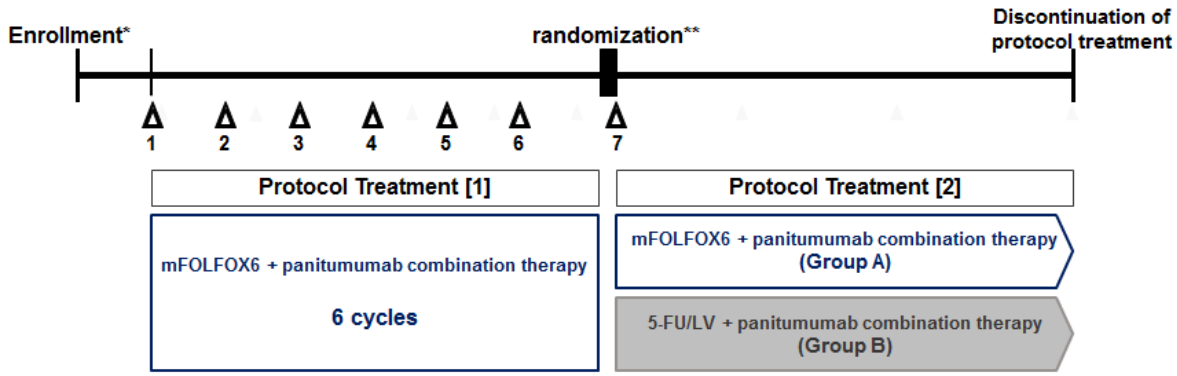
Test product: Panitumumab

Study title:
SAPPHIRE study（A phase II randomized study comparing the efficacy and safety of mFOLFOX6 + panitumumab combination therapy and 5-FU/LV + panitumumab combination therapy in the patients with chemotherapy-naïve unresectable advanced recurrent colorectal carcinoma of *KRAS* wild-type after 6 cycles of combination therapy with mFOLFOX6 + panitumumab）

Protocol number: 183/NRP-005

Study type: Exploratory study

Study design:



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

Objective:
To exploratorily examine efficacy and safety in the patients with chemotherapy-naïve unresectable, advanced/recurrent colorectal carcinoma of *KRAS* wild-type who have been treated with 6 cycles of first-line mFOLFOX6 + panitumumab combination therapy and then assigned to two groups, i.e., a group receiving 5-FU/LV + panitumumab combination therapy and a group receiving mFOLFOX6 + panitumumab combination therapy.

Study population:
The patients with chemotherapy-naïve unresectable, advanced/recurrent colorectal carcinoma of *KRAS* wild-type

Planned number of subjects:

mFOLFOX6 + panitumumab arm (Group A): 50

5-FU/LV + panitumumab arm (Group B): 50

Number of study sites: 40

Method of administration:
In both Protocol Treatment [1] and Protocol Treatment [2] (Group A and Group B), one cycle consists of two weeks, and the drugs will be administered at the following doses according to the following schedule.

Protocol Treatment [1]
mFOLFOX6 + panitumumab combination therapy, once every two weeks, 6 cycles
OXA: 85 mg/m^2/day 1
l-LV: 200 mg/m^2/day 1
bolus 5-FU: 400 mg/m^2/day 1
infusional 5-FU: 2400 mg/m^2/day 1-3
panitumumab: 6 mg/kg

Protocol Treatment [2]

Group A: mFOLFOX6 + panitumumab combination therapy, once every two weeks
OXA: 85 mg/m^2/day 1
l-LV: 200 mg/m^2/day 1
bolus 5-FU: 400 mg/m^2/day 1
infusional 5-FU: 2400 mg/m^2/day 1-3
panitumumab: 6 mg/kg

Group B: 5-FU/LV + panitumumab combination therapy, once every two weeks
l-LV: 200 mg/m^2/day 1
bolus 5-FU: 400 mg/m^2/day 1
infusional 5-FU: 2400 mg/m^2/day 1-3
panitumumab: 6 mg/kg

Duration of treatment (approximately): 12 months (Period from the day of first administration in Protocol Treatment [1] to PD or intolerance)

Inclusion criteria

Inclusion criteria for enrollment:

(1) Patients with unresectable adenocarcinoma originating in the large intestine (excluding carcinoma of the appendix and anal canal cancer)

(2) Patients with measurable lesion(s) according to the RECIST ver. 1.1

(3) Patients who have not received chemotherapy for colorectal cancer. Patients who experience relapse more than 6 months after the final dose of perioperative adjuvant chemotherapy with fluoropyrimidine agents may be enrolled.

(4) Aged ≥20 years at the time of informed consent

(5) Patients classified as *KRAS* wild-type*. However, the criteria will be changed to all patients who are verified to be of *KRAS* and *NRAS* wild-type when the *KRAS* and *NRAS* tests come to be covered by National Health Insurance, and the tests become feasible at medical institutions.

*: Patients with no mutation in any of the codons shown below are considered 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

**: To be considered when the test comes to be covered by insurance and becomes feasible at medical institutions.

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

1) Neutrophil count ≥ 1,500/mm^3
2) White blood cell count ≥ 3,000/mm^3
3) Platelet count ≥ 10.0 × 104/mm^3
4) Hemoglobin ≥ 9.0 g/dL

5) Total bilirubin ≤ 2.0 mg/dL
6) AST ≤ 100 IU/L (≤ 200 IU/L if liver metastases are present)
7) ALT ≤ 100 IU/L (≤ 200 IU/L if liver metastases are present)
8) Serum creatinine ≤ 1.5 mg/dL

(7) ECOG performance status (PS) of 0 or 1
(8) Life expectancy of ≥ 6 months after enrollment
(9) Patients who have given written consent to take part in the study after detailed explanation of the study prior to enrollment

Inclusion criteria for randomization:

(1) Patients who have received 6 cycles＊ (Protocol Treatment [1]) of mFOLFOX6 + panitumumab combination therapy
*: Protocol Treatment [1] without discontinuation in all cycles (6 cycles) of Protocol Treatment [1]. However, bolus 5-FU and panitumumab are an exception.
(2) ECOG performance status (PS) of 0-1 before administration of the 7th cycle.
(3) Patients for whom PD or not evaluable has been denied on the Response Evaluation Criteria in Solid Tumors (RECIST) based on imaging tests conducted after administration of 6 cycles.

Exclusion criteria

Exclusion criteria for enrollment:

(1) Radiotherapy received for a measurable lesion(s)
(2) Radiotherapy received within 4 weeks prior to enrollment except measurable lesion(s). However, the treatment to relieve the pain of metastatic bone tumor is allowed
(3) Known brain metastasis or strongly suspected of brain metastasis
(4) 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) 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) Active hemorrhage requiring blood transfusion
(8) Disease requiring systemic steroids for treatment (excluding topical steroids)
(9) Intestinal resection and colostomy within 2 weeks prior to enrollment
(10) History or obvious and extensive CT findings of interstitial pulmonary disease (interstitial pneumonia, pulmonary fibrosis, etc.)
(11) Serious drug hypersensitivity
(12) Local or systemic active infection requiring treatment, or fever indicating infection
(13) Intestinal paralysis, gastrointestinal obstruction, or uncontrollable diarrhoea (incapacitating symptoms despite adequate treatment)
(14) Active hepatitis B and/or C
(15) Known HIV infection
(16) Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study

Exclusion criteria for randomization:

(1) Patients in whom interstitial pneumonia has been newly diagnosed during the period from registration to randomization
(2) Patients who have received radiotherapy during the period from registration to randomization. However,

the treatment to relieve the pain of metastatic bone tumor is allowed

(3) Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study

Endpoints:

[Primary endpoint]

- Efficacy

Progression-Free Survival (PFS) at 9 months after the day of randomization

[Secondary endpoints]

- Efficacy
  - Progression-Free Survival (PFS)
  - Overall survival (OS)
  - Response rate (RR)
  - Time to treatment failure (TTF)
- Safety
  - Incidence rate of adverse events and severity by incidence rate
  - Incidence rate of peripheral nerve disorders
  - Incidence rate of skin disorders
- Additional endpoint
  - Percentage of maintenance of Performance Status (PS)
  - Percentage of continuation of OXA in mFOLFOX6 + panitumumab group (Group A)
  - Percentage of continuation of panitumumab in both groups

Statistical method:

The purpose of this study is to explorethe the analysis of PFS compared mFOLFOX6 + panitumumab arm with 5-FU/LV + panitumumab arm.

The PFS is the period from the day of randomization (Day 0) until the day of judgment of exacerbation from the day of randomization, or until death by all causes, whichever comes earlier.

For each treatment group, calculate the progression-free survival rate at a given time point and its 95% confidence interval (two-sided) by Kaplan-Meier method, and calculate the quartile of PFS and its 95% confidence interval (two-sided). At the same time, draw a Kaplan-Meier chart for the progression-free survival rate. If the median value of observed PFS is 9 months or more in each group, the treatment regimen concerned will be regarded as being of worth of further investigation.

Moreover, for the sake of reference, calculate the hazard ratio of Group B to Group A and its 95% confidence interval (two-sided) on the basis of the stratified Cox regression model and apply the log-rank test.

Rationale for planned number of subjects:

This study will be designed as a phase II randomized screening comparison study which does not use direct comparison for primary analysis.

In the phase III study (PRIME Study) in which FOLFOX4 therapy was combined with bi-weekly administration of panitumumab 6 mg/kg as a first-line therapy, the median PFS in the patients of KRAS wild-type as the primary endpoint was reported as 9.6 months[12]. Moreover, in PEAK study in which panitumumab and bevacizumab were compared as the drugs to be administered in combination with mFOLFOX6 therapy, the median PFS in the mFOLFOX6 therapy + panitumumab group was reported as 10.9 months. The percentage of the cases in which any events occurred or the study was cut off within 3 months in PRIME Study and PEAK Study was approximately 10% of all cases.

The subjects of this study will be the patients who receive mFOLFOX6 + panitumumab combination therapy for 3 months, and can continue OXA administration. Since the PFS 40% point in PRIME Study and PEAK Study

was approximately 13 months, the median PFS in Group A in this study is expected to be approximately 10 months, which is obtained by subtracting 3 months from the 40% point. The median PFS in Group B is assumed to be comparable to that in Group A.

In the primary analysis, a test based on the method of Brookmeyer-Crowley will be conducted for the null hypothesis, "true median PFS will be lower than the threshold median PFS for judgment as ineffective", separately in Group A and Group B on the basis of the observed median PFS. When the threshold median PFS is regarded as 6 months, true median PFS as 10 months, enrollment period as 12 months, follow-up period as 12 months, one-sided significance level as 5%, and power of test as 80%, the number of subjects required in Group A and Group B will become 54 subjects each. Considering the cases of discontinuation, the target number of subjects to be randomised was set at 60 patients for each group (120 patients in total).

3.0 LIST OF ABBREVIATIONS

Abbreviation	Unabbreviated expression
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ALP	alkaline phosphatase
ASCO	American society of clinical oncology
BRAF	v–raf murine sarcoma viral oncogene homolog B1
BSC	best supportive care
CEA	carcinoembryonic antigen
COI	conflict of interest
CR	complete response
CRO	contract research organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	deepness of response
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
ETS	early tumor shrinkage
FAS	full analysis set
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FFPE	Formalin-Fixed Paraffin-Embedded
G-CSF	granulocyte colony stimulating factor
γ-GTP	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
ICH	International Conference on Harmonisation
INR	International normalized ratio
IRB	institutional review board
JCOG	Japan Clinical Oncology Group
KRAS	Kirsten rat Sarcoma-2 virus
LDH	lactate dehydrogenase
LLN	lower limit of normal
l-LV	Leucovorin
mCRC	metastatic colorectal cancer

Abbreviation	Unabbreviated expression
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
NE	Not Evaluable
NRAS	
OS	Overall survival
OXA	Oxaliplatin
PD	progressive disease
PFS	Progression free survival
PPS	per-protocol analysis set
PR	partial response
P.S.	performance status
PT	Preferred Term
PI3K	Phosphoinositide 3-kinase
RAS	rat sarcoma
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TTF	Time to Treatment Failure
ULN	upper limit of normal
UMIN-CTR	University Hospital Medical Information Network - Clinical Trials Registry
UPC	urine protein creatinine
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
WT	wild type
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

4.1.1 Etiology of target disease

According to "Cancer Statistics 2013,"[1)] and "Site-specific Cancer Prevalence" in 2008 in Japan, colon cancer was the third most prevalent cancer in men (15.0%) and the second in women (15.1%). According to "Site-specific Cancer Deaths (2012)," in men, lung cancer was the leading cause of cancer death (accounting for 23.9% of cancer deaths), followed by gastric cancer (15.0%) and hepatic cancer (9.3%); 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 (13.8%) was also the leading cause of cancer death, followed by gastric cancer (11.6%) and pancreatic cancer (9.9%); 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 target disease

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 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 chemotherapy regimens for the patients with unresectable, advanced/recurrent colorectal carcinoma necessitating powerful treatment that have been demonstrated to be useful in clinical studies and are currently covered by national health insurance in Japan are presented below. There is a consensus that cetuximab and panitumumab should be used only for *KRAS* wild-type (WT) colorectal cancer.

(1) FOLFOX therapy or CapeOX therapy +bevacizumab[*1]
FOLFOX therapy: combination chemotherapy with fluorouracil (hereinafter referred to as 5-FU), Isovorin (hereinafter referred to as *l*-LV), and oxaliplatin (hereinafter referred to as OXA)
CapeOX therapy: combination chemotherapy with capecitabine and OXA

(2) FOLFIRI therapy + bevacizumab[*1]
FOLFIRI therapy: combination chemotherapy with irinotecan (hereinafter referred to as IRI), 5-FU, and *l*-LV

(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], CapeOX + bevacizumab[*1] or UFT + LV
UFT: combination preparation of tegafur and uracil

*1: Combination with molecular-targeted drugs such as bevacizumab and epidermal growth factor receptor (EGFR) antibody is recommended, but if this cannot be indicated, chemotherapy alone will be provided.
*2: Indicated only for *KRAS* wild-type.
*3: infusional 5-FU + *l*-LV

FOLFOX-based therapy is more frequently selected as first-line chemotherapy 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.

For third-line treatment, regorafenib or symptomatic therapy is currently recommended.

4.1.3 Efficacy and safety of mFOLFOX6 in patients with unresectable, advanced or recurrent colorectal cancer

As therapy for unresectable, advanced/recurrent colorectal cancer, regimens mainly based on fluoropyrimidine anticancer agents are considered to be the standard for a long term[3]. Based on the evidence showing that 5-FU combined with *l*-LV is superior to 5-FU monotherapy, the combination therapy with 5-FU and *l*-LV (hereinafter referred to as 5-FU/LV therapy) had been considered as standard chemotherapy for colorectal cancer for a long time. The type I topoisomerase inhibitor IRI and the third generation of platinum-based anticancer drug OXA were then developed, and have been shown to improve treatment outcome in a number of large scale controlled trials[4) to 9)]. At present, continuous infusion of 5-FU/LV in combination with OXA (FOLFOX therapy) or in combination with IRI (FOLFIRI therapy) is the standard chemotherapy regimen for advanced/recurrent colorectal cancer[3), 10)]. FOLFOX and FOLFIRI therapies were compared in the GERCOR V308 study[9)], in which the median final overall survival (hereinafter referred to as OS) was similar between the precedent FOLFIRI and the precedent FOLFOX arms (21.5 months vs. 20.6 months), and thereby both of the therapies are used as the standard for unresectable colorectal cancer. The development of these therapies provided improvement of the median survival time of unresectable advanced colorectal cancer from 12 months with 5-FU/LV therapy to 20 months or more with 5-FU/LV therapy in combination with IRI or OXA.

Among several FOLFOX regimens, FOLFOX4 therapy and modified FOLFOX6 (hereinafter referred to as mFOLOFX6) therapy, which include OXA at the approved dosage (85 mg/m^2) in Japan, are covered by national health insurance, and simpler and easier mFOLFOX6 therapy is more frequently used.

4.1.4 Efficacy and safety of panitumumab in patients with unresectable, advanced or recurrent colorectal cancer

4.1.4.1 Panitumumab

EGFR, 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 (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.

4.1.4.2 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 or advanced, EGFR-positive colorectal cancer that became resistant to fluoropyrimidine agents, OXA, and IRI (BSC arm, 232 patients; BSC + panitumumab arm, 231 patients) [11]. The primary endpoint of median progression free survival (hereinafter referred to as PFS) was 8 weeks and significantly longer in the BSC + panitumumab therapy, showing the efficacy of panitumumab therapy as compared with 7.3 weeks in the BSC alone arm (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 arms (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 arm received follow-up therapy with panitumumab.

With regard to 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 1,180 patients (590 in each arm)[12]. The primary endpoint of median PFS in *KRAS* wild-type patients was 9.6 months and significantly longer in the FOLFOX4 + panitumumab arm as compared with 8.0 months in the FOLFOX4 alone arm (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 arm, but there were no major differences in the incidence of other adverse events between the two arms. 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. [13] The primary endpoints were PFS and OS in *KRAS* wild-type patients. In *KRAS* wild-type patients, the median PFS was 5.9 months and significantly longer in the FOLFIRI + panitumumab arm than 3.9 months in the FOLFIRI alone arm (HR, 0.73; two-sided 95% CI, 0.59 to 0.90; p = 0.004). On the other hand, OS was 14.5 months in the FOLFIRI + panitumumab arm and 12.5 months in the FOLFIRI alone arm, with no statistically significant difference between the two arms (HR, 0.85; two-sided 95% CI, 0.70 to 1.04; p = 0.12). The response rate (hereinafter referred to as RR) was 35% and higher in the FOLFIRI +

panitumumab arm as compared with 10% in the FOLFIRI alone arm. 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 arm; however, there were no major differences in the incidence of toxicities including hematologic toxicities between the two arms, and the incidence of infusion reaction was not more than 1%.

Both the PRIME Study[12)] and Study 20050181[13)] described above, in which *KRAS* mutation status 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.

4.1.4.3 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. Again, in this study, panitumumab showed a good tolerability profile.

In a Japanese phase II clinical study of panitumumab monotherapy[14)], 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 median PFS of 8.0 weeks (two-sided 95% CI: 7.4 to 11.4), and a median 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 incurable/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 Events	Panitumumab Monotherapy (n = 52)			
	All		≥ Grade 3	
	n	%	N	%
Any adverse drug reaction	51	98	6	12
Skin disorder	51	98	3	6
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	
Malaise	13	25	0	
Stomatitis	12	23	0	
Anorexia	11	21	1	2

4.1.4.4 Result of the post-marketing Surveillance (overall survey) in Japan

In a study conducted during a certain post-marketing period by enrolling all patients[15)], the median treatment duration (first day of administration to last day of administration) in 3,085 patients included in safety evaluation was 113 days (range: 1-559 days), and the incidence rate of adverse

drug reactions was 84.1% (≥Grade 3, 25.8%). The incidence rate in 1,254 patients in the group treated with panitumumab monotherapy was 80.1% (≥Grade 3, 19.7%) and that in 1,831 patients in the group treated with panitumumab + chemotherapy was 86.9% (≥Grade 3, 30.0%). The status of occurrence of adverse drug reactions of special interest is shown in Table 4.b.

Table 4.b Adverse Drug Reactions (ADRs) of special interest on Post-marketing survey in Japan

Overall incidence of Post-marketing survey	Panitumumab Monotherapy (n=1,254)				Combination therapy (n=1,831)			
	All		≥ Grade 3		All		≥ Grade 3	
ADRs of special interest	n	%	n	%	n	%	N	%
Skin and 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
Hypomagnesemia	257	20.5	61	4.9	263	14.4	62	3.4
Hypocalcemia	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

* : Based on the evaluation of the ILD

4.1.5 Adverse reactions to OXA

Major dose-limiting toxicities of OXA are neurological manifestations, which are peripheral sensory nerve disorders characterized by dysaesthesia or paraesthesia in four limbs. They may accompany convulsion and are induced by exposure to coldness. Hochster et al.[16] reported that these symptoms appeared in 85% to 95% of the patients who received FOLFOX therapy in combination with bevacizumab, that the duration became longer as the administration cycles increased, and that the incidence of functional disorders after administration of a cumulative dose of 800 mg/m^2 was approximately 15%. In many cases, these neurological manifestations remit or disappear after discontinuation of administration. Acute sensory neurological manifestations appear within several hours after administration, and are induced by exposure to coldness. They may appear as transient paraesthesia, dysaesthesia, hypoaesthesia or acute laryngopharyngeal dysaesthesia syndrome.

In addition to nerve disorders, acute laryngopharyngeal dysaesthesia syndrome is estimated to occur with an incidence of 1% to 2%. It is characterized by respiratory disorders without cyanosis and hypoxia, sensation of dyspnoea without direct effects on the respiratory functions such as dysphagia, decreased SaO_2, laryngospasm, and bronchospasm without wheezing in the upper and lower respiratory tracts. Convulsion in the jaw, abnormal feeling in the tongue, dysarthria, eye pain, and chest pressure sensation are also observed[17]. These symptoms improve reversely without treatment. The incidence of acute laryngopharyngeal dysaesthesia syndrome is suggested to decrease as the duration of administration becomes longer.

Among these adverse reactions, nerve disorders in particular make continuous administration of OXA difficult, and may lead to modification of the FOLFOX therapy regimen involving molecular-targeted drugs. For the patients responding to the therapy, they may miss the patients of important opportunities of treatment (internal data).

4.1.6 Examination of the method of administration of OXA in first-line therapy

Reduction of neurological manifestations associated with FOLFOX as standard chemotherapy for unresectable, advanced/ recurrent colorectal carcinoma is urgently needed for improvement of the QOL of patients and for realization of long-term treatment. According to the reports of Tournigand et al[18]., OPTIMOX1 (Stop and Go method) is able to achieve recovery from neurological manifestations during the period of sLV5FU2 therapy without OXA after FOLFOX. Moreover, it may be possible to reduce hematological toxicity and non-hematological toxicity during this period. Concerning the treatment effect, the response rate was 59.2% and MST was 21.2 months. Furthermore, the final report of OPTIMOX2 by F Maindrault-Goebel et al.[19] showed that the OS in the administration schedule of OPTIMOX1 (Stop and Go method) was 26 months.

4.2 Rationale for the proposed study

In Japan, mFOLFOX6 therapy is conducted most frequently as the first-line therapy for unresectable, advanced/ recurrent colorectal carcinoma. Peripheral nerve disorders induced by OXA contained in mFOLFOX6 therapy may cause a clinical problem because they become a cause of deterioration of the patients' QOL, thereby making continuous treatment impossible. When peripheral nerve disorders as mentioned above have occurred, mFOLFOX6 therapy as the baseline therapy is switched to FOLFIRI therapy in some cases in spite of favorable responses to the first-line therapy, instead of discontinuing OXA which is the cause of peripheral nerve disorders. This is deemed to lead to a loss of the opportunity of treatment for the patients. Moreover, it is possible that long-term administration of OXA induces peripheral nerve disorders. For patients who discontinue administration of OXA after having received the drug for a certain period and who have experienced no peripheral nerve disorders during the treatment period, re-introduction of OXA in the later stage of treatment may remain as a treatment option. With regard to the discontinuaiton and resumption of OXA administration in FOLFOX therapy as the first line therapy at present, the evaluation for efficacy and safety of OPTIMOX study[18] have been presented. However, appropriate administration method of OXA in first-line therapy with mFOLFOX6 + panitumumab has not been revealed.

For these reasons, this study was planned on the basis of the judgment that efficacy and safety in the group in which OXA is discontinued after 6 cycles of the treatment and the group in which OXA is continued need to be examined in the patients responding to mFOLFOX6 + panitumumab combination therapy.

5.0 OBJECTIVE AND ENDPOINTS OF THE STUDY

5.1 Objective

To exploratorily examine efficacy and safety in the patients with chemotherapy-naïve unresectable, advanced/recurrent colorectal carcinoma of *KRAS* wild-type who have been treated with 6 cycles of first-line mFOLFOX6 + panitumumab combination therapy and then assigned to two groups, i.e., a group receiving 5-FU/LV + panitumumab combination therapy and a group receiving mFOLFOX6 + panitumumab combination therapy.

5.2 Endpoints

See Section 13.1.3 for Efficacy analysis.

5.2.1 Primary endpoint

- Efficacy
  - Progression-free survival (PFS) at 9 months after the day of randomization

5.2.2 Secondary endpoints

- Efficacy
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - Response rate (RR)
  - Time to treatment failure (TTF)
- Safety
  - Incidence rate of adverse events, and severity by incidence rate
  - Incidence rate of peripheral nerve disorders
  - Incidence rate of skin disorders

5.2.3 Additional endpoint

- Percentage of maintenance of Performance Status (PS)
- Percentage of continuation of OXA in mFOLFOX6 + panitumumab group (Group A)
- Percentage of continuation of panitumumab in both groups

5.3 Rationale for the endpoints

5.3.1 Primary endpoint

The PFS was selected as the best indicator for evaluation of efficacy of the regimen with and without OXA after 6 cycles of mFOLFOX6 + panitumumab combination therapy without being affected by the after-treatment.

5.3.2 Secondary endpoints

The OS was selected as the secondary endpoint because it is the true endpoint. As a help for interpretation of primary efficacy results, RR and TTF were selected as secondary endpoints.

Concerning safety, the appropriateness of continuing and discontinuing OXA and panitumumab was evaluated in an exploratory manner. The incidence rate of adverse events, the incidences of peripheral nerve disorders and skin disorders were selected as secondary endpoints because they are important factors for the choice of treatment.

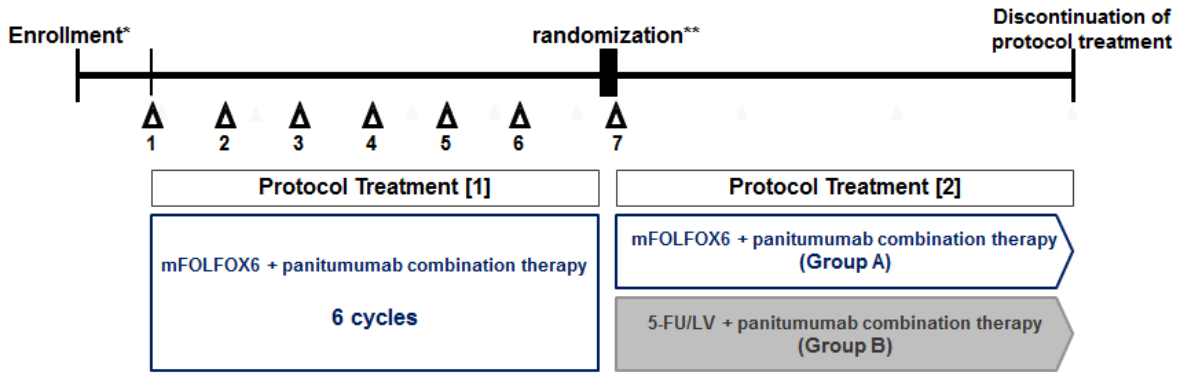
6.0 STUDY DESIGN

6.1 Study design

This is a phase II, multi-center joint, open-label, parallel-group randomized controlled study to exploratorily examine the efficacy and safety in the patients with chemotherapy-naïve unresectable, advanced/recurrent colorectal carcinoma of *KRAS* wild-type after treating them with 6 cycles of mFOLFOX6 + panitumumab combination therapy and subsequently assigning them to a group continuing mFOLFOX6 + panitumumab combination therapy (Group A) and a group in which OXA is discontinued and 5-FU/LV + panitumumab combination therapy is provided (Group B).

Patients who are judged eligible for the study based on the inclusion criteria at the time of enrollment will be registered within 14 days before the first administration (1st cycle), and will be treated with 6 cycles of mFOLFOX6 + panitumumab combination therapy (Protocol Treatment [1]). The patients for whom continuation of mFOLFOX6 + panitumumab combination therapy is judged appropriate on the basis of the examination before administration of the 7th cycle and imaging test after administration of the 6th cycle, who satisfy the inclusion criteria for randomization, and who do not fall under any of the exclusion criteria for randomization will be randomly assigned to either the mFOLFOX6 + panitumumab combination group (Group A) or the 5-FU/LV + panitumumab combination group (Group B) at the ratio of 1:1 before administration of the 7th cycle (TBD). After randomization, treatment in Group A or Group B will be continued according to the administration standards for Protocol Treatment [2] until the "8.8. Criteria for discontinuation of protocol treatment" are met. The reasons for the failure to meet the subject inclusion criteria at the time of randomization will be collected. The patients who fall under the criteria for extension of administration on the examination before administration of the 7th cycle will be examined again after an appropriate interval. The patients who satisfy the subject inclusion criteria on the re-examination will be randomized, and will receive the protocol treatment of the assigned group. Both inpatients and outpatients are eligible. Refer to "8.2 Treatment regimen" for details about the protocol treatment ([1] and [2]).

See "13.3 Determination of the planned number of subjects" for the number of subjects.



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

Figure 6.a Outline of study design

6.2 Rationale for study design, dose and endpoints

6.2.1 Study population

The timing at which OXA-induced peripheral nerve disorders occurs most frequently has been reported to be the time point at which the accumulated amount of OXA administered reaches 780-850 mg/m^2 [20]. This amount is equivalent to 9 or 10 doses when converted using the dose of 85 mg/m^2 of OXA administered at a time in Protocol Treatment [1] and [2]. According to the report by Hochster et al[16]. who investigated the mean number of doses administered continuously in FOLFOX therapy in initial therapy in routine medical care, the number was 10 times in the FOLFOX + bevacizumab combination therapy in first-line therapy (TREE2). In the report by Giantonio et al.[21], the mean number of doses administered continuously in FOLFOX±bevacizumab combination therapy in the second-line therapy (ECOG3200) for the patients with a history of chemotherapy was 7 to 10 times. This study aims at comparing efficacy and safety in the group continuing OXA from the 7th cycle and the group discontinuing OXA in the patients receiving first-line mFOLFOX6 + panitumumab combination therapy before the occurrence of peripheral nerve disorders. Since the above-described status of the frequency of OXA administration also seems to suggest that discontinuation of OXA after 6th administration in Protocol Treatment [1] does not greatly deviate from the situation in routine medical care, the number of cycles of OXA administration given before randomization was set at 6.

Moreover, since no significant differences were seen in the duration of disease control and PFS in OPTIMOX study, the duration of treatment is not expected to differ significantly even when OXA is discontinued after 6 cycles of mFOLFOX6 + panitumumab therapy while 5-FU/LV + panitumumab combination therapy is continued. Furthermore, although concomitant administration of panitumumab does not cause differences in time to treatment failure and PFS, discontinuation of OXA before the occurrence of peripheral nerve disorders enables re-introduction of OXA. Therefore, differences larger than in OPTIMOX study may be expected for OS. In addition, it may become possible to propose, for combination therapy of mFOLFOX6 and panitumumab, an approach which enables long-term continuation of treatment through prevention of the occurrence of OXA-induced peripheral nerve disorders.

6.2.2 Treatment regimens and planned number of subjects

See "13.3 Determination of the planned number of subjects" for details.

6.3 Discontinuation of entire study or discontinuation at a study site

6.3.1 Criteria for discontinuation of entire study

The sponsor should immediately discontinue the study when it is notified by the data monitoring committee and/or the steering committee that at least one of the following criteria is applicable.

- Occurrence of serious event/violation which endangers safety of subjects.
- 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.

6.3.2 Procedures of study suspension and discontinuation of entire study or study at a study site

When the sponsor or the IRB such as the ethics review committee determines suspension or discontinuation of the entire study or the study at a certain study site, the sponsor will instruct the procedures specified for the relevant study. The relevant study site should observe the procedures for study suspension or discontinuation.

6.4 Procedures for revision of the protocol

When a need arises to revise the protocol, the sponsor will consult with the representative researcher to make a decision.

Details of the protocol revision will be notified to investigators of all study sites.

When the investigator of each study site receives the notification, he should arrange the revised protocol to be reviewed by the IRB such as the ethics review committee again as necessary according to the stipulation at each study site and obtain approval of the director of study site.

7.0 SELECTION OF STUDY SUBJECTS

7.1 Inclusion criteria

7.1.1 Inclusion criteria for enrollment

Patients who satisfy all the criteria below will be enrolled in this study.

(1) Patients with unresectable adenocarcinoma originating in the large intestine (excluding carcinoma of the appendix and anal canal cancer)

(2) Patients with measurable lesion(s) according to the RECIST ver. 1.1

(3) Patients who have not received chemotherapy for colorectal cancer. Patients who experience relapse more than 6 months after the final dose of perioperative adjuvant chemotherapy with fluoropyrimidine agents may be enrolled.

(4) Aged ≥20 years at the time of informed consent

(5) Patients classified as *KRAS* wild-type*. However, the criteria will be changed to all patients who are verified to be of *KRAS* and *NRAS* wild-type when the *KRAS* and *NRAS* tests come to be covered by National Health Insurance, and the tests become feasible at medical institutions.

*: Patients with no mutation in any of the codons shown below are considered 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

**: To be considered when the test comes to be covered by insurance and becomes feasible at medical institutions.

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

1) Neutrophil count ≥ 1,500/mm^3
2) White blood cell count ≥ 3,000/mm^3
3) Platelet count ≥ 10.0×10^4/mm^3
4) Hemoglobin ≥ 9.0 g/dL
5) Total bilirubin ≤ 2.0 mg/dL
6) AST ≤ 100 IU/L (≤ 200 IU/L if liver metastases are present)
7) ALT ≤ 100 IU/L (≤ 200 IU/L if liver metastases are present)
8) Serum creatinine ≤ 1.5 mg/dL

(7) ECOG performance status (PS) of 0 or 1

(8) Life expectancy of ≥ 6 months after enrollment

(9) Patients who have given written consent to take part in the study after detailed explanation of the study prior to enrollment

7.1.2 Inclusion criteria for randomization

Patients who satisfy all the criteria below will be randomized. If possible, randomization will be conducted immediately before administration of the 7th cycle.

(1) Patients who have received 6 cycles* (Protocol Treatment [1]) of mFOLFOX6 + panitumumab combination therapy

*: Defined as administration of 5-FU/LV and OXA according to the designated dosage regimen for Protocol Treatment [1] without discontinuation in all cycles (6 cycles) of Protocol Treatment [1]. However, bolus 5-FU and panitumumab are an exception.

(2) ECOG performance status (PS) of 0-1 before administration of the 7th cycle.

(3) Patients for whom PD or not evaluable has been denied on the Response Evaluation Criteria in Solid Tumors (RECIST) based on imaging tests conducted after administration of 6 cycles.

7.2 Exclusion criteria

7.2.1 Exclusion criteria for enrollment

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

(1) Radiotherapy received for a measurable lesion(s)

(2) Radiotherapy received within 4 weeks prior to enrollment except measurable lesion(s). However, the treatment to relieve the pain of metastatic bone tumor is allowed.

(3) Known brain metastasis or strongly suspected of brain metastasis

(4) 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) 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) Active hemorrhage requiring blood transfusion

(8) Disease requiring systemic steroids for treatment (excluding topical steroids)

(9) Intestinal resection and colostomy within 2 weeks prior to enrollment

(10) History or obvious and extensive CT findings of interstitial pulmonary disease (interstitial pneumonia, pulmonary fibrosis, etc.)

(11) Serious drug hypersensitivity

(12) Local or systemic active infection requiring treatment, or fever indicating infection

(13) Intestinal paralysis, gastrointestinal obstruction, or uncontrollable diarrhoea (incapacitating symptoms despite adequate treatment)

(14) Active hepatitis B and/or C

(15) Known HIV infection

(16) Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study

7.2.2 Exclusion criteria for randomization

Patients who meet any of the criteria below will not be randomized.

(1) Patients in whom interstitial pneumonia has been newly diagnosed during the period from registration to randomization

(2) Patients who have received radiotherapy during the period from registration to randomization. However, the treatment to relieve the pain of metastatic bone tumor is allowed.

(3) Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study

8.0 TREATMENT

The protocol treatment, contraindicated drugs/therapies, and recommended supportive care/combination therapies in this study are explained in this section. Commercially available drugs used at the study sites will be used in this study. See the latest package insert for details and handling of each drug.

8.1 Protocol treatment

The study period in this study is defined as the period consisting of Protocol Treatment [1] and Protocol Treatment [2].

8.1.1 Protocol Treatment [1]

OXA and infusional 5-FU will be administered in all of the 6 cycles. The dose can be reduced. Panitumumab will also be administered in all the possible 6 cycles but suspension due to the occurrence of skin disorders will be allowed.

8.1.2 Protocol Treatment [2]

Even if each drug of the criteria specified in "8.5 Criteria for dose change." is met, treatment with the other drugs will be continued unless any of the criteria specified in "8.8 Criteria for discontinuation of protocol treatment" is met.

8.2 Treatment regimen

8.2.1 Protocol Treatment [1]

During the period of Protocol Treatment [1], mFOLFOX6 + panitumumab combination therapy will be given once in two weeks according to the following treatment regimen until any of the criteria specified in "8.8 Criteria for discontinuation of protocol treatment" is met (one administration will be regarded as one cycle). For administration of each drug, see "8.4 Criteria for initiation of protocol treatment (common for Protocol Treatment [1] and [2])" and "8.5 Criteria for dose change".

For the patients aged 80 years or older at the time of enrollment, the drug can be administered at a dose one level lower than the designated dose from Cycle 1.

Table 8.a Treatment regimen of mFOLFOX6 + panitumumab combination therapy

Drug	Dose	Method of administration (recommended)	Date of administration
Panitumumab	6 mg/kg	div 60 min*	Day 1
OXA	85 mg/m^2	div 120 min	Day 1
***l*-LV**	200 mg/m^2	div 120 min	Day 1
5-FU (iv)	400 mg/m^2	iv <15 min	Day 1
5-FU (civ)	2400 mg/m^2	civ 46 hrs	Day 1-2

div: intravenous drip infusion, iv: intravenous infusion, civ: continuous intravenous infusion

*: When the dose at one time exceeds 1000 mg, intravenously administer it over 90 min or longer after dilution with JP physiological saline to make approximately 150 mL.

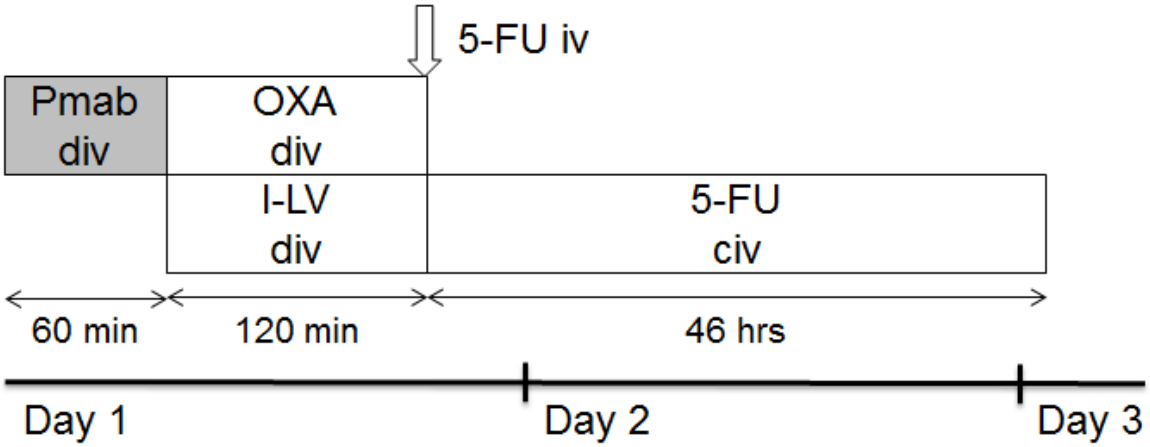


Figure 8.a mFOLFOX6 + panitumumab combination therapy

8.2.2 Protocol Treatment [2]

If the dose of the drug has been reduced during the period of Protocol Treatment [1], the drug will be administered at the reduced dose from Cycle 7.

8.2.2.1 mFOLFOX6 + panitumumab combination therapy (Group A)

See Section 8.2.1 for Protocol Treatment [1]. The term of Protocol Treatment [1] is regarded as Protocol Treatment [2].

8.2.2.2 5-FU/LV + panitumumab combination therapy (Group B)

During the period of Protocol Treatment [2], 5-FU/LV + panitumumab combination therapy will be given once in two weeks according to the following treatment regimen until any of the criteria specified in "8.8 Criteria for discontinuation of protocol treatment" is met (one administration will be regarded as one cycle). For administration of each drug, see "8.4 Criteria for initiation of protocol treatment (common for Protocol Treatment [1] and [2])" and "8.5 Criteria for dose change".

Table 8.b Treatment regimen of 5-FU/LV + panitumumab combination therapy

Drug	Dose	Method of administration (recommended)	Date of administration
Panitumumab	6 mg/kg	div 60 min*	Day 1
***l*-LV**	200 mg/m^2	div 120 min	Day 1
5-FU (iv)	400 mg/m^2	iv < 15 min	Day 1
5-FU (civ)	2400 mg/m^2	civ 46 hrs	Day 1-2

div: intravenous drip infusion, iv: intravenous infusion, civ: continuous intravenous infusion
*: When the dose at one time exceeds 1000 mg, intravenously administer it over 90 min or longer after dilution with JP physiological saline to make approximately 150 mL.

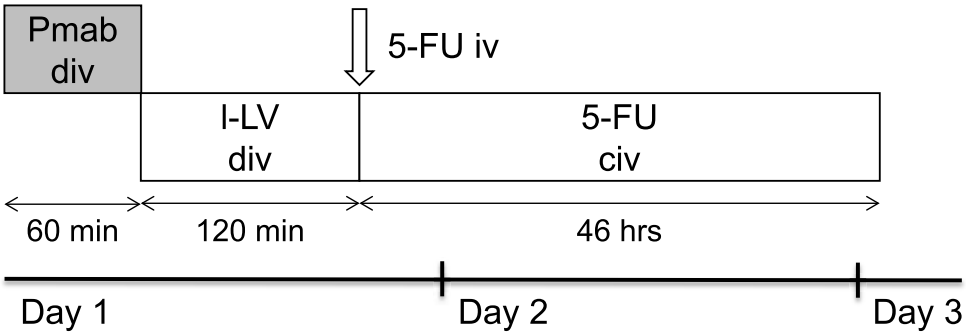


Figure 8.b 5-FU/LV + panitumumab combination therapy

8.3 Recommended dose of protocol treatment

The dose will be calculated based on the body surface area and body weight at the time of study entry. At the time of study entry, the enrollment center will announce the body surface area, which is calculated using the DuBois & DuBois formula, as well as the dose, which is calculated according to the criteria for truncation described below and will serve as the reference value. The dose should be recalculated and confirmed at the study site. The calculated dose of each drug at one time may be adjusted according to the description below. The dose should be recalculated for 10% change in body weight, in principle, but at the discretion of the study site.

Panitumumab : round down in unit of 10 mg

OXA : round down in unit of 10 mg

l-LV : round down in unit of 25 mg

Bolus 5-FU : round down in unit of 50 mg

Infusional 5-FU: round down in unit of 50 mg

8.4 Criteria for initiation of protocol treatment (common for Protocol Treatment [1] and [2])

In principle, the day (Day 13 to 18) 2 weeks after the day of treatment (Day 1) in the previous cycle will be Day 1 of the subsequent cycle. Postponement due to holidays is allowed. It should be confirmed that all of the criteria for initiation of protocol treatment (Table 8.c to Table 8.e) are satisfied on the day of treatment. However, the latest data obtained from 2 days before treatment to the day of treatment may be used for blood tests.

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.

When treatment is postponed, the date of starting treatment after postponement will be designated as Day 1 of the cycle and serve as the reference point for the subsequent schedule.

Protocol treatment should be discontinued when the subsequent cycle of treatment has not been started 28 days later than scheduled (on Day 43 with the date of starting the previous cycle as Day 1). Postponement due to holidays is allowed.

Table 8.c Criteria for initiation of treatment cycle

Item	Criteria for initiation
White blood cell count	≥ 2,500/mm^3
Neutrophil count	≥ 1,200/mm^3
Platelet count	≥ 7.5 x 10^4/mm^3
Total bilirubin	≤ 2.0 mg/dL
Infection	Absence of fever (≥ 38°C) indicating infection
Nausea, vomiting, diarrhoea, stomatitis	≤ Grade 1
Initiation of treatment may be postponed at the discretion of the investigator due to adverse events not listed above.	

8.5 Criteria for dose change

8.5.1 Protocol Treatment [1]

8.5.1.1 Criteria for dose reduction/suspension of mFOLFOX6

The criteria for dose reduction and the doses of OXA and 5-FU (bolus/infusional) during the period of Protocol Treatment [1] are shown in Table 8.d and Table 8.e, respectively. The dose of *l*-LV should not be changed.

Table 8.d Criteria for dose reduction of OXA and 5-FU (Protocol Treatment [1])

Adverse events in previous cycle	Grade	Dose adjustment of OXA and 5-FU
Neutropenia, thrombopenia	4	Dose reduction of both OXA and 5-FU (bolus/infusional) by 1 level
Grade 3 neutropenia or thrombopenia that persists for more than 7 days	3	
Febrile neutropenia, infection, nausea, vomiting, diarrhoea, fatigue	3	
Sensory nerve disorder*	3	Discontinuation of protocol treatment*
	2	Discontinuation of protocol treatment* Or dose reduction of OXA by 1 level
Allergic reaction	3	Discontinuation of protocol treatment*
Dose reduction is allowed as necessary at the discretion of the investigator due to adverse events not listed above. However, protocol treatment will be discontinued at the time point of suspension of OXA and infusional 5-FU.		

*: When allergic reaction occurs during treatment with OXA, the treatment should be stopped immediately. The decision of restarting this cycle will be entrusted to the study site. If the allergic reaction is Grade 2 or less, protocol treatment with care is allowed under actions such as providing appropriate supportive care or slowing the infusion speed for the treatment after the next course.

Table 8.e Doses of OXA and 5-FU (Protocol Treatment [1])

Dose reduction level	OXA	5-FU iv	5-FU civ
Initial dose	85 mg/m^2	400 mg/m^2	2400 mg/m^2
-1	65 mg/m^2	200 mg/m^2	2000 mg/m^2
-2	50 mg/m^2	0 mg/m^2 (discontinuation)	1600 mg/m^2
-3	Discontinuation of protocol treatment*	0 mg/m^2 (discontinuation)	Discontinuation of protocol treatment*

iv: intravenous infusion, civ: continuous intravenous infusion
*: See "8.8 Criteria for discontinuation of protocol treatment" for details.

8.5.1.2 Criteria for dose reduction/suspension of panitumumab

The criteria for dose reduction and the dose of panitumumab during the period of Protocol Treatment are shown in Table 8.f and Table 8.g, respectively.

Table 8.f Criteria for dose reduction of panitumumab

Item	Grade	Dose adjustment of panitumumab
Skin disorder	3	Dose reduction by 1 level with dose postponement (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.
	2	Dose postponement (suspension) is allowed. (Suspension is not essential.) If the symptom has become milder than the Grade as of the time of onset after the suspension, the drug will be administered at the dose before suspension.
	1	
Hypomagnesaemia*	3	Dose reduction by 1 level 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.
Infusion reaction***	3	Discontinuation of protocol treatment
Dose reduction/suspension is allowed as necessary at the discretion of the investigator 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

***: When infusion reaction occurs during infusion, the treatment should be stopped immediately. The decision of restarting this cycle will be entrusted to the study site. If the infusion reaction is Grade 2 or less, protocol treatment with care is allowed under actions such as providing appropriate supportive care or slowing the infusion speed by 50% for the treatment after the next course.

Table 8.g Dose of panitumumab

Dose reduction level	Panitumumab
Initial dose	6 mg/kg
-1	4.8 mg/kg
-2	3.6 mg/kg
-3	0 mg/kg (discontinuation)

8.5.2 Protocol Treatment [2]

8.5.2.1 Criteria for dose reduction/suspension of mFOLFOX6

The criteria for dose reduction of OXA and 5-FU (bolus/infusional) during the period of Protocol Treatment [2] is shown in Table 8.h. Refer to Table 8.i for the doses of OXA and 5-FU (bolus/infusional), respectively.

Table 8.h Criteria for dose reduction of OXA and 5-FU (Protocol Treatment [2])

Adverse events in previous cycle	Grade	Dose adjustment of OXA and 5-FU
Neutropenia, thrombopenia	4	Dose reduction of both OXA and 5-FU (bolus/infusional) by 1 level
Grade 3 neutropenia or thrombopenia that persists for more than 7 days	3	
Febrile neutropenia, infection, nausea, vomiting, diarrhoea, fatigue	3	
Sensory nerve disorder*	3	Discontinuation of OXA** (no resumption)
	2	Discontinuation** of OXA (no resumption) Or dose reduction of OXA by 1 level
Allergic reaction	3	Discontinuation of OXA** (no resumption)
Dose reduction/suspension is allowed as necessary at the discretion of the investigator due to adverse events not listed above.		

*: OXA may be resumed when nerve disorder has improved after suspension.
**: When Allergic reaction occurs during treatment, the treatment should be stopped immediately. The decision of restarting this cycle will be entrusted to the study site. If the Allergic reaction is Grade 2 or less, protocol treatment with care is allowed under actions such as providing appropriate supportive care or slowing the infusion speed for the treatment after the next course.

Table 8.i Doses of OXA and 5-FU (Protocol Treatment [2])

Dose reduction level	OXA	5-FU iv	5-FU civ
Initial dose	85 mg/m^2	400 mg/m^2	2400 mg/m^2
-1	65 mg/m^2	200 mg/m^2	2000 mg/m^2
-2	50 mg/m^2	0 mg/m^2 (discontinuation)	1600 mg/m^2
-3	0 mg/m^2 (discontinuation)	0 mg/m^2 (discontinuation)	0 mg/m^2 (discontinuation)

iv: intravenous infusion, civ: continuous intravenous infusion

8.5.2.2 Criteria for dose reduction/suspension of panitumumab

Refer to "8.5.1.2 Criteria for dose reduction/suspension of panitumumab".

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 Overdose of panitumumab

Overdose of panitumumab is defined as below regardless of whether or not adverse events have occurred.

① Administration at doses higher than the approved dose of panitumumab (6 mg/kg)

② The next dose is administered within 10 days after the date of previous administration.

Aiming at consistent entry of significant safety information regarding overdose in the database, the investigator or subinvestigator will record all cases of overdose (irrespective of the presence or absence of adverse events) in the page of overdose of the Case Report Forms. Adverse events associated with overdose will be recorded in the page of "Adverse Events" in the Case Report Forms according to "10.0 ADVERSE EVENTS".

Serious adverse events (SAE) associated with overdose will be reported according to the procedure described in "10.2.2. Collection and reporting of serious adverse events."

In the cases of overdose of panitumumab, the investigator or subinvestigator will provide treatment appropriate for the symptoms.

8.8 Criteria for discontinuation of protocol treatment

The protocol treatment specified below 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 decides on discontinuation of protocol treatment. The investigator should record the main reason for discontinuation of protocol treatment in the case report form according to the classification described below. See "9.3 Records of subjects who discontinued before enrollment"for subjects withdrawn from the study before enrollment.

<Common for Protocol Treatment [1] and [2]>

1. Adverse event
   When protocol treatment is postponed for 43 days or more after the day of starting the last cycle, or when the next protocol treatment cannot be resumed because of adverse events even after the passage of at least 43 days after the start of the last cycle of the protocol treatment. However, postponement due to holidays is allowed.

2. 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 randomization of protocol treatment has not been observed.

3. Lost to follow-up
   When a subject fail to make visits and cannot be contacted. That attempts were made to contact the subject should be recorded in the source documents.

4. Voluntary discontinuation
   When a subject wishes to discontinue study participation.

5. Discontinuation of entire study
   When study discontinuation is decided by the sponsor, or IRB such as the ethics review committee.

6. Pregnancy
   When a female subject is found out to be pregnant.
   Note: Study participation should be immediately discontinued when pregnancy is known.

7. Lack of efficacy
   When PD is evident in the clinical or imaging evaluation

8. Death during protocol treatment
   Death before discontinuation of protocol treatment is decided

9. When surgery aimed at curative resection (complete resection: R0 resection) of colorectal cancer is scheduled

10. Other
    When protocol treatment cannot be started after subject allocation, collect the reason (e.g., the criteria for initiation of protocol treatment were not met

<Protocol Treatment [1] >

11. Not satisfying at least one of the inclusion criteria for randomization or meeting any of the exclusion criteria <specify the applicable inclusion/exclusion criteria>

8.9 Contraindicated drugs/therapies

The drugs and therapies shown below are contraindicated from informed consent until 28 days (4 weeks) after discontinuation of protocol treatment. The investigator and/or subinvestigator (hereinafter referred to as the investigator) should instruct the patients not to use any drugs including over-the counter drugs other than the prescribed drugs without prior consultation. The following therapies are allowed to be started without waiting for the specified period only when the scheduled tests are performed until the next treatment upon starting it within 28 days (4weeks) after discontinuation of protocol treatment.

- ✓ Chemotherapy other than protocol treatment
- ✓ Hormone therapy
- ✓ Immunotherapy
  - ➢ Cellular immunotherapy

- ➢ Vaccine therapy
- ➢ Cytokine therapy
- ➢ Biological response modifiers (BRM)
- ➢ Antibody therapy
- ➢ Gene therapy

✓ Other antibody therapy

✓ Radiotherapy

However, the treatment to relieve the pain of metastatic bone tumor is allowed.

✓ Hyperthermia therapy

✓ Denosumab*

*: Use of bisphosphonates is allowed.

✓ Study drug and unapproved drug

8.10 Allowed supportive care and combination medications

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

- Neutropenia
  Administration of G-CSF products is recommended. G-CSF should be administered according to the NHI indications and should not be prophylactically used.

- Nausea, vomiting
  Premedication including prophylactic administration of antiemetics is allowed. Premedication with 5-HT_3 (serotonin) receptor antagonists, NK1 (neurokinin 1) receptor antagonists, steroids, and antihistamines may be carried out using the method employed at each study site.

- Allergic reaction
  Treatment with adrenal corticosteroids, antihistamines, etc. may be considered at the time of onset or for premedication at the start of protocol treatment. Careful administration of panitumumab by slowing the infusion speed may be considered.

- Interstitial pneumonia
  Interstitial pneumonia should be treated according to the severity (e.g., steroid pulse therapy).

- Other
  Drugs for treatment of adverse events may be coadministered at the discretion of the investigator. 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 when any of panitumumab-related adverse events shown below is observed. The absence of supporting therapy does not constitute a protocol deviation.

- It is recommended that oral minocycline, etc. be administered when skin disorder is observed.

- At the time of onset of skin disorder
  External salicylic acid petrolatum (10%)
  External steroid therapy (example)
  Face: hydrocortisone butyrate (0.1%)
  Trunk: difluprednate (0.05%)

It is recommended the following skin care prophylactically against the skin disorder from the start of protocol treatment [1].
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).

- At the time of onset of 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

8.11 Handling of surgery aimed at curative resection (complete resection: R0 resection) of colorectal cancer

Surgery is recommended for patients who can tolerate curative resection (complete resection: R0 resection) thanks to the antitumor effect after initiation of protocol treatment.

Protocol treatment should be discontinued when surgery aimed at curative resection (complete resection: R0 resection) of colorectal cancer is scheduled, and all tests and observation scheduled at discontinuation of protocol treatment should be conducted (see “9.1 Study calendar”).

8.12 Recommended follow-up therapy

8.12.1 Recommended second-line treatment

- Group A: Administration of bevacizumab in combination with IRI-based chemotherapy is recommended.
- Group B: Readministration of bevacizumab in combination with OXA-based chemotherapy is recommended.

8.12.2 Recommended third-line or subsequent treatment

- Group A: All approved drugs (regorafenib, etc.) should be administered appropriately as best as possible.
- Group B: Administration of bevacizumab in combination with the IRI-based chemotherapy is recommended. After that, all approved drugs (regorafenib, etc.) should be administered appropriately as best as possible.

9.0 PROTOCOL, EVALUATION ITEMS AND PROCEDURES FOR OBSERVATIONS

9.1 Study calendar

The investigator should collect data according to the following procedures. The same investigator should perform tests/observation/evaluation of subjects in principle.

Table 9.a Study calendar (Protocol Treatment [1])

Item	Enrollment	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Discontinuation of protocol treatment*7
Informed consent	●*							
Eligibility	●							
Subject background	●							
Clinical findings (physical examination) *1	●	●	●	●	●	●	●	●
Vital signs*1		●	●	●	●	●	●	●
Height, body weight*1,*2	●		○	○	○	○	○	
ECOG P.S. *1	●	●	●	●	●	●	●	●
Treatment compliance		●	●	●	●	●	●	
Laboratory tests								
Hematology*1	●*3	●	●	●	●	●	●	●
Serum chemistry*1	●*3	●	●	●	●	●	●	●
Tumor markers*1	●*3	●						○*4
Imaging test *1 (thoracoabdominal-pelvic CT/MRI)	●*5	●		●				○*6
NRAS test	●*8							
Adverse Event	—	←			●		→	

●: Mandatory, ○: Perform as necessary

*: Consent should be obtained at enrollment

*1: Perform before initiation of each cycle of protocol treatment.

*2: Measure and record only body weight when the dose is changed.

*3: The test in Cycle 1 may be skipped when the entry test has been performed 0 to 2 days before treatment in Cycle 1. The test in Cycle 1 will be performed before treatment in Cycle 1 when the entry test has been performed more than 2 days before treatment in Cycle 1.

*4: Measure only when more than 56 days (8 weeks) have passed after the previous measurement.

*5: If the imaging test before enrollment is performed within 14 days prior to Cycle 1, the test of first cycle can be omitted, but an imaging test should be preferably conducted immediately before administration of the 1st cycle.

*6: Perform the imaging test within 28 days (4 weeks) after decision on discontinuation for subjects withdrawn from the study for any reason other than PD.

*7: Perform within 28 days (4 weeks) after discontinuation. Perform until the next treatment when it will be startied within 28 days (4weeks) after discontinuation.

*8: Perform the test in the patients who agree to participate in the study before *NRAS* test comes to be covered by insurance, and the patients who agree to participate in the study after *NRAS* test comes to be covered by insurance but before the test becomes feasible at the study site and who give consents to the conduct of the test. The timing of submission of samples does not need to be upon registration.

Table 9.b Study calendar (Protocol Treatment [2])

Item	Randomization	Cycle 7§	Cycle 8	Cycle 9	Cycle 10	Cycle 11～§	9 months after a randomization	Discontinuation of protocol treatment*[7]	Follow-up period *[10]
Eligibility	●								
Clinical findings (physical examination)*[1]	●	●	●	●	●	●	●	●	
Vital signs *[1]		●	●	●	●	●	●	●	
Height, body weight *[3]		○	○	○	○	○	○		
ECOG P.S.*[1]		●	●	●	●	●	●	●	
Treatment compliance (incluing the test at discontinuation)		●	●	●	●	●	●	●	
Laboratory tests									
Hematology *[1]		●*[2]	●	●	●	●	●	●	
Serum chemistry *[1]		●*[2]	●	●	●	●	●	●	
Tumor markers§, *[1]		●*[2]				●	○§	○*[8]	
Imaging test (thoracoabdominal-pelvic CT/MRI)§	●*[4]					●*[5]	●*[6]	○*[9]	○
Follow-up therapy									●
Survival survey									●
Adverse Event	←				●		→		–

●: Mandatory, ○: Perform as necessary

§: As a rule, tests of tumor markers and imaging tests will be conducted in the (4n + 3)th administration cycle. However, when the administration interval becomes longer because of the criteria for extension of administration period, the tests will be conducted at appropriate timings.

*1: Perform before initiation of each cycle of protocol treatment.

*2: The test in Cycle 7 may be skipped when the test at randomization has been performed 0 to 2 days before treatment in Cycle 7.

*3: Measure and record only body weight when the dose is changed.

*4: Masure between the day of administration in 6th cycle and randomization.

*5: Reduce the frequency of imaging test to once every 112 days (16 weeks) 14 days (± 2 weeks) when two years have passed since initiation of protocol treatment.

*6: Perform the imaging test when a § rule and 9 months after a randomization

*7: Perform within 28 days (4 weeks) after discontinuation.

*8: Perform only when 56 days (8 weeks) or more have passed after the previous measurement.

*9: Perform the imaging test within 28 days (4 weeks) after decision on discontinuation for subjects withdrawn from the study for any reason other than PD.

*10: Perform every 6 months (approximately) after discontinuation of protocol treatment.

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

The investigator will perform the following as scheduled in “9.1 Study calendar.”

9.2.1 Informed consent procedure

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

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

A unique subject ID code will be assigned to each subject when explanation is given to obtain consent. The subject ID code will be used throughout the study period.

9.2.2 Procedures for registration and allocation of drugs

9.2.2.1 Procedures for registration and initiation of protocol treatment

The investigator will register subjects according to the following procedures.

1) The investigator or study collaborator should record the necessary items in subject screening list for a subject who was selected to receive explanation for obtaining consent for study enrollment.

2) The investigator or study collaborator should input the necessary items into the Web case registration system for a subject who has given consent.*
*: The study collaborator may input into the Web case registration system by instruction of the investigator.

3) Eligibility of a prospective subject is judged by the Web case registration system and a protocol study group will be assigned when the subject is eligible.

4) The investigator and study collaborator will check the registration result and assigned protocol study group on the Web case registration system. The registration result and assigned protocol study group will be sent via e-mail from the Web case registration system to the investigator and study collaborator.

5) The investigator should start the allocated protocol treatment within 15 days of formal registration (including the same day of week as the day of enrollment).

6) The investigator or study collaborator should immediately contact the sponsor and input necessary items in the Web subject registration system when the study drug is not administered for reasons such as withdrawal of consent after allocation, or when a change related to allocation is made to the data of the registered subject.

9.2.2.2 Preparation and storage of allocation procedures

The allocation manager (person designated by the sponsor) should prepare the allocation procedures and manage allocation information of subjects. Minimization method should be used for allocation of protocol treatment using the allocation factors of the study site, age (20 to 64 years/65 to 79 years), and presence/absence of liver metastasis. The allocation information should be stored in a safe place and made accessible only by the authorized persons.

9.2.3 Subject demographics

The following demographic data will be collected: date of birth and sex at the time of enrollment.

The following data concerning the target disease of colorectal cancer will be collected.

1) Tissue type
The tissue type will be assessed based on the histological findings in the “Japanese Classification of Colorectal Carcinoma” and recorded in the case report form with the date and site of sampling for diagnosis.

   - Date of initial diagnosis
   - Date of diagnosis of Stage 4 (no need for input the case report form when it is the day of the initial diagnosis)

2) History of treatment

- History of surgery
  - ✧ For subjects with a history of surgery, the date of surgery, surgery site (primary/metastatic lesion), and the number of lymph nodes resected. Endoscopic surgery, which is not considered a history of surgery, should not be entered into the case report form.
- History of radiotherapy
  - ✧ For subjects with a history of radiotherapy, the final irradiated date.
- History of preoperative and/or postoperative adjuvant chemotherapy
  - ✧ For subjects with a history of adjuvant chemotherapy, the type of preoperative and/or postoperative adjuvant chemotherapy, date of final treatment.

3) Information on metastatic organ

- Number of metastatic organs (0, 1, 2 or more)*
  *: The primary lesion/regional lymph node is not included, and the distant lymph node is counted as "one organ" even if there is more than one.
- Metastatic organs (liver, lung, peritoneum, lymph node*, bone, adrenal gland, skin, other**)
  *: distant lymph node is counted as "one organ" even if there is more than one.
  **: The name of the organ will be recorded in the case report form.

9.2.4 Medical history

A medical history is defined as any clinically problematic disease or symptom that has resolved within one year prior to initiation of protocol treatment. Any notable medical history will be recorded in the case report form.

9.2.5 Current medical condition

A current medical condition is defined as any symptom or disease present at initiation of protocol treatment. Any notable current medical condition will be recorded in the case report form. Clinically problematic laboratory test data, ECG findings, and abnormal physical examination findings observed immediately before initiation of protocol treatment should be handled as a current medical condition at the discretion of the investigator.

9.2.6 Clinical findings (physical examination)

The following locations and parts of the body will be examined:
(1) eyes, (2) ears, nose, and throat, (3) cardiovascular system, (4) respiratory system, (5) gastrointestinal system, (6) dermatologic system, (7) extremities, (8) musculoskeletal system, (9) nervous system, (10) lymph nodes, (11) other.

In particular, subjects will be checked for the following symptoms at the physical examination: allergic reaction, fatigue, rash acneiform, dry skin, paronychia, infusion related reaction, palmar-plantar erythrodysaesthesia syndrome, anorexia, diarrhoea, nausea, vomiting, oral mucositis, febrile neutropenia, infection, hemorrhage, pain, peripheral motor neuropathy, peripheral sensory neuropathy, alopecia, thromboembolism, gastrointestinal perforation, pneumonitis, and pulmonary fibrosis.

For diagnosis after initiation of protocol treatment, evaluate the clinically problematic abnormality compared with the result of diagnosis before initiation of protocol treatment.

9.2.7 Body weight and height

Body weight and height will be measured before enrollment. Body weight (kg) will be measured to the first decimal place and rounded off to the first decimal place when the second decimal place is known. Height (cm) determined will be expressed in integer value (rounded off to integer).
In principle, measurement is unnecessary during the treatment period. However, body weight should be recorded in the case report form when the measured value is used to change the dose of protocol treatment.

9.2.8 Vital signs

The following vital signs will be measured: body temperature and blood pressure and pulse rate (bpm) at sitting position (after rest for 5 min or longer). In particular, subjects will be checked for fever and hypertension.

9.2.9 ECOG P.S.

ECOG P.S. will be assessed according to Table 9.c. Assess again immediately before administration of the 1st cycle when the entry test has been performed more than 14 days away before enrollment.

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

Grade	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

9.2.10 Treatment compliance (Protocol Treatment [1] and [2] implementation status)

The investigator should record the compliance with protocol treatment in the case report form as follows:

- When protocol treatment is administered: The dose and the date of treatment should be recorded. The reason for dose reduction should also be recorded when appropriate.
- When any drug used in protocol treatment is suspended: The date of suspension should be recorded.

- When any drug used in protocol treatment is discontinued: The date and reason for discontinuation should be recorded.

9.2.11 Laboratory tests

The laboratory tests performed at each time point during the study are shown in Table 9.d to Table 9.g. The laboratory tests will be performed at each study site.

The investigator should evaluate the reported laboratory test results. The representative investigator at each site should be administer and store the standard value of laboratory tests.

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

Hematology	Serum chemistry	Tumor marker
WBC	Total bilirubin	CEA
Neutrophil count	ALT	CA19-9
Platelet count	AST	
Hemoglobin content	Creatinine	

Immunology
HBs antigen
Hepatitis tests including anti-HCV

Table 9.e Laboratory tests performed before the start of each cycle of treatment (Protocol Treatment [1])

Hematology	Serum chemistry	Tumor marker
WBC*	Total bilirubin*	CEA*, †
Neutrophil count*	ALT*	CA19-9*, †
Platelet count*	AST*	
Hemoglobin content*	Creatinine*	
	Mg	
	ALP	
	LDH	
	Albumin	
	Na	
	K	
	Ca	
	Cl	

*: The test in Cycle 1 may be skipped when the entry test has been performed 0 to 2 days before treatment in Cycle 1. The test in Cycle 1 will be performed before treatment in Cycle 1 when the entry test has been performed more than 2 days before treatment in Cycle 1.
†: Measure before the initiation of 1st cycle only.

Table 9.f Laboratory tests performed before the start of each cycle of treatment (Protocol Treatment [2])

Hematology	Serum chemistry	Tumor marker
WBC	Total bilirubin	CEA*
Neutrophil count	ALT	CA19-9*
Platelet count	AST	
Hemoglobin content	Creatinine	
	Mg	
	ALP	
	LDH	
	Albumin	
	Na	
	K	
	Ca	
	Cl	

*: Perform every 8 weeks.

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

Hematology	Serum chemistry	Tumor marker
WBC	Total bilirubin	CEA*
Neutrophil count	ALT	CA19-9*
Platelet count	AST	
Hemoglobin content	Creatinine	
	Mg	
	ALP	
	LDH	
	Albumin	
	Na	
	K	
	Ca	
	Cl	

*: Measure only when more than 56 days (8 weeks) have passed after the previous measurement.

9.2.12 Imaging test (thoracoabdominal-pelvic CT/MRI)

Imaging test before enrollment will be performed within 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 28 days prior to enrollment.

During the period of Protocol Treatment [1], imaging test will be performed before administration in the 1st cycle and the 3rd cycle. The results of imaging tests before administration in the 1st cycle will be handled as the image data for measurable lesion, and the test will be performed within 14 days prior to initiation of Protocol Treatment [1] (including the same day of week as the day of enrollment). If the imaging test before enrollment is performed within 14 days prior to initiation of Protocol Treatment [1], the imaging test can be omitted, but an imaging test should be preferably conducted immediately before administration of the 1st cycle.

Imaging test before initiation of Protocol Treatment [2] will be conducted between administration of the 6th cycle and randomization. It will be performed every 8 weeks after initiation of Protocol Treatment [2] (See "Table 9.b Study calendar (Protocol Treatment [2])" for details.)

Thoracoabdominal-pelvic CT (in principle, contrast CT with a slice width of 5 mm or less, but MRI is also acceptable) will be used for imaging test, and the modality and the date of imaging test will be recorded in the case report form.

The same modality should be used during protocol treatment throughout the study period.

The investigator should evaluate the test results according to the RECIST v1.1 and record the evaluation results in the case report form.

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 for protocol treatment should be performed within 4 weeks including the day of decision (including the same day of week as the day of decision).

9.2.13 *NRAS* test

9.2.13.1 Subjects

The subjects will be the patients who agree to participate in the study before *NRAS* test comes to be covered by insurance, and the patients who agree to participate in the study after *NRAS* test comes to be covered by insurance but before the test becomes feasible at the study site and who give consents to the conduct of the test.

For the patients who receive *NRAS* test at the study site after *NRAS* test has come to be covered by insurance, test results regarding each codon shown in Table 9.h will be recorded in the case report forms.

9.2.13.2 Samples and submission

For the patients who have given a consent to the test, the tumor tissue samples which have been collected in surgery or biopsy performed prior to informed consent, and which are used for evaluation of *KRAS* will be used for the test. From paraffin-embedded samples, 5-μm slices will be obtained, and 5 pathological samples fixed on slide glasses will be submitted to [redacted]. It is also acceptable to submit samples in the form of paraffin-embedded samples. When paraffin-embedded samples are submitted, [redacted] will prepare a necessary number of slide glass samples, and will return the remaining sample to the study site.

Investigators will use the materials prepared by [redacted] in advance at the beginning of the study and send the samples to [redacted]. Details are described in the written procedure prepared separately. [redacted] will send in advance the materials necessary for storing and sending samples to the study sites where enrollment of study subjects has become possible.

Details regarding submission of tumor tissues will be described in the written procedure prepared separately.

9.2.13.3 Data

Among the subjects specified in "9.2.13.1 Subjects", the investigators will enter the following issues regarding the submitted tumor tissues in the case report forms for the subjects for whom the samples required for the test have been submitted to [redacted]. However, recording of the results of *NRAS* measurement in the case report forms will be unnecessary.

1) Procedure of sample collection

2) Timing of sample collection

3) Number of slides submitted in the case of pathological slides

For the patients who are enrolled in the study after *NRAS* test has come to be covered by insurance and who receive *NRAS* tests at the study sites, the investigators will record the presence or absence of mutation of each of the following codons in the case report forms.

Table 9.h EXON and codon verified on *NRAS* test

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

9.2.14 Surgery aimed at curative resection (complete resection: R0 resection) of colorectal cancer

When surgery is performed for patients who are expected to tolerate curative resection of colorectal cancer during protocol treatment, the operative procedure, date of surgery, and postoperative assessment of residual tumor should be recorded in the case report form. The residual tumor is assessed according to the table shown below, and the histological results of resection specimens should be recorded in the case report form wherever possible. The date when surgery aimed at curative resection (complete resection: R0 resection) of colorectal cancer is scheduled is considered as the date of discontinuation of protocol treatment

When surgery aimed at curative resection is performed in more than one session, the number of sessions should be recorded in the case report form. As for the postoperative assessment of residual tumor, data obtained by the time of initiation of subsequent treatment should be recorded in the case report form. Data generated after initiation of subsequent treatment will be collected through monitoring and assessed by the steering committee for the validity.

Table 9.i Residual tumor after surgical treatment

Classification	Criteria
RX	The presence of residual tumor cannot be assessed.
R0	No residual tumor
R1	Resected, but tumor on the margins of a surgical resection specimen or the radial margin
R2	Macroscopic residual tumor

9.2.15 Survival survey

All subjects will be followed up after discontinuation of protocol treatment to confirm survival of subjects. Survival survey should be continued until a subject dies or the sponsor terminates the study.

- Date of death or date of last confirmation of survival

9.2.16 Follow-up therapy

When follow-up therapy is performed after discontinuation of Protocol Treatment [2], the following information on follow-up therapy should be collected until a subject dies or the sponsor terminates the study.

- Name of regimen (name of drugs used)

9.3 Records of subjects who discontinued before enrollment

For subjects withdrawn from the study before enrollment of protocol treatment, the main reason for discontinuation should be recorded in the case report form according to the following categories.

- Not satisfying at least one of the inclusion criteria or meeting any of the exclusion criteria <specify the applicable inclusion/exclusion criteria>
- Serious deviation from the protocol
- Lost to follow-up
- Voluntary discontinuation <specify the reason>
- Discontinuation of the entire study
- Other <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 all untoward 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 treatment
- Requiring invasive diagnostic treatment
- Requiring discontinuation or change in the dose of protocol treatment (chemotherapy, panitumumab and bevacizumab) or concomitant drugs under use
- Considered unfavorable by the investigator

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. Any adverse events that could not be expressed in medical terminology (name of diagnosis) should be recorded with signs or symptoms observed.

Laboratory test findings:

Abnormal laboratory values and ECG findings are recorded as adverse events when the investigator judges the course to be clinically problematic (in other words, when certain action or treatment is required, or the investigator judges the change to have exceeded the normal physiological variation range of the subject).

Retest and continued monitoring of abnormality are not considered treatment. Also, repeated or additional conduct of non-invasive test for verification, evaluation and monitoring of abnormality are not considered treatment.

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 is recorded as an adverse event and the investigator should record in the case report form that the adverse event as aggravation of the complication (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 should record it so that a reported adverse event name is a change from the baseline (e.g., aggravation of XX).

Aggravation of adverse events:

When any secondary sign/symptom develops due to an adverse event, it should be considered as a new adverse event and recorded in the case report form. The investigator should record it so that a reported adverse event name is a change from the baseline (e.g., aggravation of XX).When the severity of an adverse event is changed, the event should be recorded once at the highest degree of severity (grade based on the CTCAE [Japanese edition JCOG version 4.03]).

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. 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, clinical or imaging progression of the preexisting cancer (including new metastasis) is considered a serious adverse event when the severity satisfies any of the criteria for seriousness specified in Section 10.1.3.

Overdose of panitumumab:

Overdose of panitumumab which does not accompany the occurrence of events will not be regarded as adverse events, but the overdose of panitumumab will be recorded in the page of overdose in the case report form. If any events have occurred, they will be recorded as adverse events in the page of adverse events in the case report form.

10.1.3 Serious adverse events

Of all the unfavorable medical events that developed by 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.

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.

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. Requires inpatient hospitalization or prolongation of existing hospitalization.
   Hospitalization described below is not considered 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 Noteworthy adverse events for the sponsor

The events listed in "Takeda Medically Significant AE List" in Table 10.a will be handled as noteworthy adverse events by the sponsor irrespective of the severity determined by the principal investigator or investigator. Of the events listed in Table 10.a, the adverse event that the principal investigator or investigator determines to be serious should be handled as a 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 and defined as follows based on the CTCAE (Japanese edition JCOG version 4.03):

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

*: 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 (OXA, 5-FU, or panitumumab) and adverse events 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 with treatment discontinuation (including clinical course after discontinuation). Possibly due to protocol treatment (chemotherapy 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 or panitumumab). Very likely due to other factors such as underlying disease, complications, and concomitant drugs/treatment.

10.1.7 Date of onset

Judge the date of onset of adverse event according to the following criteria:

Adverse event, etc.	Date of onset
Signs, symptoms, diseases (diagnosis name)	Record the date when the subject or the investigator noticed the first signs and symptoms of adverse event.
Asymptomatic disease	Record the date of obtaining a definite diagnosis after conducting a test for diagnosis. Record the date of obtaining a definite diagnosis even when the test findings show old findings or suggest approximate timing of onset.
Aggravation of complications	Record the date when the subject or the investigator noticed the signs and symptoms of adverse event for the first time.
Abnormal laboratory findings after initiation of protocol treatment	Record the date of test where abnormal laboratory values considered clinically problematic were observed.
Abnormality was observed on the test at initiation of protocol treatment, and aggravation was shown on subsequent tests.	Record the date of tests when values were medically judged to be obviously increased and decreased based on the changes in test values.

10.1.8 Date of resolution

The date when adverse event resolved (or resolved with sequelae). Date of death when a subject died of the concerned adverse event. When recovery cannot be confirmed at study completion, it is considered ongoing.

10.1.9 Incidence

When the investigator considers the first occurrence up to the final remission of a series of adverse events which repeatedly appear to be resolved or recurred as one event (e.g., constipation, diarrhoea, vomiting, etc.), it is considered to be “intermittent”. Other events are considered “ongoing”.

10.1.10 Action taken for protocol treatment

The action taken for OXA, 5-FU, or panitumumab in protocol treatment is classified and defined as follows:

Treatment discontinued	Treatment with OXA, 5-FU, or panitumumab in protocol treatment was discontinued due to the adverse event.
Not applicable	Treatment with OXA, 5-FU, or panitumumab in protocol treatment had already been completed or discontinued by the time of the onset of the adverse event.

10.1.11 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
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 (no need for recording the date of death in this case)
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.
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 four weeks after discontinuation of protocol treatment.

10.2.1.2 Reporting of adverse events

At each visit, the investigator should assess the onset of subjective symptoms are present. 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 should follow up all subjects who developed adverse events irrespective of a causal relationship with protocol treatment until disappearance of symptoms or return of abnormal laboratory values to the value at initiation/dose reduction of protocol treatment, or until observed changes can be sufficiently explained for other events (persistent/irreversible adverse event, etc.).

All adverse events should be recorded in the case report form. The name of an adverse event, date of onset, date of disappearance, frequency, severity, causal relationship with protocol treatment (unrelated or related), action taken for protocol treatment (chemotherapy and panitumumab), outcome, and seriousness should be recorded.

Follow-up period of adverse events is until recovery of an adverse event, or the investigator judges that further follow-up would not be necessary.

When requested by the representative researcher, the investigator should check the additional necessary information and data and complete recording them in the case report form within the designated period.

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 judges that a serious adverse event has occurred based on the reporting by a subject, etc. and the result of various tests, imaging findings or definitive diagnosis, a report should be submitted to the director of the study site and the representative researcher (see attached sheet for contact information) within one working day and a report should be made via the sponsor to the investigators of other sites jointly performing the clinical study. In addition, the investigator should submit a formal detailed report within 10 calendar days.

The following items are the requisite for reporting within one working day, and other items should be reported as best as possible.

- Study title
- Subject ID code
- Name of study site
- Name of investigator
- Name of serious adverse event, course (date of onset, reason for the judgment of "serious", protocol treatment given, causal relationship with protocol treatment, course, and outcome)
- Action taken for the serious adverse event (suspension of new enrollment, revision of the written informed consent, newly obtaining consent from other subjects)

10.2.3 Dissemination of a serious adverse event to study sites jointly performing the clinical study

When the head of study site receives a report of a serious adverse event from the investigator, he/she should obtain the opinions of the IRB such as the ethics review committee, add the following item to the report of the investigator, and disseminate it via the sponsor to the data monitoring committee and the study sites jointly performing the clinical study.

- Date of review by the IRB such as the ethics review committee, summary of review, result, and necessary actions, etc.

10.3 Follow-up of serious adverse events

The investigator 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 should submit a report specifying details of the change to the head of study site and the sponsor. When requested by the sponsor or the IRB 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.

10.4 Reporting of additional information on adverse events

When the sponsor requests the principal investigator or investigator to provide additional information on an adverse event for reporting to regulatory authorities and other agencies, the principal investigator or investigator, after verifying the required additional information, must enter it in an electronic CRF system or submit a written report within the period determined by the sponsor.

10.5 10.5 Notification of serious adverse events to IRB such as an ethics review committee and regulatory authorities

When the director of the study site has received a report of an SAE from the principal investigator, the director will seek advice from the IRB such as the ethics review committee, and notify the SAE to other study sites via the sponsor or the contract research organization (CRO).

If the SAE reported from the principal investigator is unexpected, the director of the study site will prepare a written report of the unexpected SAE containing the information reported from the principal investigator plus the following information, and submit the report to the Minister of Health, Labour and Welfare, and notify it to other clinical study sites (The director of the study site may report it to the Minister of Health, Labour and Welfare via the sponsor, and notify it to other clinical study sites via the sponsor).

- Actions taken for the SAE
  (e.g., any interruption of enrollment of new subjects, revision of the informed consent form, re-consent from other subjects currently in the study)

- Date reviewed by the IRB such as the ethics review committee, review summary, review results, and necessary actions to be taken, etc.

- Notification to other study sites

The sponsor must report an unexpected SAE, and other SAE which meets the local criteria for an expedited report, to regulatory authorities, the principal investigator, and the director of the study site, according to the regulations.

The sponsor or the CRO must submit the expedited reporting of an unexpected or expected SAE to regulatory authorities in compliance with the reporting time frames determined by the regulations after first knowledge of the event or acquisition of the additional information. In addition, the sponsor must submit the expedited reporting of other important safety information which is expected to greatly affect the risk benefit of the study drug, continuation of the treatment with the study drug, or continuation of the clinical study, in the same way. The study site will submit the copy of the document of expedited reporting to the IRB such as the ethics review committee.

11.0 COMMIITTEES ESTABLISHED FOR ADMINISTRATIVE STRUCTURE AND 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 steering committee members and biostatistician, and the sponsor or the person designated by the sponsor will act as the secretariat.

See the supplement for the research steering committee members.
The research steering committee will not be informed of the treatment allocation throughout the study period.

Details of the research steering committee will be specified in a separately prepared SOP.

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 person designated by the sponsor will act as the secretariat. See the supplement for the DMC member.

The DMC will notify a DMC advisory report on continuation/discontinuation of the study and change of the study plan according to the safety analysis results for evaluation 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.

12.0 DATA MANAGEMENT AND STORAGE OF RECORDS

Detailed procedures concerning data management will be specified in the data management plan. Adverse events, medical history, and concurrent conditions should be coded using the MedDRA.

12.1 Case report form

The investigator should prepare the case report form for all subjects who have provided informed 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 and study collaborators with training for utilization of EDC. The case report form will be used to report the information collected during the study period to the sponsor. The case report form will be prepared in Japanese. Data will be directly entered into the case report form.

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

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

The data below will be directly recorded into the case report form.

- Severity and causal relationship of adverse event with “OXA”, “5-FU”, or “panitumumab” in protocol treatment

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

The sponsor or its designee should confirm the accuracy and completeness of the case report form during a visit to a study site. The sponsor or its designee should access to the medical records of study subjects and in-house records to ensure the accuracy of the case report form. The completed case report form is the property of the sponsor, and the investigator should not divulge the information to a third party other than the regulatory authority without a written permission of the sponsor.

12.2 Time limit for data input into the EDC

It is recommended that data obtained after informed consent be entered into the EDC 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 efforts be made to adhere to the time frame.

1) At enrollment: within two weeks after enrollment

2) During protocol treatment: within two weeks after discontinuation of each cycle of protocol treatment

3) At discontinuation of protocol treatment: within four weeks after discontinuation of protocol treatment

4) Imaging test results: within two weeks after evaluation of efficacy

5) Follow-up period: within two weeks after request for follow-up

6) Inquiry about data input into the EDC: within two weeks after inquiry

12.3 Storage of records

The investigator or the head of study site should store the following materials including those specified in Section 12.1 and study specific documents for use by the investigation or audit by the regulatory authority and the sponsor or their designee. 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 case report form (copy)/electronic copy of electronic case report form containing audit trail. The investigator and the head of study site should store the essential documents until five years after discontinuation or completion of the study. However, when the sponsor requires a longer storage period, the head of study site will discuss the period and methods of storage with the sponsor.

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

13.0 STATISTICAL ANALYSIS METHODS

13.1 Statistical and analytical plans

The statistician in charge should prepare and finalize the statistical analysis plan (SAP) before data fixation. Detailed definition of endpoints and analysis methods should be specified in the SAP to cope with the purpose of all studies.

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.

13.1.1 Analysis set

Two analysis sets, "full analysis set" and "safety population", are used in this study. "Full analysis set" is defined as "randomized subjects," and the "safety population" is defined as "the subjects who received at least one dose of protocol treatment after randomization."

The sponsor should confirm the definition of analysis sets and appropriateness of analytical handling rules of the subject data in the analysis sets before data fixation, add handling of problematic issues which have not been prescribed in the planning stage, and finalize the SAP.

13.1.2 Analysis of demographic and other baseline characteristics

The following analysis should be conducted in "full analysis set."

Concerning major subject background factors, frequency analysis should be conducted for numerical data and summary statistics should be calculated for quantitative data for each treatment group and collectively for all treatment groups.

13.1.3 Efficacy analysis

13.1.3.1 Primary endpoint and analysis method

[Primary endpoint]

Progression-Free Survival (PFS)

The PFS is the period from the day of randomization (Day 0) until the day of judgment of exacerbation from the day of randomization, or until death by all causes, whichever comes earlier.

Progression includes both PD based on diagnostic imaging according to RECIST Guidelines (ver 1.1) and progression of the underlying disease which cannot be confirmed on diagnostic imaging (clinical progression). If progression is diagnosed on the basis of diagnostic imaging, the date of the imaging test will be regarded as the date of progression, and the date of clinical judgment will be regarded as the date of progression in the case of clinical progression. Even when a condition is regarded as PD according to the criteria for efficacy evaluation, such as in the cases of extreme shrinkage of the tumor size, but "progression is obviously ruled out" from a clinical point of view, PD according to the efficacy evaluation criteria will be given priority and the condition will be regarded as progression (in this case, clinical judgment will be prioritized with respect to whether or not protocol treatment should be continued). When the condition is not regarded as PD according to the efficacy evaluation criteria but it is obviously deemed as progression from a clinical point of view, the clinical judgment will be prioritized and the condition will be regarded as progression. The study will be cut off for the surviving patients without a diagnosis of progression on the last day of clinical confirmation of the absence of progression (date of last confirmation of progression-free survival; Confirmation of the absence of progression on imaging test and sample

test is not essential. Clinical confirmation of the absence of progression at outpatient clinic will suffice. Reporting by telephone only will not be accepted). Even in the cases of protocol treatment discontinuation for such reasons as toxicity and patients' withdrawal in which other treatment has been given in the after-care, events and cutoff will be handled in the same manner. In other words, the timing of discontinuation of treatment or the date of the start of after care will not be regarded as the cut-off dates.
[Main analysis]

Perform the following analysis for the “full analysis set”.

For each treatment group, calculate the progression-free survival rate at a given time point and its 95% confidence interval (two-sided) by Kaplan-Meier method, and calculate the quartile of PFS and its 95% confidence interval (two-sided). At the same time, draw a Kaplan-Meier chart for the progression-free survival rate. If the median value of observed PFS is 9 months or more in each group, the treatment regimen concerned will be regarded as being of worth of further investigation.

Moreover, for the sake of reference, calculate the hazard ratio of Group B to Group A and its 95% confidence interval (two-sided) on the basis of the stratified Cox regression model and apply the log-rank test.

13.1.3.2 Secondary endpoints and analysis method

[Secondary endpoints]

Overall survival（OS）

OS is defined as the period from the day of randomization (Day 0) until death by all causes.
[Analysis method]

For OS, perform the same analysis as that for the primary endpoint for the "full analysis set."

・Response rate（RR）

RR is defined as the percentage of subjects who have shown complete response or partial response as the best overall response in RECIST ver 1.1 after randomization. The overall response will be complete response, followed by partial response, stable disease, progression, and nonevaluable in this order.

[Analysis method]

In "full analysis set," RR and two-sided 95% confidence interval will be calculated for each group. At the same time, the inter-group difference of RR (Group B－Group A) and the two-sided 95% confidence interval will be calculated.

・Time to treatment failure（TTF）

TTF is defined as the period from the date of randomization (counted as Day 0) to the date of judgment of discontinuation of protocol treatment, the date of judgment of progression, or the date of death for all causes, whichever has come earliest.

[Analysis method]

For TTF, perform the same analysis as that for the primary endpoint for the "full analysis set."

13.1.3.3 Other efficacy endpoints

See "5.2 Endpoints".

13.1.3.4 Data conversion method and handling of missing data

The subjects who have not experienced any events at the end of study on the data cutoff date in the analyses of PFS and OS will be handled as the cutoff cases.

For the cutoff cases, the last day of available image evaluation results prior to the data cutoff date for image test will be regarded as the timing of cutoff in the analysis of PFS, and the data cutoff date or the date of last confirmation of survival, whichever comes earlier, will be regarded as the timing of cutoff in the analysis of OS. Date of last confirmation of progression-free survival on which absence of clinical progression has been confirmed.

Details about the method of conversion of other data and handling of missing data will be specified separately in the SPA.

13.1.3.5 Level of significance, confidence coefficient

- Level of significance: 5%
- Confidence coefficient: 95% (two-sided estimation)

13.1.4 Safety analysis

Perform the following analyses in the “safety population”.

13.1.4.1 Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAE) are the adverse events which developed after initiation of protocol treatment after randomization.

For TEAE, perform the following analyses for each treatment group. Code TEAE using the MedDRA to summarize them by Preferred Term (PT) and System Organ Class (SOC).

- Frequency tabulation of all TEAE
- Frequency tabulation of TEAE for which the causal relationship with any of the protocol treatments was judged as “related”
- Frequency tabulation of all TEAE by severity
- Frequency tabulation of TEAE by severity for which the causal relationship with any of protocol treatment was judged as “related”
- Table of TEAE by frequency with the action taken for any of protocol treatment was handled as “discontinuation”
- Frequency tabulation of serious TEAE
- Frequency tabulation of TEAE of peripheral nerve disorders (secondary endpoint)

Peripheral nerve disorders will be defined as the events classified with the preferred term of "peripheral neuropathy" according to the Standardised MedDRA Queries, and skin disorders will be defined as the events classified with the System Organ Class of "Skin and subcutaneous tissue disorders" or the events classified as with the Preferred Term of "paronychia." The interstitial pneumonia will be the events of the Preferred Terms of the MedDRA Standard Search Formula.

13.1.5 Predetermined subgroup analysis

In this study, the following subgroup analysis will be conducted.

- Subgroup analysis based on *NRAS* test

13.2 Criteria for interim analysis and premature discontinuation

Interim analysis will not be conducted.

13.3 Determination of the planned number of subjects

This study will be designed as a phase II randomized screening comparison study which does not use direct comparison for primary analysis[22].

In the phase III study (PRIME Study) in which FOLFOX4 therapy was combined with bi-weekly administration of panitumumab 6 mg/kg as a first-line therapy, the median PFS in the patients of *KRAS* wild-type as the primary endpoint was reported as 9.6 months[12]. Moreover, in PEAK study[23] in which panitumumab and bevacizumab were compared as the drugs to be administered in combination with mFOLFOX6 therapy, the median PFS in the mFOLFOX6 therapy + panitumumab group was reported as 10.9 months. The percentage of the cases in which any events occurred or the study was cut off within 3 months in PRIME Study and PEAK Study was approximately 10% of all cases.

The subjects of this study will be the patients who receive mFOLFOX6 + panitumumab combination therapy for 3 months, and can continue OXA administration. Since the PFS 40% point in PRIME Study and PEAK Study was approximately 13 months, the median PFS in Group A in this study is expected to be approximately 10 months, which is obtained by subtracting 3 months from the 40% point. The median PFS in Group B is assumed to be comparable to that in Group A.

In the primary analysis, a test based on the method of Brookmeyer-Crowley[24] will be conducted for the null hypothesis, "true median PFS will be lower than the threshold median PFS for judgment as ineffective", separately in Group A and Group B on the basis of the observed median PFS. When the threshold median PFS is regarded as 6 months, true median PFS as 10 months, enrollment period as 12 months, follow-up period as 12 months, one-sided significance level as 5%, and power of test as 80%, the number of subjects required in Group A and Group B will become 54 subjects each. Considering the cases of discontinuation, the target number of subjects to be randomised was set at 60 patients for each group (120 patients in total).

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. During site visit monitoring, the data recorded in EDC are checked against source documents. Source documents are the original documents, data and records. The investigator and the head of study site will ensure that the sponsor or its designee and the IRB such as the ethics review committee have access to the source documents.

The sponsor or its designee will access the records including the subject code list, medical records, signed and dated original consent forms to confirm that the study is appropriately conducted in compliance with the protocol. The investigator and other persons involved in the study will spare sufficient time to facilitate monitoring procedures during visits to the study site.

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.

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

See separately prepared monitoring plan for the frequency and procedures of site visit monitoring.

14.2 Protocol deviations

The investigator should record all deviations from the protocol. When a deviation is disclosed, the investigator will immediately notify the head of study site and the sponsor in writing. Revision of the protocol should be discussed with the sponsor when necessary, and when the protocol is revised, the revised protocol should be submitted to the head of study site and approved by the IRB such as the ethics review committee.

14.3 Quality assurance and regulatory agency inspections

The sponsor or its designee 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 the site of collecting laboratory test samples and other sites to be used during the study. This study may also be audited by overseas regulatory authorities (e.g., Food and Drug Administration [FDA], Medicines and Healthcare Products Regulatory Agency [MHRA]). The study site will immediately notify the sponsor when the study site is contacted by the regulatory authority concerning an audit. The investigator and the head of study site should ensure that the auditor has access to all the source documents listed in Section 14.1.

15.0 ETHICAL CONDUCT OF A STUDY

This study will be conducted in compliance with the protocol and ethical principles based on the Declaration of Helsinki to preserve the interest of study participants (subjects). Each investigator should conduct a study based on the regulatory requirements and in compliance with the "Responsibilities of the investigator" in Attachment A.

15.1 Conflict of interests

Prior to the study, the investigator should obtain the review/approval by the IRB such as the COI committee that this study has no conflict of interests (COI)[25)-29)].

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

15.2 Approval by the institutional review board including the ethics review committee

The institutional review board (IRB) including the ethics review committee is constituted according to local regulations applicable to the study site. The sponsor or its designee should obtain the document listing the name and title of each IRB member. When the IRB members are directly participating in this study, a document should be obtained that they are not taking part in deliberation and voting.

The sponsor or its designee should provide related documents to the IRB 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 IRB or the IRB of each study site such as the ethics review committee to obtain approval. The sponsor or its designee should obtain written approval of the protocol and the informed consent form from the IRB such as the ethics review committee prior to initiation of protocol treatment. The IRB's approval document should contain the study title, protocol number, and date of preparation/revision of the concerned study, as well as version numbers and approval dates of other reviewed documents (e.g., informed consent form). The sponsor should notify the study site and the investigator 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 and the investigator receive the notification.

The study site should comply with all the requirements specified by the IRB such as the ethics review committee. The requirements include notifications to the IRB 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 IRB such as the ethics review committee, and study completion report. The sponsor or its designee should obtain written approval of the abovementioned items and all related materials from the IRB such as the ethics review committee.

15.3 Written information and subject's consent

The informed consent from contains specific requirements of the Declaration of Helsinki and all applicable laws and regulations. The informed consent from 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 from 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.

The investigator is responsible for preparation, content, and IRB approval of the informed consent form. The informed consent form should be approved by IRB before use.

The informed consent from should be written in a language easily understood by subjects. The investigator is responsible for providing detailed explanation of the informed consent from to subjects. Information should be provided orally and in writing as best as possible by the method deemed appropriate by the IRB.

The investigator 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 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 should also sign or write name/affix seal, and date the consent form prior to subject participation.

The investigator should store the original consent form which was signed or contains name/affixed seal. The investigator 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 name seal affixed should be provided to the subject.

The investigator should take the same procedures as those for obtaining the initial consent to newly obtain consent from the concerned subject when the informed consent from 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.

To confirm that this study is performed in compliance with the protocol, 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, representative regulatory authority, auditor designated by the sponsor, and the IRB. The investigator should obtain approval of subjects concerning access to the original medical records by a monitor and the representative regulatory authority, etc. when obtaining consent from a subject (see Section 15.3).

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

15.5 Advantages and disadvantages to subjects

15.5.1 Advantage to subjects

This study is performed as part of routine clinical practice, and no advantage is expected by participation in this study.

15.5.2 Disadvantage to subjects

This study is performed in the scope of ordinary medical examination, and no disadvantage is expected by participation in this study.

15.6 Publication, disclosure, and clinical trial registration policy

15.6.1 Publication and disclosure

The investigator should 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 regulatory authorities 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.

The sponsor may make public the data and information obtained from the study (including the data and information provided by the investigator) based on the agreement with the representative researcher.

The investigator should obtain the prior written consent of the sponsor when making public the information obtained in this study at a specialized academic meeting, etc.

15.6.2 Clinical trial 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 at least to the Clinical Trials.gov and public web site (UMIN-CTR) to comply with the applicable laws/regulations and guidelines. The city and country where a study is performed, and the subject recruitment state should be registered as well as the contact information of Takeda Pharmaceutical Company Limited. to enable general access.

15.6.3 Clinical trial results disclosure

Takeda Pharmaceutical Company Limited. will post the results of a clinical study at the Clinical Trials.gov and public web site (UMIN-CTR) as specified by the applicable laws and regulations irrespective of results.

15.7 Attribution of study results and intellectual property rights

The study results generated in this study belong to Takeda Pharmaceutical Company Limited. 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 permission from the representative researcher and the research steering committee.

15.8 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.

16.0 REFERENCES

1 The Editorial Board of Cancer Statistics in Japan. Cancer Statistics in Japan 2013. Foundation for Promotion of Cancer Research: 2013.

2 Japanese Society for Cancer of the Colon and Rectum (JSCCR). JSCCR Guidelines 2014 for the Treatment of Colorectal Cancer.

3 Moertel CG. Chemotherapy for colorectal cancer. N Engl J Med. 1994;330(16):1136-42.

4 Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med. 2000;343(13):905-14.

5 Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet. 2000;355(9209):1041-7.

6 de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000;18(16):2938-47.

7 Rothenberg ML, Oza AM, Bigelow RH, Berlin JD, Marshall JL, Ramanathan RK, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. J Clin Oncol. 2003;21(11):2059-69.

8 Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol. 2004;22(1):23-30.

9 Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004;22(2):229-37.

10 National Comprehensive CancerNetwork. Clinical Practice Guidelines in Oncology. Colon Cancer verslon 3, 2013

11 Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007;25(13):1658-64.

12 Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol. 2010;28(31):4697-705.

13 Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol. 2010;28(31):4706-13.

14 Muro K, Yoshino T, Doi T, Shirao K, Takiuchi H, Hamamoto Y, et al. A phase 2 clinical trial of panitumumab monotherapy in Japanese patients with metastatic colorectal cancer. Jpn J Clin Oncol. 2009;39(5):321-6.

15 Boku N, Sugihara K, Kitagawa Y, Hatake K, Gemma A, Yamazaki N, et al. Panitumumab in Japanese Patients with Unresectable Colorectal Cancer: A Post-marketing Surveillance Study of 3085 Patients. Jpn J Clin Oncol. 2014;44(3):214-223.

16 Hochster HS, Hart LL, Ramanathan RK, Hainsworth JD, Hedrick EE, Childs BH. Safety and efficacy of oxaliplatin/fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer (mCRC): Final analysis of the TREE-Study. J Clin Oncol 2006;24(18S) 3510.

17 Summary of product characteristics, December 2003: Sanofi-Synthelabo.

18 Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, et al. OPTIMOX1:A Randomized Study of FOLFOX4 or FOLFOX7 With Oxaliplatin in a Stop-and-Go Fashion in Advanced Colorectal Cancer—A GERCOR Study. J Clin Oncol 2006;24(3):394-400.

19 Maindrault-Goebel F, et al. Final results of OPTIMOX2, a large randomized phase Ⅱ study of maintenance herapy or chemotherapy–free intervals(CFI) after FOLFOX in patients with metastatic colorectal cancer(MRC) : A GERCOR study. ASCO Meeting Abstructs, Jun 2007;25:4013.

20 Saif MW, Reardon J. Management of oxaliplatin-induced peripheral neuropathy. Therapeutics and Clinical Risk Management 2005;1(4):249–258.

21 Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007;25(12):1539-44.

22 Buyse M. Randomized designs for early trials of new cancer treatments - an overview. Drug Inf J 2000; 34: 387-396.

23 Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, et al. PEAK: A Randomized, Multicenter Phase II Study of Panitumumab Plus Modified Fluorouracil, Leucovorin, and Oxaliplatin (mFOLFOX6) or Bevacizumab Plus mFOLFOX6 in Patients With Previously Untreated, Unresectable, Wild-Type KRAS Exon 2 Metastatic Colorectal Cancer. J Clin Oncol. 2014.

24 Brookmeyer R and Crowley, JJ. A confidence interval for the median survival time. Biometrics 1982; 38: 29-41.

25 Report of the Working Group on Conflict of Interest (Ministry of Education, Culture, Sports, Science and Technology dated November 1, 2002)

26 Guidelines for determining the conflict of interest polity for clinical researches (Review group for ethical aspects of clinical researches and conflict of interest, March 2006)

27 Guidelines on the Management of Conflict of Interest (COI) in Health and Labour Sciences Research (March 31, 2008)

28 Guidelines for management of COI in medical reserach (COI Committee of Japan Association of Medical Sciences, February 2011)

29 Common guidelines for conflict of interest (COI) in clinical research (Japanese Society of Internal Medicine, Japan Society of Hepatology, Japanese Circulation Society, Japan Endocrine Society, Japan Diabetes Society, Japanese Respiratory Society, Japanese Society of Hematology, Japanese Society of Allergology, Japanese Association for Infectious Diseases, August 2011)

Appendix A Responsibilities of the investigator

1 To appropriately conduct the clinical study in compliance with the protocol and in consideration of the human rights, safety and welfare of subjects.

2 To request COI committee of each study site to review and approve that there is no COI issues with this study.

3 When assigning a part of important duties related to this study to subinvestigators or study collaborators, prepare a list of assigned duties and persons, submit it in advance to the head of study site, and to obtain approval.

4 To prepare the informed consent form and revise it as necessary.

5 To check the contents of the study contract.

6 To provide sufficient information on the protocol, drug and duties of each person to subinvestigators and study collaborators, and to provide them with guidance and supervision.

7 To select subjects who satisfy the protocol, give explanation using written information, and obtain consent in writing.

8 To be responsible for all medical judgments related to the study.

9 To ensure together with the head 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.

10 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 then prepare the record.

11 When emergency report of serious adverse events, etc. is required, immediately report it in writing to the head of the study site and the sponsor.

12 To prepare accurate and complete EDC and submit it to the sponsor with an electronic signature.

13 To inspect and check the contents of EDC prepared by subinvestigators, or transcribed by study collaborators from the source data, and submit it to the sponsor with an electronic signature.

14 To discuss a revision of the protocol, etc. when proposed by the sponsor.

15 To report the study completion in writing to the head of study site.

SAPPHIRE study

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

Sponsor	Takeda Pharmaceutical Company Limited
Protocol number	183/NRP-005
Product name	Panitumumab
Creation date	Aug 21, 2014

1.0 STUDY ADMINISTRATIVE STRUCTURE AND PRINCIPLES

1.1 Study Administrative Structure

See Appendix for the contacts and study-related responsibilities.

1.2 Principles of the study

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.
- International Conference on Harmonisation E6 Good Clinical Practice (hereinafter referred to as "GCP").
- All applicable laws and regulations, including, without limitation, data privacy laws, conflict of interest guidelines, Ethical Guideline for Clinical Research (the Ministry of Health, Labour and Welfare, revised in 2008).

TABLE OF CONTENTS

Figures and Tables List

2.0 STUDY SUMMARY

Sponsor: Takeda Pharmaceutical Company Limited

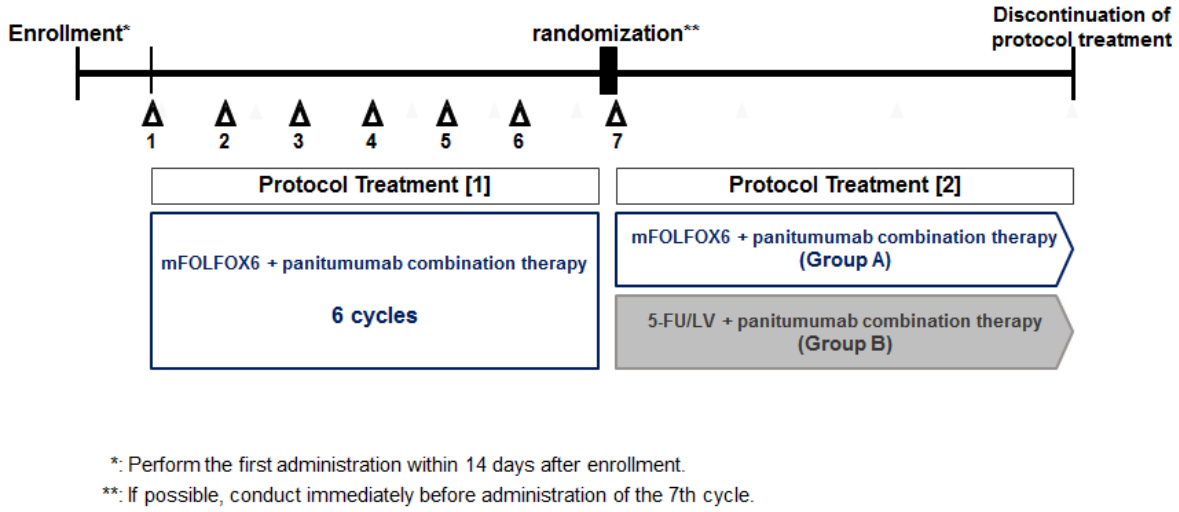
Test product: Panitumumab

Study title:
A phase II randomized study comparing the efficacy and safety of mFOLFOX6 + panitumumab combination therapy and 5-FU/LV + panitumumab combination therapy in the patients with chemotherapy-naïve unresectable advanced recurrent colorectal carcinoma of *KRAS* wild-type after 6 cycles of combination therapy with mFOLFOX6 + panitumumab

Protocol number: 183/NRP-005

Study type: Exploratory study

Study design:



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

Objective:
To exploratorily examine efficacy and safety in the patients with chemotherapy-naïve unresectable, advanced/recurrent colorectal carcinoma of *KRAS* wild-type who have been treated with 6 cycles of first-line mFOLFOX6 + panitumumab combination therapy and then assigned to two groups, i.e., a group receiving 5-FU/LV + panitumumab combination therapy and a group receiving mFOLFOX6 + panitumumab combination therapy.

Study population:
The patients with chemotherapy-naïve unresectable, advanced/recurrent colorectal carcinoma of *KRAS* wild-type

Planned number of subjects:

mFOLFOX6 + panitumumab arm (Group A): 60

5-FU/LV + panitumumab arm (Group B): 60

Number of study sites: TBD

Method of administration:
In both Protocol Treatment [1] and Protocol Treatment [2] (Group A and Group B), one cycle consists of two weeks, and the drugs will be administered at the following doses according to the following schedule.

Protocol Treatment [1]
mFOLFOX6 + panitumumab combination therapy, once every two weeks, 6 cycles
OXA: 85 mg/m^2/day 1
l-LV: 200 mg/m^2/day 1
bolus 5-FU: 400 mg/m^2/day 1
infusional 5-FU: 2400 mg/m^2/day 1-3
panitumumab: 6 mg/kg

Protocol Treatment [2]

Group A: mFOLFOX6 + panitumumab combination therapy, once every two weeks
OXA: 85 mg/m^2/day 1
l-LV: 200 mg/m^2/day 1
bolus 5-FU: 400 mg/m^2/day 1
infusional 5-FU: 2400 mg/m^2/day 1-3
panitumumab: 6 mg/kg

Group B: 5-FU/LV + panitumumab combination therapy, once every two weeks
l-LV: 200 mg/m^2/day 1
bolus 5-FU: 400 mg/m^2/day 1
infusional 5-FU: 2400 mg/m^2/day 1-3
panitumumab: 6 mg/kg

Duration of treatment (approximately): 10 months (Period from the day of first administration in Protocol Treatment [1] to PD or intolerance)

Inclusion criteria

Inclusion criteria for enrollment:

(1) Patients with unresectable adenocarcinoma originating in the large intestine (excluding carcinoma of the appendix and anal canal cancer)

(2) Patients with measurable lesion(s) according to the RECIST ver. 1.1

(3) Patients who have not received chemotherapy for colorectal cancer. Patients who experience relapse more than 6 months after the final dose of perioperative adjuvant chemotherapy with fluoropyrimidine agents may be enrolled.

(4) Aged ≥20 years at the time of informed consent

(5) Patients classified as *KRAS* wild-type*. However, the criteria will be changed to all patients who are verified to be of *KRAS* and *NRAS* wild-type when the *KRAS* and *NRAS* tests come to be covered by National Health Insurance, and the tests become feasible at medical institutions.

*: Patients with no mutation in any of the codons shown below are considered 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

**: To be considered when the test comes to be covered by insurance and becomes feasible at medical institutions.

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

1) Neutrophil count ≥ 1,500/mm^3
2) White blood cell count ≥ 3,000/mm^3
3) Platelet count ≥ 10.0 × 104/mm^3
4) Hemoglobin ≥ 9.0 g/dL

5) Total bilirubin ≤ 2.0 mg/dL
6) AST ≤ 100 IU/L (≤ 200 IU/L if liver metastases are present)
7) ALT ≤ 100 IU/L (≤ 200 IU/L if liver metastases are present)
8) Serum creatinine ≤ 1.5 mg/dL

(7) ECOG performance status (PS) of 0 or 1
(8) Life expectancy of ≥ 6 months after enrollment
(9) Patients who have given written consent to take part in the study after detailed explanation of the study prior to enrollment

Inclusion criteria for randomization:

(1) Patients who have received 6 cycles＊ (Protocol Treatment [1]) of mFOLFOX6 + panitumumab combination therapy
*: Protocol Treatment [1] without discontinuation in all cycles (6 cycles) of Protocol Treatment [1]. However, bolus 5-FU is an exception.
(2) Patients who are deemed to be able to receive 5-FU/LV, OXA and panitumumab during the period of Protocol Treatment [2] on the examination before administration of the 7th cycle.
(3) ECOG performance status (PS) of 0-1 before administration of the 7th cycle.
(4) Patients for whom PD or not evaluable has been denied on the Response Evaluation Criteria in Solid Tumors (RECIST) based on imaging tests conducted after administration of 6 cycles.

Exclusion criteria

Exclusion criteria for enrollment:

(1) Radiotherapy received within 4 weeks prior to enrollment
(2) Known brain metastasis or strongly suspected of brain metastasis
(3) 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.).
(4) Body cavity fluid that requires treatment (pleural effusion, ascites, pericardial effusion, etc.)
(5) Patients who do not want to use contraception to prevent pregnancy, and women who are pregnant or breast-feeding, or test positive for pregnancy
(6) Active hemorrhage requiring blood transfusion
(7) Disease requiring systemic steroids for treatment (excluding topical steroids)
(8) Intestinal resection and colostomy within 2 weeks prior to enrollment
(9) History or obvious and extensive CT findings of interstitial pulmonary disease (interstitial pneumonia, pulmonary fibrosis, etc.)
(10) Serious drug hypersensitivity
(11) Local or systemic active infection requiring treatment, or fever indicating infection
(12) Intestinal paralysis, gastrointestinal obstruction, or uncontrollable diarrhoea (incapacitating symptoms despite adequate treatment)
(13) Active hepatitis B and/or C
(14) Known HIV infection
(15) Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study

Exclusion criteria for randomization:

(1) Patients in whom interstitial pneumonia has been newly diagnosed during the period from registration to randomization
(2) Patients who have received radiotherapy during the period from registration to randomization

(3) Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study

Endpoints:
[Primary endpoint]

- Efficacy

Progression-Free Survival (PFS)

[Secondary endpoints]

- Efficacy
  - Overall survival (OS)
  - Response rate (RR)
  - Time to treatment failure (TTF)
- Safety
  - Incidence rate of adverse events and severity by incidence rate
  - Incidence rate of peripheral nerve disorders
  - Incidence rate of skin disorders

Statistical method:
The purpose of this study is to explorethe the analysis of PFS compared mFOLFOX6 + panitumumab arm with 5-FU/LV + panitumumab arm.

The PFS is the period from the day of randomization (Day 0) until the day of judgment of exacerbation from the day of randomization, or until death by all causes, whichever comes earlier.

For each treatment group, calculate the progression-free survival rate at a given time point and its 95% confidence interval (two-sided) by Kaplan-Meier method, and calculate the quartile of PFS and its 95% confidence interval (two-sided). At the same time, draw a Kaplan-Meier chart for the progression-free survival rate. If the median value of observed PFS is 9 months or more in each group, the treatment regimen concerned will be regarded as being of worth of further investigation.

Moreover, for the sake of reference, calculate the hazard ratio of Group B to Group A and its 95% confidence interval (two-sided) on the basis of the stratified Cox regression model and apply the log-rank test.

Rationale for planned number of subjects:

This study will be designed as a phase II randomized screening comparison study which does not use direct comparison for primary analysis.

In the phase III study (PRIME Study) in which FOLFOX4 therapy was combined with bi-weekly administration of panitumumab 6 mg/kg as a first-line therapy, the median PFS in the patients of KRAS wild-type as the primary endpoint was reported as 9.6 months[12]. Moreover, in PEAK study in which panitumumab and bevacizumab were compared as the drugs to be administered in combination with mFOLFOX6 therapy, the median PFS in the mFOLFOX6 therapy + panitumumab group was reported as 10.9 months. The percentage of the cases in which any events occurred or the study was cut off within 3 months in PRIME Study and PEAK Study was approximately 10% of all cases.

The subjects of this study will be the patients who receive mFOLFOX6 + panitumumab combination therapy for 3 months, and can continue OXA administration. Since the PFS 40% point in PRIME Study and PEAK Study was approximately 13 months, the median PFS in Group A in this study is expected to be approximately 10 months, which is obtained by subtracting 3 months from the 40% point. The median PFS in Group B is assumed to be comparable to that in Group A.

In the primary analysis, a test based on the method of Brookmeyer-Crowley will be conducted for the null hypothesis, "true median PFS will be lower than the threshold median PFS for judgment as ineffective", separately in Group A and Group B on the basis of the observed median PFS. When the threshold median PFS is regarded as 6 months, true median PFS as 10 months, enrollment period as 12 months, follow-up period as 12 months, one-sided significance level as 5%, and power of test as 80%, the number of subjects required in Group A and Group B will become 54 subjects each. Considering the cases of discontinuation, the target number of

subjects to be randomised was set at 60 patients for each group (120 patients in total).

3.0 LIST OF ABBREVIATIONS

Abbreviation	Unabbreviated expression
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ALP	alkaline phosphatase
ASCO	American society of clinical oncology
BRAF	v–raf murine sarcoma viral oncogene homolog B1
BSC	best supportive care
CEA	carcinoembryonic antigen
COI	conflict of interest
CR	complete response
CRO	contract research organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	deepness of response
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
ETS	early tumor shrinkage
FAS	full analysis set
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FFPE	Formalin-Fixed Paraffin-Embedded
G-CSF	granulocyte colony stimulating factor
γ-GTP	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
ICH	International Conference on Harmonisation
INR	International normalized ratio
IRB	institutional review board
JCOG	Japan Clinical Oncology Group
KRAS	Kirsten rat Sarcoma-2 virus
LDH	lactate dehydrogenase
LLN	lower limit of normal
l-LV	Leucovorin
mCRC	metastatic colorectal cancer

Abbreviation	Unabbreviated expression
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
NE	Not Evaluable
NRAS	
OS	Overall survival
OXA	Oxaliplatin
PD	progressive disease
PFS	Progression free survival
PPS	per-protocol analysis set
PR	partial response
P.S.	performance status
PT	Preferred Term
PI3K	Phosphoinositide 3-kinase
RAS	rat sarcoma
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TTF	Time to Treatment Failure
ULN	upper limit of normal
UMIN-CTR	University Hospital Medical Information Network - Clinical Trials Registry
UPC	urine protein creatinine
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
WT	wild type
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

4.1.1 Etiology of target disease

According to "Cancer Statistics 2013,"[1)] and "Site-specific Cancer Prevalence" in 2008 in Japan, colon cancer was the third most prevalent cancer in men (15.0%) and the second in women (15.1%). According to "Site-specific Cancer Deaths (2012)," in men, lung cancer was the leading cause of cancer death (accounting for 23.9% of cancer deaths), followed by gastric cancer (15.0%) and hepatic cancer (9.3%); 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 (13.8%) was also the leading cause of cancer death, followed by gastric cancer (11.6%) and pancreatic cancer (9.9%); 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 target disease

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 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 chemotherapy regimens for the patients with unresectable, advanced/recurrent colorectal carcinoma necessitating powerful treatment that have been demonstrated to be useful in clinical studies and are currently covered by national health insurance in Japan are presented below. There is a consensus that cetuximab and panitumumab should be used only for *KRAS* wild-type (WT) colorectal cancer.

(1) FOLFOX therapy or CapeOX therapy ± bevacizumab[*1]
FOLFOX therapy: combination chemotherapy with fluorouracil (hereinafter referred to as 5-FU), Isovorin (hereinafter referred to as *l*-LV), and oxaliplatin (hereinafter referred to as OXA)
CapeOX therapy: combination chemotherapy with capecitabine and OXA

(2) FOLFIRI therapy ± bevacizumab[*1]
FOLFIRI therapy: combination chemotherapy with irinotecan (hereinafter referred to as IRI), 5-FU, and *l*-LV

(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], CapeOX + bevacizumab[*1] or UFT + LV
UFT: combination preparation of tegafur and uracil

*1: Combination with molecular-targeted drugs such as bevacizumab and epidermal growth factor receptor (EGFR) antibody is recommended, but if this cannot be indicated, chemotherapy alone will be provided.
*2: Indicated only for *KRAS* wild-type.
*3: infusional 5-FU + *l*-LV

FOLFOX-based therapy is more frequently selected as first-line chemotherapy 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.

For third-line treatment, regorafenib or symptomatic therapy is currently recommended.

4.1.3 Efficacy and safety of mFOLFOX6 in patients with unresectable, advanced or recurrent colorectal cancer

As therapy for unresectable, advanced/recurrent colorectal cancer, regimens mainly based on fluoropyrimidine anticancer agents are considered to be the standard for a long term[3)]. Based on the evidence showing that 5-FU combined with *l*-LV is superior to 5-FU monotherapy, the combination therapy with 5-FU and *l*-LV (hereinafter referred to as 5-FU/LV therapy) had been considered as standard chemotherapy for colorectal cancer for a long time. The type I topoisomerase inhibitor IRI and the third generation of platinum-based anticancer drug OXA were then developed, and have been shown to improve treatment outcome in a number of large scale controlled trials[4) to 9)]. At present, continuous infusion of 5-FU/LV in combination with OXA (FOLFOX therapy) or in combination with IRI (FOLFIRI therapy) is the standard chemotherapy regimen for advanced/recurrent colorectal cancer[3), 10)]. FOLFOX and FOLFIRI therapies were compared in the GERCOR V308 study[9),] in which the median final overall survival (hereinafter referred to as OS) was similar between the precedent FOLFIRI and the precedent FOLFOX arms (21.5 months vs. 20.6 months), and thereby both of the therapies are used as the standard for unresectable colorectal cancer. The development of these therapies provided improvement of the median survival time of unresectable advanced colorectal cancer from 12 months with 5-FU/LV therapy to 20 months or more with 5-FU/LV therapy in combination with IRI or OXA.

Among several FOLFOX regimens, FOLFOX4 therapy and modified FOLFOX6 (hereinafter referred to as mFOLOFX6) therapy, which include OXA at the approved dosage (85 mg/m^2) in Japan, are covered by national health insurance, and simpler and easier mFOLFOX6 therapy is more frequently used.

4.1.4 Efficacy and safety of panitumumab in patients with unresectable, advanced or recurrent colorectal cancer

4.1.4.1 Panitumumab

EGFR, 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 (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.

4.1.4.2 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 or advanced, EGFR-positive colorectal cancer that became resistant to fluoropyrimidine agents, OXA, and IRI (BSC arm, 232 patients; BSC + panitumumab arm, 231 patients) [11]. The primary endpoint of median progression free survival (hereinafter referred to as PFS) was 8 weeks and significantly longer in the BSC + panitumumab therapy, showing the efficacy of panitumumab therapy as compared with 7.3 weeks in the BSC alone arm (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 arms (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 arm received follow-up therapy with panitumumab.

With regard to 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 1,180 patients (590 in each arm)[12]. The primary endpoint of median PFS in *KRAS* wild-type patients was 9.6 months and significantly longer in the FOLFOX4 + panitumumab arm as compared with 8.0 months in the FOLFOX4 alone arm (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 arm, but there were no major differences in the incidence of other adverse events between the two arms. 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. [13] The primary endpoints were PFS and OS in *KRAS* wild-type patients. In *KRAS* wild-type patients, the median PFS was 5.9 months and significantly longer in the FOLFIRI + panitumumab arm than 3.9 months in the FOLFIRI alone arm (HR, 0.73; two-sided 95% CI, 0.59 to 0.90; p = 0.004). On the other hand, OS was 14.5 months in the FOLFIRI + panitumumab arm and 12.5 months in the FOLFIRI alone arm, with no statistically significant difference between the two arms (HR, 0.85; two-sided 95% CI, 0.70 to 1.04; p = 0.12). The response rate (hereinafter referred to as RR) was 35% and higher in the FOLFIRI +

panitumumab arm as compared with 10% in the FOLFIRI alone arm. 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 arm; however, there were no major differences in the incidence of toxicities including hematologic toxicities between the two arms, and the incidence of infusion reaction was not more than 1%.

Both the PRIME Study[12)] and Study 20050181[13)] described above, in which *KRAS* mutation status 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.

4.1.4.3 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. Again, in this study, panitumumab showed a good tolerability profile.

In a Japanese phase II clinical study of panitumumab monotherapy[14)], 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 median PFS of 8.0 weeks (two-sided 95% CI: 7.4 to 11.4), and a median 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 incurable/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 Events	Panitumumab Monotherapy (n = 52)			
	All		≥ Grade 3	
	n	%	N	%
Any adverse drug reaction	51	98	6	12
Skin disorder	51	98	3	6
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	
Malaise	13	25	0	
Stomatitis	12	23	0	
Anorexia	11	21	1	2

4.1.4.4 Result of the post-marketing Surveillance (overall survey) in Japan

In a study conducted during a certain post-marketing period by enrolling all patients[15)], the median treatment duration (first day of administration to last day of administration) in 3,085 patients included in safety evaluation was 113 days (range: 1-559 days), and the incidence rate of adverse

drug reactions was 84.1% (≥Grade 3, 25.8%). The incidence rate in 1,254 patients in the group treated with panitumumab monotherapy was 80.1% (≥Grade 3, 19.7%) and that in 1,831 patients in the group treated with panitumumab + chemotherapy was 86.9% (≥Grade 3, 30.0%). The status of occurrence of adverse drug reactions of special interest is shown in Table 4.b.

Table 4.b Adverse Drug Reactions (ADRs) of special interest on Post-marketing survey in Japan

Overall incidence of Post-marketing survey	Panitumumab Monotherapy (n=1,254)				Combination therapy (n=1,831)			
	All		≥ Grade 3		All		≥ Grade 3	
ADRs of special interest	n	%	n	%	n	%	N	%
Skin and 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
Hypomagnesemia	257	20.5	61	4.9	263	14.4	62	3.4
Hypocalcemia	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

* : Based on the evaluation of the ILD

4.1.5 Adverse reactions to OXA

Major dose-limiting toxicities of OXA are neurological manifestations, which are peripheral sensory nerve disorders characterized by dysaesthesia or paraesthesia in four limbs. They may accompany convulsion and are induced by exposure to coldness. Hochster et al.[16] reported that these symptoms appeared in 85% to 95% of the patients who received FOLFOX therapy in combination with bevacizumab, that the duration became longer as the administration cycles increased, and that the incidence of functional disorders after administration of a cumulative dose of 800 mg/m^2 was approximately 15%. In many cases, these neurological manifestations remit or disappear after discontinuation of administration. Acute sensory neurological manifestations appear within several hours after administration, and are induced by exposure to coldness. They may appear as transient paraesthesia, dysaesthesia, hypoaesthesia or acute laryngopharyngeal dysaesthesia syndrome.

In addition to nerve disorders, acute laryngopharyngeal dysaesthesia syndrome is estimated to occur with an incidence of 1% to 2%. It is characterized by respiratory disorders without cyanosis and hypoxia, sensation of dyspnoea without direct effects on the respiratory functions such as dysphagia, decreased SaO_2, laryngospasm, and bronchospasm without wheezing in the upper and lower respiratory tracts. Convulsion in the jaw, abnormal feeling in the tongue, dysarthria, eye pain, and chest pressure sensation are also observed[17]. These symptoms improve reversely without treatment. The incidence of acute laryngopharyngeal dysaesthesia syndrome is suggested to decrease as the duration of administration becomes longer.

Among these adverse reactions, nerve disorders in particular make continuous administration of OXA difficult, and may lead to modification of the FOLFOX therapy regimen involving molecular-targeted drugs. For the patients responding to the therapy, they may miss the patients of important opportunities of treatment (internal data).

4.1.6 Examination of the method of administration of OXA in first-line therapy

Reduction of neurological manifestations associated with FOLFOX as standard chemotherapy for unresectable, advanced/ recurrent colorectal carcinoma is urgently needed for improvement of the QOL of patients and for realization of long-term treatment. According to the reports of Tournigand et al[18)]., OPTIMOX1 (Stop and Go method) is able to achieve recovery from neurological manifestations during the period of sLV5FU2 therapy without OXA after FOLFOX. Moreover, it may be possible to reduce hematological toxicity and non-hematological toxicity during this period. Concerning the treatment effect, the response rate was 59.2% and MST was 21.2 months. Furthermore, the final report of OPTIMOX2 by F Maindrault-Goebel et al.[19)] showed that the OS in the administration schedule of OPTIMOX1 (Stop and Go method) was 26 months.

4.2 Rationale for the proposed study

In Japan, mFOLFOX6 therapy is conducted most frequently as the first-line therapy for unresectable, advanced/ recurrent colorectal carcinoma. Peripheral nerve disorders induced by OXA contained in mFOLFOX6 therapy may cause a clinical problem because they become a cause of deterioration of the patients' QOL, thereby making continuous treatment impossible. When peripheral nerve disorders as mentioned above have occurred, mFOLFOX6 therapy as the baseline therapy is switched to FOLFIRI therapy in some cases in spite of favorable responses to the first-line therapy, instead of discontinuing OXA which is the cause of peripheral nerve disorders. This is deemed to lead to a loss of the opportunity of treatment for the patients. Moreover, it is possible that long-term administration of OXA induces peripheral nerve disorders. For patients who discontinue administration of OXA after having received the drug for a certain period and who have experienced no peripheral nerve disorders during the treatment period, re-introduction of OXA in the later stage of treatment may remain as a treatment option. With regard to the discontinuaiton and resumption of OXA administration in FOLFOX therapy as the first line therapy at present, the evaluation for efficacy and safety of OPTIMOX study[18)] have been presented. However, appropriate administration method of OXA in first-line therapy with mFOLFOX6 + panitumumab has not been revealed.

For these reasons, this study was planned on the basis of the judgment that efficacy and safety in the group in which OXA is discontinued after 6 cycles of the treatment and the group in which OXA is continued need to be examined in the patients responding to mFOLFOX6 + panitumumab combination therapy.

5.0 OBJECTIVE AND ENDPOINTS OF THE STUDY

5.1 Objective

To exploratorily examine efficacy and safety in the patients with chemotherapy-naïve unresectable, advanced/recurrent colorectal carcinoma of *KRAS* wild-type who have been treated with 6 cycles of first-line mFOLFOX6 + panitumumab combination therapy and then assigned to two groups, i.e., a group receiving 5-FU/LV + panitumumab combination therapy and a group receiving mFOLFOX6 + panitumumab combination therapy.

5.2 Endpoints

See Section 13.1.3 for Efficacy analysis.

5.2.1 Primary endpoint

- Efficacy
  - Progression-free survival (PFS)

5.2.2 Secondary endpoints

- Efficacy
  - Overall survival (OS)
  - Response rate (RR)
  - Time to treatment failure (TTF)
- Safety
  - Incidence rate of adverse events, and severity by incidence rate
  - Incidence rate of peripheral nerve disorders
  - Incidence rate of skin disorders

5.2.3 Additional endpoint

- Percentage of maintenance of Performance Status (PS)
- Percentage of continuation of OXA in mFOLFOX6 + panitumumab group (Group A)
- Percentage of continuation of panitumumab in both groups

5.3 Rationale for the endpoints

5.3.1 Primary endpoint

The PFS was selected as the best indicator for evaluation of efficacy of the regimen with and without OXA after 6 cycles of mFOLFOX6 + panitumumab combination therapy without being affected by the after-treatment.

5.3.2 Secondary endpoints

The OS was selected as the secondary endpoint because it is the true endpoint. As a help for interpretation of primary efficacy results, RR and TTF were selected as secondary endpoints.

Concerning safety, the appropriateness of continuing and discontinuing OXA and panitumumab was evaluated in an exploratory manner. The incidence rate of adverse events, the incidences of peripheral nerve disorders and skin disorders were selected as secondary endpoints because they are important factors for the choice of treatment.

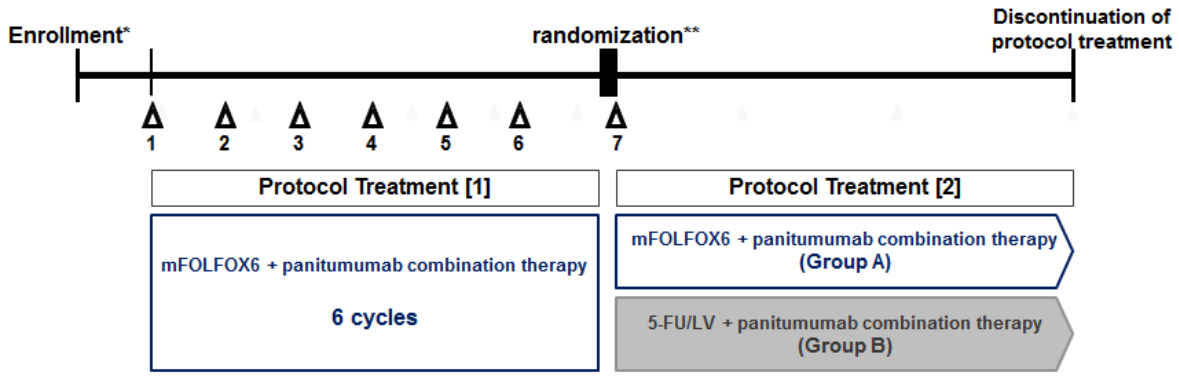
6.0 STUDY DESIGN

6.1 Study design

This is a phase II, multi-center joint, open-label, parallel-group randomized controlled study to exploratorily examine the efficacy and safety in the patients with chemotherapy-naïve unresectable, advanced/recurrent colorectal carcinoma of *KRAS* wild-type after treating them with 6 cycles of mFOLFOX6 + panitumumab combination therapy and subsequently assigning them to a group continuing mFOLFOX6 + panitumumab combination therapy (Group A) and a group in which OXA is discontinued and 5-FU/LV + panitumumab combination therapy is provided (Group B).

Patients who are judged eligible for the study based on the inclusion criteria at the time of enrollment will be registered within 14 days before the first administration (1st cycle), and will be treated with 6 cycles of mFOLFOX6 + panitumumab combination therapy (Protocol Treatment [1]). The patients for whom continuation of mFOLFOX6 + panitumumab combination therapy is judged appropriate on the basis of the examination before administration of the 7th cycle and imaging test after administration of the 6th cycle, who satisfy the inclusion criteria for randomization, and who do not fall under any of the exclusion criteria for randomization will be randomly assigned to either the mFOLFOX6 + panitumumab combination group (Group A) or the 5-FU/LV + panitumumab combination group (Group B) at the ratio of 1:1 before administration of the 7th cycle (TBD). After randomization, treatment in Group A or Group B will be continued according to the administration standards for Protocol Treatment [2] until the "8.8. Criteria for discontinuation of protocol treatment" are met. The reasons for the failure to meet the subject inclusion criteria at the time of randomization will be collected. The patients who fall under the criteria for extension of administration on the examination before administration of the 7th cycle will be examined again after an appropriate interval. The patients who satisfy the subject inclusion criteria on the re-examination will be randomized, and will receive the protocol treatment of the assigned group. Both inpatients and outpatients are eligible. Refer to "8.2 Treatment regimen" for details about the protocol treatment ([1] and [2]).

See "13.3 Determination of the planned number of subjects" for the number of subjects.



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

Figure 6.a Outline of study design

6.2 Rationale for study design, dose and endpoints

6.2.1 Study population

The timing at which OXA-induced peripheral nerve disorders occurs most frequently has been reported to be the time point at which the accumulated amount of OXA administered reaches 780-850 mg/m^2 [20]. This amount is equivalent to 9 or 10 doses when converted using the dose of 85 mg/m^2 of OXA administered at a time in Protocol Treatment [1] and [2]. According to the report by Hochster et al[16]. who investigated the mean number of doses administered continuously in FOLFOX therapy in initial therapy in routine medical care, the number was 10 times in the FOLFOX + bevacizumab combination therapy in first-line therapy (TREE2). In the report by Giantonio et al.[21], the mean number of doses administered continuously in FOLFOX±bevacizumab combination therapy in the second-line therapy (ECOG3200) for the patients with a history of chemotherapy was 7 to 10 times. This study aims at comparing efficacy and safety in the group continuing OXA from the 7th cycle and the group discontinuing OXA in the patients receiving first-line mFOLFOX6 + panitumumab combination therapy before the occurrence of peripheral nerve disorders. Since the above-described status of the frequency of OXA administration also seems to suggest that discontinuation of OXA after 6th administration in Protocol Treatment [1] does not greatly deviate from the situation in routine medical care, the number of cycles of OXA administration given before randomization was set at 6.

Moreover, since no significant differences were seen in the duration of disease control and PFS in OPTIMOX study, the duration of treatment is not expected to differ significantly even when OXA is discontinued after 6 cycles of mFOLFOX6 + panitumumab therapy while 5-FU/LV + panitumumab combination therapy is continued. Furthermore, although concomitant administration of panitumumab does not cause differences in time to treatment failure and PFS, discontinuation of OXA before the occurrence of peripheral nerve disorders enables re-introduction of OXA. Therefore, differences larger than in OPTIMOX study may be expected for OS. In addition, it may become possible to propose, for combination therapy of mFOLFOX6 and panitumumab, an approach which enables long-term continuation of treatment through prevention of the occurrence of OXA-induced peripheral nerve disorders.

6.2.2 Treatment regimens and planned number of subjects

See "13.3 Determination of the planned number of subjects" for details.

6.3 Discontinuation of entire study or discontinuation at a study site

6.3.1 Criteria for discontinuation of entire study

The sponsor should immediately discontinue the study when it is notified by the data monitoring committee and/or the steering committee that at least one of the following criteria is applicable.

- Occurrence of serious event/violation which endangers safety of subjects.
- 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.

6.3.2 Procedures of study suspension and discontinuation of entire study or study at a study site

When the sponsor or the IRB such as the ethics review committee determines suspension or discontinuation of the entire study or the study at a certain study site, the sponsor will instruct the procedures specified for the relevant study. The relevant study site should observe the procedures for study suspension or discontinuation.

6.4 Procedures for revision of the protocol

When a need arises to revise the protocol, the sponsor will consult with the representative researcher to make a decision.

Details of the protocol revision will be notified to investigators of all study sites.

When the investigator of each study site receives the notification, he should arrange the revised protocol to be reviewed by the IRB such as the ethics review committee again as necessary according to the stipulation at each study site and obtain approval of the director of study site.

7.0 SELECTION OF STUDY SUBJECTS

7.1 Inclusion criteria

7.1.1 Inclusion criteria for enrollment

Patients who satisfy all the criteria below will be enrolled in this study.

(1) Patients with unresectable adenocarcinoma originating in the large intestine (excluding carcinoma of the appendix and anal canal cancer)

(2) Patients with measurable lesion(s) according to the RECIST ver. 1.1

(3) Patients who have not received chemotherapy for colorectal cancer. Patients who experience relapse more than 6 months after the final dose of perioperative adjuvant chemotherapy with fluoropyrimidine agents may be enrolled.

(4) Aged ≥20 years at the time of informed consent

(5) Patients classified as *KRAS* wild-type*. However, the criteria will be changed to all patients who are verified to be of *KRAS* and *NRAS* wild-type when the *KRAS* and *NRAS* tests come to be covered by National Health Insurance, and the tests become feasible at medical institutions.

*: Patients with no mutation in any of the codons shown below are considered 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

**: To be considered when the test comes to be covered by insurance and becomes feasible at medical institutions.

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

1) Neutrophil count ≥ 1,500/mm^3
2) White blood cell count ≥ 3,000/mm^3
3) Platelet count ≥ 10.0×10^4/mm^3
4) Hemoglobin ≥ 9.0 g/dL
5) Total bilirubin ≤ 2.0 mg/dL
6) AST ≤ 100 IU/L (≤ 200 IU/L if liver metastases are present)
7) ALT ≤ 100 IU/L (≤ 200 IU/L if liver metastases are present)
8) Serum creatinine ≤ 1.5 mg/dL

(7) ECOG performance status (PS) of 0 or 1

(8) Life expectancy of ≥ 6 months after enrollment

(9) Patients who have given written consent to take part in the study after detailed explanation of the study prior to enrollment

7.1.2 Inclusion criteria for randomization

Patients who satisfy all the criteria below will be randomized. If possible, randomization will be conducted immediately before administration of the 7th cycle.

(1) Patients who have received 6 cycles* (Protocol Treatment [1]) of mFOLFOX6 + panitumumab combination therapy

*: Defined as administration of 5-FU/LV and OXA according to the designated dosage regimen for Protocol Treatment [1] without discontinuation in all cycles (6 cycles) of Protocol Treatment [1]. However, bolus 5-FU is an exception.

(2) Patients who are deemed to be able to receive 5-FU/LV, OXA and panitumumab during the period of Protocol Treatment [2] on the examination before administration of the 7th cycle.

(3) ECOG performance status (PS) of 0-1 before administration of the 7th cycle.

(4) Patients for whom PD or not evaluable has been denied on the Response Evaluation Criteria in Solid Tumors (RECIST) based on imaging tests conducted after administration of 6 cycles.

7.2 Exclusion criteria

7.2.1 Exclusion criteria for enrollment

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

(1) Radiotherapy received within 4 weeks prior to enrollment

(2) Known brain metastasis or strongly suspected of brain metastasis

(3) 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.).

(4) Body cavity fluid that requires treatment (pleural effusion, ascites, pericardial effusion, etc.)

(5) Patients who do not want to use contraception to prevent pregnancy, and women who are pregnant or breast-feeding, or test positive for pregnancy

(6) Active hemorrhage requiring blood transfusion

(7) Disease requiring systemic steroids for treatment (excluding topical steroids)

(8) Intestinal resection and colostomy within 2 weeks prior to enrollment

(9) History or obvious and extensive CT findings of interstitial pulmonary disease (interstitial pneumonia, pulmonary fibrosis, etc.)

(10) Serious drug hypersensitivity

(11) Local or systemic active infection requiring treatment, or fever indicating infection

(12) Intestinal paralysis, gastrointestinal obstruction, or uncontrollable diarrhoea (incapacitating symptoms despite adequate treatment)

(13) Active hepatitis B and/or C

(14) Known HIV infection

(15) Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study

7.2.2 Exclusion criteria for randomization

Patients who meet any of the criteria below will not be randomized.

(1) Patients in whom interstitial pneumonia has been newly diagnosed during the period from registration to randomization

(2) Patients who have received radiotherapy during the period from registration to randomization

(3) Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study

8.0 TREATMENT

The protocol treatment, contraindicated drugs/therapies, and recommended supportive care/combination therapies in this study are explained in this section. Commercially available drugs used at the study sites will be used in this study. See the latest package insert for details and handling of each drug.

8.1 Protocol treatment

The study period in this study is defined as the period consisting of Protocol Treatment [1] and Protocol Treatment [2].

8.1.1 Protocol Treatment [1]

OXA and infusional 5-FU will be administered in all of the 6 cycles. The dose can be reduced. Panitumumab will also be administered in all the possible 6 cycles but suspension due to the occurrence of skin disorders will be allowed.

8.1.2 Protocol Treatment [2]

Even if each drug of the criteria specified in "8.5 Criteria for dose change." is met, treatment with the other drugs will be continued unless any of the criteria specified in "8.8 Criteria for discontinuation of protocol treatment" is met.

8.2 Treatment regimen

8.2.1 Protocol Treatment [1]

During the period of Protocol Treatment [1], mFOLFOX6 + panitumumab combination therapy will be given once in two weeks according to the following treatment regimen until any of the criteria specified in "8.8 Criteria for discontinuation of protocol treatment" is met (one administration will be regarded as one cycle). For administration of each drug, see "8.4 Criteria for initiation of protocol treatment (common for Protocol Treatment [1] and [2])" and "8.5 Criteria for dose change".

For the patients aged 80 years or older at the time of enrollment, the drug can be administered at a dose one level lower than the designated dose from Cycle 1.

Table 8.a Treatment regimen of mFOLFOX6 + panitumumab combination therapy

Drug	Dose	Method of administration (recommended)	Date of administration
Panitumumab	6 mg/kg	div 60 min*	Day 1
OXA	85 mg/m^2	div 120 min	Day 1
***l*-LV**	200 mg/m^2	div 120 min	Day 1
5-FU (iv)	400 mg/m^2	iv <15 min	Day 1
5-FU (civ)	2400 mg/m^2	civ 46 hrs	Day 1-2

div: intravenous drip infusion, iv: intravenous infusion, civ: continuous intravenous infusion

*: When the dose at one time exceeds 1000 mg, intravenously administer it over 90 min or longer after dilution with JP physiological saline to make approximately 150 mL.

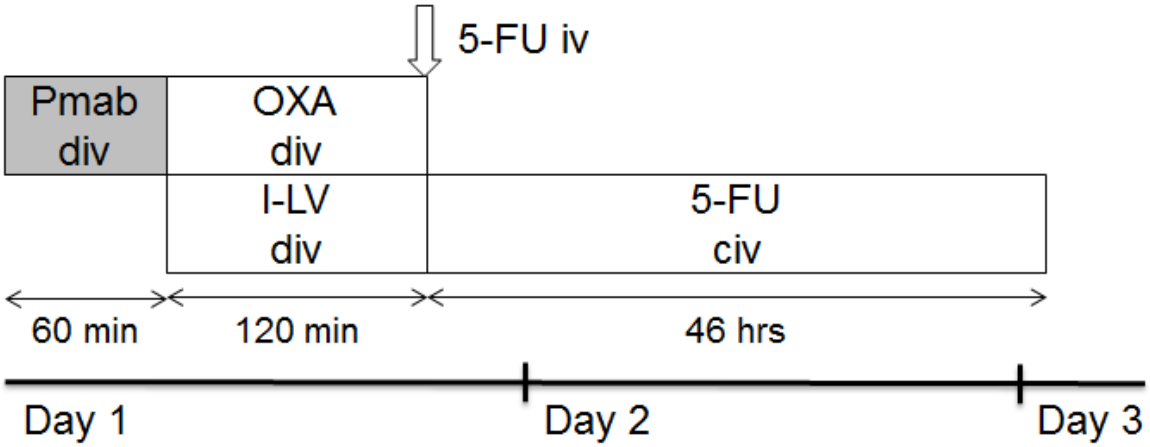


Figure 8.a mFOLFOX6 + panitumumab combination therapy

8.2.2 Protocol Treatment [2]

If the dose of the drug has been reduced during the period of Protocol Treatment [1], the drug will be administered at the reduced dose from Cycle 7.

8.2.2.1 mFOLFOX6 + panitumumab combination therapy (Group A)

See Section 8.2.1 for Protocol Treatment [1]. The term of Protocol Treatment [1] is regarded as Protocol Treatment [2].

8.2.2.2 5-FU/LV + panitumumab combination therapy (Group B)

During the period of Protocol Treatment [2], 5-FU/LV + panitumumab combination therapy will be given once in two weeks according to the following treatment regimen until any of the criteria specified in "8.8 Criteria for discontinuation of protocol treatment" is met (one administration will be regarded as one cycle). For administration of each drug, see "8.4 Criteria for initiation of protocol treatment (common for Protocol Treatment [1] and [2])" and "8.5 Criteria for dose change".

Table 8.b Treatment regimen of 5-FU/LV + panitumumab combination therapy

Drug	Dose	Method of administration (recommended)	Date of administration
Panitumumab	6 mg/kg	div 60 min*	Day 1
***l*-LV**	200 mg/m^2	div 120 min	Day 1
5-FU (iv)	400 mg/m^2	iv < 15 min	Day 1
5-FU (civ)	2400 mg/m^2	civ 46 hrs	Day 1-2

div: intravenous drip infusion, iv: intravenous infusion, civ: continuous intravenous infusion
*: When the dose at one time exceeds 1000 mg, intravenously administer it over 90 min or longer after dilution with JP physiological saline to make approximately 150 mL.

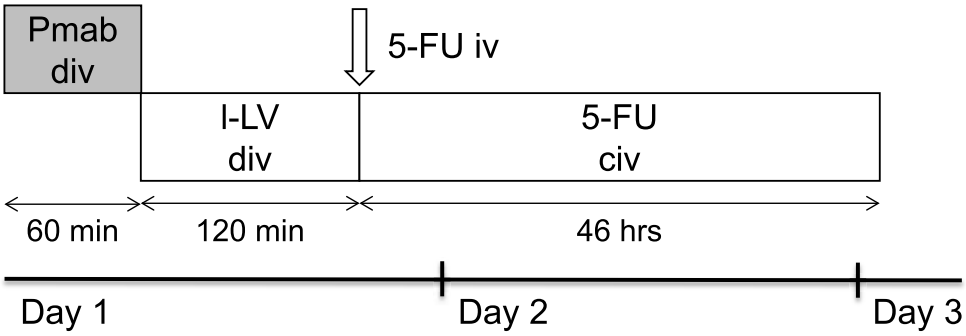


Figure 8.b 5-FU/LV + panitumumab combination therapy

8.3 Recommended dose of protocol treatment

The dose will be calculated based on the body surface area and body weight at the time of study entry. At the time of study entry, the enrollment center will announce the body surface area, which is calculated using the DuBois & DuBois formula, as well as the dose, which is calculated according to the criteria for truncation described below and will serve as the reference value. The dose should be recalculated and confirmed at the study site. The calculated dose of each drug at one time may be adjusted according to the description below. The dose should be recalculated for 10% change in body weight, in principle, but at the discretion of the study site.

Panitumumab : round down in unit of 10 mg

OXA : round down in unit of 10 mg

l-LV : round down in unit of 25 mg

Bolus 5-FU : round down in unit of 50 mg

Infusional 5-FU: round down in unit of 50 mg

8.4 Criteria for initiation of protocol treatment (common for Protocol Treatment [1] and [2])

In principle, the day (Day 13 to 18) 2 weeks after the day of treatment (Day 1) in the previous cycle will be Day 1 of the subsequent cycle. Postponement due to holidays is allowed. It should be confirmed that all of the criteria for initiation of protocol treatment (Table 8.c to Table 8.e) are satisfied on the day of treatment. However, the latest data obtained from 2 days before treatment to the day of treatment may be used for blood tests.

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.

When treatment is postponed, the date of starting treatment after postponement will be designated as Day 1 of the cycle and serve as the reference point for the subsequent schedule.

Protocol treatment should be discontinued when the subsequent cycle of treatment has not been started 28 days later than scheduled (on Day 43 with the date of starting the previous cycle as Day 1). Postponement due to holidays is allowed.

Table 8.c Criteria for initiation of treatment cycle

Item	Criteria for initiation
White blood cell count	≥ 2,500/mm^3
Neutrophil count	≥ 1,500/mm^3
Platelet count	≥ 7.5 x 10^4/mm^3
Total bilirubin	≤ 2.0 mg/dL
Infection	Absence of fever (≥ 38°C) indicating infection
Nausea, vomiting, diarrhoea, stomatitis	≤ Grade 1
Initiation of treatment may be postponed at the discretion of the investigator due to adverse events not listed above.	

8.5 Criteria for dose change

8.5.1 Protocol Treatment [1]

8.5.1.1 Criteria for dose reduction/suspension of mFOLFOX6

The criteria for dose reduction and the doses of OXA and 5-FU (bolus/infusional) during the period of Protocol Treatment [1] are shown in Table 8.d and Table 8.e, respectively. The dose of *l*-LV should not be changed.

Table 8.d Criteria for dose reduction of OXA and 5-FU (Protocol Treatment [1])

Adverse events in previous cycle	Grade	Dose adjustment of OXA and 5-FU
Neutropenia, thrombopenia	4	Dose reduction of both OXA and 5-FU (bolus/infusional) by 1 level
Grade 3 neutropenia or thrombopenia that persists for more than 7 days	3	
Febrile neutropenia, infection, nausea, vomiting, diarrhoea, fatigue	3	
Sensory nerve disorder*	3	Discontinuation of protocol treatment*
	2	Discontinuation of protocol treatment* Or dose reduction of OXA by 1 level
Allergic reaction	3	Discontinuation of protocol treatment*
	2	Careful administration of OXA by slowing the infusion speed
Dose reduction is allowed as necessary at the discretion of the investigator due to adverse events not listed above. However, protocol treatment will be discontinued at the time point of suspension of OXA and infusional 5-FU.		

*: See "8.8 Criteria for discontinuation of protocol treatment" for details.

Table 8.e Doses of OXA and 5-FU (Protocol Treatment [1])

Dose reduction level	OXA	5-FU iv	5-FU civ
Initial dose	85 mg/m^2	400 mg/m^2	2400 mg/m^2
-1	65 mg/m^2	200 mg/m^2	2000 mg/m^2
-2	50 mg/m^2	0 mg/m^2 (discontinuation)	1600 mg/m^2
-3	Discontinuation of protocol treatment*	0 mg/m^2 (discontinuation)	Discontinuation of protocol treatment*

iv: intravenous infusion, civ: continuous intravenous infusion
*: See "8.8 Criteria for discontinuation of protocol treatment" for details.

8.5.1.2 Criteria for dose reduction/suspension of panitumumab

The criteria for dose reduction and the dose of panitumumab during the period of Protocol Treatment are shown in Table 8.f and Table 8.g, respectively.

Table 8.f Criteria for dose reduction of panitumumab

Item	Grade	Dose adjustment of panitumumab
Skin disorder	3	Dose reduction by 1 level with dose postponement (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.
	2	Dose postponement (suspension) is allowed. (Suspension is not essential.) If the symptom has become milder than the Grade as of the time of onset after the suspension, the drug will be administered at the dose before suspension.
	1	
Hypomagnesaemia*	3	Dose reduction by 1 level 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.
Infusion reaction**	3	Discontinuation of protocol treatment
	2	Careful administration by slowing the infusion speed***
	1	Careful administration by slowing the infusion speed***
Dose reduction/suspension is allowed as necessary at the discretion of the investigator 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

***: In the event that Grade 1 or 2 infusion reaction occurs during infusion, the infusion speed should be decreased by 50%.

Table 8.g Dose of panitumumab

Dose reduction level	Panitumumab
Initial dose	6 mg/kg
-1	4.8 mg/kg
-2	3.6 mg/kg
-3	0 mg/kg (discontinuation)

8.5.2 Protocol Treatment [2]

8.5.2.1 Criteria for dose reduction/suspension of mFOLFOX6

The criteria for dose reduction of OXA and 5-FU (bolus/infusional) during the period of Protocol Treatment [2] is shown in Table 8.h. Refer to Table 8.i for the doses of OXA and 5-FU (bolus/infusional), respectively.

Table 8.h Criteria for dose reduction of OXA and 5-FU (Protocol Treatment [2])

Adverse events in previous cycle	Grade	Dose adjustment of OXA and 5-FU
Neutropenia, thrombopenia	4	Dose reduction of both OXA and 5-FU (bolus/infusional) by 1 level
Grade 3 neutropenia or thrombopenia that persists for more than 7 days	3	
Febrile neutropenia, infection, nausea, vomiting, diarrhoea, fatigue	3	
Sensory nerve disorder*	3	Discontinuation of OXA** (no resumption)
	2	Discontinuation** of OXA (no resumption) Or dose reduction of OXA by 1 level
Allergic reaction	3	Discontinuation of OXA** (no resumption)
	2	Careful administration of OXA by slowing the infusion speed
Dose reduction/suspension is allowed as necessary at the discretion of the investigator due to adverse events not listed above.		

*: OXA may be resumed when nerve disorder has improved after suspension.
**: Continue the Protocol Treatment until "8.8 Criteria for discontinuation of protocol treatment" is met.

Table 8.i Doses of OXA and 5-FU (Protocol Treatment [2])

Dose reduction level	OXA	5-FU iv	5-FU civ
Initial dose	85 mg/m^2	400 mg/m^2	2400 mg/m^2
-1	65 mg/m^2	200 mg/m^2	2000 mg/m^2
-2	50 mg/m^2	0 mg/m^2 (discontinuation)	1600 mg/m^2
-3	0 mg/m^2 (discontinuation)	0 mg/m^2 (discontinuation)	0 mg/m^2 (discontinuation)

iv: intravenous infusion, civ: continuous intravenous infusion

8.5.2.2 Criteria for dose reduction/suspension of panitumumab

Refer to "8.5.1.2 Criteria for dose reduction/suspension of panitumumab".

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 Overdose of panitumumab

Overdose of panitumumab is defined as below regardless of whether or not adverse events have occurred.

① Administration at doses higher than the approved dose of panitumumab (6 mg/kg)

② The next dose is administered within 10 days after the date of previous administration.

Aiming at consistent entry of significant safety information regarding overdose in the database, the investigator or subinvestigator will record all cases of overdose (irrespective of the presence or absence of adverse events) in the page of overdose of the Case Report Forms. Adverse events associated with overdose will be recorded in the page of "Adverse Events" in the Case Report Forms according to "10.0 ADVERSE EVENTS".

Serious adverse events (SAE) associated with overdose will be reported according to the procedure described in "10.2.2. Collection and reporting of serious adverse events."

In the cases of overdose of panitumumab, the investigator or subinvestigator will provide treatment appropriate for the symptoms.

8.8 Criteria for discontinuation of protocol treatment

The protocol treatment specified below 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 decides on discontinuation of protocol treatment. The investigator should record the main reason for discontinuation of protocol treatment in the case report form according to the classification described below. See "9.3 Records of subjects who discontinued before enrollment"for subjects withdrawn from the study before enrollment.

<Common for Protocol Treatment [1] and [2]>

1. Adverse event
   When protocol treatment is postponed for 43 days or more after the day of starting the last cycle, or when the next protocol treatment cannot be resumed because of adverse events even after the passage of at least 43 days after the start of the last cycle of the protocol treatment. However, postponement due to holidays is allowed.

2. 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 randomization of protocol treatment has not been observed.

3. Lost to follow-up
   When a subject fail to make visits and cannot be contacted. That attempts were made to contact the subject should be recorded in the source documents.

4. Voluntary discontinuation
   When a subject wishes to discontinue study participation.

5. Discontinuation of entire study
   When study discontinuation is decided by the sponsor, or IRB such as the ethics review committee.

6. Pregnancy
   When a female subject is found out to be pregnant.
   Note: Study participation should be immediately discontinued when pregnancy is known.

7. Lack of efficacy
   When PD is evident in the clinical or imaging evaluation

8. Death during protocol treatment
   Death before discontinuation of protocol treatment is decided

9. When surgery aimed at curative resection (complete resection: R0 resection) of colorectal cancer is scheduled

10. Other
    When protocol treatment cannot be started after subject allocation, collect the reason (e.g., the criteria for initiation of protocol treatment were not met

<Protocol Treatment [1] >

11. Not satisfying at least one of the inclusion criteria for randomization or meeting any of the exclusion criteria <specify the applicable inclusion/exclusion criteria>

8.9 Contraindicated drugs/therapies

The drugs and therapies shown below are contraindicated from informed consent until 28 days (4 weeks) after discontinuation of protocol treatment. The investigator and/or subinvestigator (hereinafter referred to as the investigator) should instruct the patients not to use any drugs including over-the counter drugs other than the prescribed drugs without prior consultation. The following therapies are allowed to be started without waiting for the specified period only when the scheduled tests are performed until the next treatment upon starting it within 28 days (4weeks) after discontinuation of protocol treatment.

- ✓ Chemotherapy other than protocol treatment
- ✓ Hormone therapy
- ✓ Immunotherapy
  - ➢ Cellular immunotherapy
  - ➢ Vaccine therapy
  - ➢ Cytokine therapy
  - ➢ Biological response modifiers (BRM)
  - ➢ Antibody therapy
  - ➢ Gene therapy
- ✓ Other antibody therapy
- ✓ Radiotherapy
- ✓ Hyperthermia therapy
- ✓ Denosumab*

  *: Use of bisphosphonates is allowed.

- ✓ Study drug and unapproved drug

8.10 Allowed supportive care and combination medications

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

- Neutropenia
  Administration of G-CSF products is recommended. G-CSF should be administered according to the NHI indications and should not be prophylactically used.

- Nausea, vomiting
  Premedication including prophylactic administration of antiemetics is allowed. Premedication with 5-HT_3 (serotonin) receptor antagonists, NK1 (neurokinin 1) receptor antagonists, steroids, and antihistamines may be carried out using the method employed at each study site.

- Allergic reaction
  Treatment with adrenal corticosteroids, antihistamines, etc. may be considered at the time of onset or for premedication at the start of protocol treatment. Careful administration of panitumumab by slowing the infusion speed may be considered.

- Interstitial pneumonia
  Interstitial pneumonia should be treated according to the severity (e.g., steroid pulse therapy).

- Other
  Drugs for treatment of adverse events may be coadministered at the discretion of the investigator. 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 when any of panitumumab-related adverse events shown below is observed. The absence of supporting therapy does not constitute a protocol deviation.

- It is recommended that oral minocycline, etc. be administered when skin disorder is observed.

- At the time of onset of skin disorder
  External salicylic acid petrolatum (10%)
  External steroid therapy (example)
  Face: hydrocortisone butyrate (0.1%)
  Trunk: difluprednate (0.05%)

  It is recommended the following skin care prophylactically against the skin disorder from the start of protocol treatment [1].
  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).

- At the time of onset of 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

8.11 Handling of surgery aimed at curative resection (complete resection: R0 resection) of colorectal cancer

Surgery is recommended for patients who can tolerate curative resection (complete resection: R0 resection) thanks to the antitumor effect after initiation of protocol treatment.

Protocol treatment should be discontinued when surgery aimed at curative resection (complete resection: R0 resection) of colorectal cancer is scheduled, and all tests and observation scheduled at discontinuation of protocol treatment should be conducted (see “9.1 Study calendar”).

8.12 Recommended follow-up therapy

8.12.1 Recommended second-line treatment

- Group A: Administration of bevacizumab in combination with IRI-based chemotherapy is recommended.
- Group B: Readministration of bevacizumab in combination with OXA-based chemotherapy is recommended.

8.12.2 Recommended third-line or subsequent treatment

- Group A: All approved drugs (regorafenib, etc.) should be administered appropriately as best as possible.
- Group B: Administration of bevacizumab in combination with the IRI-based chemotherapy is recommended. After that, all approved drugs (regorafenib, etc.) should be administered appropriately as best as possible.

9.0 PROTOCOL, EVALUATION ITEMS AND PROCEDURES FOR OBSERVATIONS

9.1 Study calendar

The investigator should collect data according to the following procedures. The same investigator should perform tests/observation/evaluation of subjects in principle.

Table 9.a Study calendar (Protocol Treatment [1])

Item	Enrollment	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Discontinuation of protocol treatment*9
Informed consent	●*							
Eligibility	●							
Subject background	●							
Clinical findings (physical examination)	●	●	●*1	●*1	●*1	●*1	●*1	●
Vital signs	●	●	●*1	●*1	●*1	●*1	●*1	●
Height, body weight	●		○*2	○*2	○*2	○*2	○*2	
ECOG P.S.	●*3		●	●	●	●	●	●
Treatment compliance		●	●	●	●	●	●	
Laboratory tests								
Hematology	●*4	●*4	●*1	●*1	●*1	●*1	●*1	●
Serum chemistry	●*4	●*4	●*1	●*1	●*1	●*1	●*1	●
Urinalysis	●*4	●*4	●*1	●*1	●*1	●*1	●*1	●
Tumor markers	●*4	●*4						○*5
Imaging test (thoracoabdominal-pelvic CT/MRI)	●*6	●*7		●*7				○*7,*8
NRAS test	●*10							
Adverse Event	—	←				●		→

●: Mandatory, ○: Perform as necessary

*: Consent should be obtained at enrollment

*1: Perform before initiation of each cycle of protocol treatment.

*2: Measure and record only body weight when the dose is changed.

*3: Assess again immediately before administration of the 1st cycle when the entry test has been performed more than 14 days away before enrollment.

*4: The test in Cycle 1 may be skipped when the entry test has been performed 1 or 2 days before treatment in Cycle 1. The test in Cycle 1 will be performed before treatment in Cycle 1 when the entry test has been performed more than 2 days before treatment in Cycle 1.

*5: Measure only when more than 56 days (8 weeks) have passed after the previous measurement.

*6: If the imaging test before enrollment is performed within 14 days prior to Cycle 1, the test of first cycle can be omitted, but an imaging test should be preferably conducted immediately before administration of the 1st cycle.

*7: Use the method employed at the enrollment for measurement.

*8: Perform the imaging test within 28 days (4 weeks) after decision on discontinuation for subjects withdrawn from the study for any reason other than PD.

*9: Perform within 28 days (4 weeks) after discontinuation. Perform until the next treatment when it will be startied within 28 days (4weeks) after discontinuation.

*10: Perform the test in the patients who agree to participate in the study before *NRAS* test comes to be covered by insurance, and the patients who agree to participate in the study after *NRAS* test comes to be covered by insurance but before the test becomes feasible at the study site and who give consents to the conduct of the test. The timing of submission of samples does not need to be upon registration.

Table 9.b Study calendar (Protocol Treatment [2])

Item	Randomization	Every 2 weeks Cycle 7 and later§	Every 8 weeks§	Discontinuation of protocol treatment*8	Follow-up period*9
Eligibility	●				
Subject background					
Clinical findings (physical examination)	●	●*1,*2		●	
Vital signs	●	●*1,*2		●	
Height, body weight		○*3			
ECOG P.S.	●	●*1,*2		●	
Treatment compliance (incluing the test at discontinuation)		●			
Laboratory tests					
Hematology	●	●*1,*2		●	
Serum chemistry	●	●*1,*2		●	
Tumor markers	●		●	●	
Imaging test (thoracoabdominal-pelvic CT/MRI)	●*4,*5		●*4,*6	○*4,*7	○*10
Follow-up therapy					●
Survival survey					●
Adverse Event	← ● →				

●: Mandatory, ○: Perform as necessary

§: As a rule, tests of tumor markers and imaging tests will be conducted in the (4n + 3)th administration cycle. However, when the administration interval becomes longer because of the criteria for extension of administration period, the tests will be conducted at appropriate timings.

*1: Perform before initiation of each cycle of protocol treatment.

*2: The test in Cycle 7 may be skipped when the test at randomization has been performed 1 or 2 days before treatment in Cycle 7. The test in Cycle 7 will be performed before treatment in Cycle 7 when the test at randomization has been performed more than 2 days before treatment in Cycle 7.

*3: Measure and record only body weight when the dose is changed.

*4: Use the method employed at randomization for measurement.

*5: Masure between the day of administration in 6th cycle and randomization.

*6: Reduce the frequency of imaging test to once every 112 days (16 weeks) 14 days (± 2 weeks) when two years have passed since initiation of protocol treatment.

*7: Perform the imaging test within 28 days (4 weeks) after decision on discontinuation for subjects withdrawn from the study for any reason other than PD.

*8: Perform within 28 days (4 weeks) after discontinuation.

*9: Perform every 6 months (approximately) after discontinuation of protocol treatment.

*10: Perform only when 56 days (8 weeks) or more have passed after the previous measurement.

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

The investigator will perform the following as scheduled in "9.1 Study calendar."

9.2.1 Informed consent procedure

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

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

A unique subject ID code will be assigned to each subject when explanation is given to obtain consent. The subject ID code will be used throughout the study period.

9.2.2 Procedures for registration and allocation of drugs

9.2.2.1 Procedures for registration and initiation of protocol treatment

The investigator will register subjects according to the following procedures.

1) The investigator or study collaborator should record the necessary items in subject screening list for a subject who was selected to receive explanation for obtaining consent for study enrollment.

2) The investigator or study collaborator should input the necessary items into the Web case registration system for a subject who has given consent.*
*: The study collaborator may input into the Web case registration system by instruction of the investigator.

3) Eligibility of a prospective subject is judged by the Web case registration system and a protocol study group will be assigned when the subject is eligible.

4) The investigator and study collaborator will check the registration result and assigned protocol study group on the Web case registration system. The registration result and assigned protocol study group will be sent via e-mail from the Web case registration system to the investigator and study collaborator.

5) The investigator should start the allocated protocol treatment within 15 days of formal registration (including the same day of week as the day of enrollment).

6) The investigator or study collaborator should immediately contact the sponsor and input necessary items in the Web subject registration system when the study drug is not administered for reasons such as withdrawal of consent after allocation, or when a change related to allocation is made to the data of the registered subject.

9.2.2.2 Preparation and storage of allocation procedures

The allocation manager (person designated by the sponsor) should prepare the allocation procedures and manage allocation information of subjects. Minimization method should be used for allocation of protocol treatment using the allocation factors of the study site, age (20 to 64 years/65 to 79 years), and presence/absence of liver metastasis. The allocation information should be stored in a safe place and made accessible only by the authorized persons.

9.2.3 Subject demographics

The following demographic data will be collected: date of birth and sex at the time of enrollment.

The following data concerning the target disease of colorectal cancer will be collected.

1) Tissue type
The tissue type will be assessed based on the histological findings in the "Japanese Classification of Colorectal Carcinoma" and recorded in the case report form with the date and site of sampling for diagnosis.

   - Date of initial diagnosis
   - Date of diagnosis of Stage 4 (no need for input the case report form when it is the day of the initial diagnosis)

2) History of treatment

   - History of surgery
     - For subjects with a history of surgery, the date of surgery, surgery site (primary/metastatic lesion), and the number of lymph nodes resected. Endoscopic surgery, which is not considered a history of surgery, should not be entered into the case report form.
   - History of radiotherapy
     - For subjects with a history of radiotherapy, the final irradiated date.
   - History of preoperative and/or postoperative adjuvant chemotherapy
     - For subjects with a history of adjuvant chemotherapy, the type of preoperative and/or postoperative adjuvant chemotherapy, date of final treatment.

3) Information on metastatic organ

   - Number of metastatic organs (0, 1, 2 or more)*
     *: The primary lesion/regional lymph node is not included, and the distant lymph node is counted as "one organ" even if there is more than one.
   - Metastatic organs (liver, lung, peritoneum, lymph node*, bone, adrenal gland, skin, other**)
     *: distant lymph node is counted as "one organ" even if there is more than one.
     **: The name of the organ will be recorded in the case report form.

9.2.4 Medical history

A medical history is defined as any clinically problematic disease or symptom that has resolved within one year prior to initiation of protocol treatment. Any notable medical history will be recorded in the case report form.

9.2.5 Current medical condition

A current medical condition is defined as any symptom or disease present at initiation of protocol treatment. Any notable current medical condition will be recorded in the case report form. Clinically problematic laboratory test data, ECG findings, and abnormal physical examination findings observed immediately before initiation of protocol treatment should be handled as a current medical condition at the discretion of the investigator.

9.2.6 Clinical findings (physical examination)

The following locations and parts of the body will be examined:
(1) eyes, (2) ears, nose, and throat, (3) cardiovascular system, (4) respiratory system, (5) gastrointestinal system, (6) dermatologic system, (7) extremities, (8) musculoskeletal system, (9) nervous system, (10) lymph nodes, (11) other.

In particular, subjects will be checked for the following symptoms at the physical examination: allergic reaction, fatigue, rash acneiform, dry skin, paronychia, infusion related reaction, palmar-plantar erythrodysaesthesia syndrome, anorexia, diarrhoea, nausea, vomiting, oral mucositis, febrile neutropenia, infection, hemorrhage, pain, peripheral motor neuropathy, peripheral sensory neuropathy, alopecia, thromboembolism, gastrointestinal perforation, pneumonitis, and pulmonary fibrosis.

For diagnosis after initiation of protocol treatment, evaluate the clinically problematic abnormality compared with the result of diagnosis before initiation of protocol treatment.

9.2.7 Body weight and height

Body weight and height will be measured before enrollment. Body weight (kg) will be measured to the first decimal place and rounded off to the first decimal place when the second decimal place is known. Height (cm) determined will be expressed in integer value (rounded off to integer).
In principle, measurement is unnecessary during the treatment period. However, body weight should be recorded in the case report form when the measured value is used to change the dose of protocol treatment.

9.2.8 Vital signs

The following vital signs will be measured: body temperature and blood pressure and pulse rate (bpm) at sitting position (after rest for 5 min or longer). In particular, subjects will be checked for fever and hypertension.

9.2.9 ECOG P.S.

ECOG P.S. will be assessed according to Table 9.c. Assess again immediately before administration of the 1st cycle when the entry test has been performed more than 14 days away before enrollment.

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

Grade	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

Grade	Definition
	chair

9.2.10 Treatment compliance (Protocol Treatment [1] and [2] implementation status)

The investigator should record the compliance with protocol treatment in the case report form as follows:

- When protocol treatment is administered: The dose and the date of treatment should be recorded. The reason for dose reduction should also be recorded when appropriate.
- When any drug used in protocol treatment is suspended: The date of suspension should be recorded.
- When any drug used in protocol treatment is discontinued: The date and reason for discontinuation should be recorded.

9.2.11 Laboratory tests

The laboratory tests performed at each time point during the study are shown in Table 9.d to Table 9.g. The laboratory tests will be performed at each study site.

The investigator should evaluate the reported laboratory test results. The representative investigator at each site should be administer and store the standard value of laboratory tests.

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

Hematology	Serum chemistry	Tumor marker
WBC	Total bilirubin	CEA
Neutrophil count	ALT	CA19-9
Platelet count	AST	
Hemoglobin content	Creatinine	

Immunology
HBs antigen
Hepatitis tests including anti-HCV

Table 9.e Laboratory tests performed before the start of each cycle of treatment (Protocol Treatment [1])

Hematology	Serum chemistry	Tumor marker
WBC*	Total bilirubin*	CEA*, †
Neutrophil count*	ALT*	CA19-9*, †
Platelet count*	AST*	
Hemoglobin content*	Creatinine*	
	Mg	
	ALP	
	LDH	
	Albumin	
	Na	
	K	
	Ca	
	Cl	

*: The test in Cycle 1 may be skipped when the entry test has been performed 1 or 2 days before treatment in Cycle 1. The test in Cycle 1 will be performed before treatment in Cycle 1 when the entry test has been performed more than 2 days before treatment in Cycle 1.
†: Measure before the initiation of 1st cycle only.

Table 9.f Laboratory tests performed before the start of each cycle of treatment (Protocol Treatment [2])

Hematology	Serum chemistry	Tumor marker
WBC	Total bilirubin	CEA*
Neutrophil count	ALT	CA19-9*
Platelet count	AST	
Hemoglobin content	Creatinine	
	Mg	
	ALP	
	LDH	
	Albumin	
	Na	
	K	
	Ca	
	Cl	

*: Perform every 8 weeks.

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

Hematology	Serum chemistry	Tumor marker
WBC	Total bilirubin	CEA*
Neutrophil count	ALT	CA19-9*
Platelet count	AST	
Hemoglobin content	Creatinine	
	Mg	
	ALP	
	LDH	
	Albumin	
	Na	
	K	
	Ca	
	Cl	

*: Measure only when more than 56 days (8 weeks) have passed after the previous measurement.

9.2.12 Imaging test (thoracoabdominal-pelvic CT/MRI)

Imaging test before enrollment will be performed within 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 28 days prior to enrollment.

During the period of Protocol Treatment [1], imaging test will be performed before administration in the 1st cycle and the 3rd cycle. The results of imaging tests before administration in the 1st cycle will be handled as the image data for measurable lesion, and the test will be performed within 14 days prior to initiation of Protocol Treatment [1] (including the same day of week as the day of enrollment). If the imaging test before enrollment is performed within 14 days prior to initiation of Protocol Treatment [1], the imaging test can be omitted, but an imaging test should be preferably conducted immediately before administration of the 1st cycle.

Imaging test before initiation of Protocol Treatment [2] will be conducted between administration of the 6th cycle and randomization. It will be performed every 8 weeks after initiation of Protocol Treatment [2] (See "Table 9.b Study calendar (Protocol Treatment [2])" for details.)

Thoracoabdominal-pelvic CT (in principle, contrast CT with a slice width of 5 mm or less, but MRI is also acceptable) will be used for imaging test, and the modality and the date of imaging test will be recorded in the case report form.

The same modality should be used during protocol treatment throughout the study period.

The investigator should evaluate the test results according to the RECIST v1.1 and record the evaluation results in the case report form.

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 for protocol treatment should be performed within 4 weeks including the day of decision (including the same day of week as the day of decision).

9.2.13 *NRAS* test

9.2.13.1 Subjects

The subjects will be the patients who agree to participate in the study before *NRAS* test comes to be covered by insurance, and the patients who agree to participate in the study after *NRAS* test comes

to be covered by insurance but before the test becomes feasible at the study site and who give consents to the conduct of the test.

For the patients who receive *NRAS* test at the study site after *NRAS* test has come to be covered by insurance, test results regarding each codon shown in Table 9.h will be recorded in the case report forms.

9.2.13.2 Samples and submission

For the patients who have given a consent to the test, the tumor tissue samples which have been collected in surgery or biopsy performed prior to informed consent, and which are used for evaluation of *KRAS* will be used for the test. From paraffin-embedded samples, 5-μm slices will be obtained, and 5 pathological samples fixed on slide glasses will be submitted to [redacted]. It is also acceptable to submit samples in the form of paraffin-embedded samples. When paraffin-embedded samples are submitted, [redacted] will prepare a necessary number of slide glass samples, and will return the remaining sample to the study site.

Investigators will use the materials prepared by [redacted] in advance at the beginning of the study and send the samples to [redacted]. Details are described in the written procedure prepared separately. [redacted] will send in advance the materials necessary for storing and sending samples to the study sites where enrollment of study subjects has become possible.

Details regarding submission of tumor tissues will be described in the written procedure prepared separately.

9.2.13.3 Data

Among the subjects specified in "9.2.13.1 Subjects", the investigators will enter the following issues regarding the submitted tumor tissues in the case report forms for the subjects for whom the samples required for the test have been submitted to [redacted]. However, recording of the results of *NRAS* measurement in the case report forms will be unnecessary.

1) Procedure of sample collection

2) Timing of sample collection

3) Number of slides submitted in the case of pathological slides

For the patients who are enrolled in the study after *NRAS* test has come to be covered by insurance and who receive *NRAS* tests at the study sites, the investigators will record the presence or absence of mutation of each of the following codons in the case report forms.

Table 9.h EXON and codon verified on *NRAS* test

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

9.2.14 Surgery aimed at curative resection (complete resection: R0 resection) of colorectal cancer

When surgery is performed for patients who are expected to tolerate curative resection of colorectal cancer during protocol treatment, the operative procedure, date of surgery, and postoperative assessment of residual tumor should be recorded in the case report form. The residual tumor is assessed according to the table shown below, and the histological results of resection specimens should be recorded in the case report form wherever possible. The date when surgery aimed at curative

resection (complete resection: R0 resection) of colorectal cancer is scheduled is considered as the date of discontinuation of protocol treatment

When surgery aimed at curative resection is performed in more than one session, the number of sessions should be recorded in the case report form. As for the postoperative assessment of residual tumor, data obtained by the time of initiation of subsequent treatment should be recorded in the case report form. Data generated after initiation of subsequent treatment will be collected through monitoring and assessed by the steering committee for the validity.

Table 9.i Residual tumor after surgical treatment

Classification	Criteria
RX	The presence of residual tumor cannot be assessed.
R0	No residual tumor
R1	Resected, but tumor on the margins of a surgical resection specimen or the radial margin
R2	Macroscopic residual tumor

9.2.15 Survival survey

All subjects will be followed up after discontinuation of protocol treatment to confirm survival of subjects. Survival survey should be continued until a subject dies or the sponsor terminates the study.

- Date of death or date of last confirmation of survival

9.2.16 Follow-up therapy

When follow-up therapy is performed after discontinuation of Protocol Treatment [2], the following information on follow-up therapy should be collected until a subject dies or the sponsor terminates the study.

- Name of regimen (name of drugs used)

9.3 Records of subjects who discontinued before enrollment

For subjects withdrawn from the study before enrollment of protocol treatment, the main reason for discontinuation should be recorded in the case report form according to the following categories.

- Not satisfying at least one of the inclusion criteria or meeting any of the exclusion criteria <specify the applicable inclusion/exclusion criteria>
- Serious deviation from the protocol
- Lost to follow-up
- Voluntary discontinuation <specify the reason>
- Discontinuation of the entire study
- Other <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 all untoward 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 treatment
- Requiring invasive diagnostic treatment
- Requiring discontinuation or change in the dose of protocol treatment (chemotherapy, panitumumab and bevacizumab) or concomitant drugs under use
- Considered unfavorable by the investigator

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. Any adverse events that could not be expressed in medical terminology (name of diagnosis) should be recorded with signs or symptoms observed.

Laboratory test findings:

Abnormal laboratory values and ECG findings are recorded as adverse events when the investigator judges the course to be clinically problematic (in other words, when certain action or treatment is required, or the investigator judges the change to have exceeded the normal physiological variation range of the subject).

Retest and continued monitoring of abnormality are not considered treatment. Also, repeated or additional conduct of non-invasive test for verification, evaluation and monitoring of abnormality are not considered treatment.

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 is recorded as an adverse event and the investigator should record in the case report form that the adverse event as aggravation of the complication (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 should record it so that a reported adverse event name is a change from the baseline (e.g., aggravation of XX).

Aggravation of adverse events:

When any secondary sign/symptom develops due to an adverse event, it should be considered as a new adverse event and recorded in the case report form. The investigator should record it so that a reported adverse event name is a change from the baseline (e.g., aggravation of XX).When the severity of an adverse event is changed, the event should be recorded once at the highest degree of severity (grade based on the CTCAE [Japanese edition JCOG version 4.03]).

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. 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, clinical or imaging progression of the preexisting cancer (including new metastasis) is considered a serious adverse event when the severity satisfies any of the criteria for seriousness specified in Section 10.1.3.

Overdose of panitumumab:

Overdose of panitumumab which does not accompany the occurrence of events will not be regarded as adverse events, but the overdose of panitumumab will be recorded in the page of overdose in the case report form. If any events have occurred, they will be recorded as adverse events in the page of adverse events in the case report form.

10.1.3 Serious adverse events

Of all the unfavorable medical events that developed by 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.

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.

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. Requires inpatient hospitalization or prolongation of existing hospitalization.
   Hospitalization described below is not considered 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 5 above. Diseases shown in Takeda Medically Significant AE List (Table 10.a) are included.

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

10.1.4 Severity of adverse events

The severity of adverse event is classified and defined as follows based on the CTCAE (Japanese edition JCOG version 4.03):

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

*: 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.

10.1.5 Causality of adverse events

Causal relationship between protocol treatment (OXA, 5-FU, or panitumumab) and adverse events 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 with treatment discontinuation (including clinical course after discontinuation). Possibly due to protocol treatment (chemotherapy 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 or panitumumab). Very likely due to other factors such as underlying disease, complications, and concomitant drugs/treatment.

10.1.6 Date of onset

Judge the date of onset of adverse event according to the following criteria:

Adverse event, etc.	Date of onset
Signs, symptoms, diseases (diagnosis name)	Record the date when the subject or the investigator noticed the first signs and symptoms of adverse event.
Asymptomatic disease	Record the date of obtaining a definite diagnosis after conducting a test for diagnosis. Record the date of obtaining a definite diagnosis even when the test findings show old findings or suggest approximate timing of onset.
Aggravation of complications	Record the date when the subject or the investigator noticed the signs and symptoms of adverse event for the first time.
Abnormal laboratory findings after initiation of protocol treatment	Record the date of test where abnormal laboratory values considered clinically problematic were observed.
Abnormality was observed on the test at initiation of protocol treatment, and aggravation was shown on subsequent tests.	Record the date of tests when values were medically judged to be obviously increased and decreased based on the changes in test values.

10.1.7 Date of resolution

The date when adverse event resolved (or resolved with sequelae). Date of death when a subject died of the concerned adverse event. When recovery cannot be confirmed at study completion, it is considered ongoing.

10.1.8 Incidence

When the investigator considers the first occurrence up to the final remission of a series of adverse events which repeatedly appear to be resolved or recurred as one event (e.g., constipation, diarrhoea, vomiting, etc.), it is considered to be “intermittent”. Other events are considered “ongoing”.

10.1.9 Action taken for protocol treatment

The action taken for OXA, 5-FU, or panitumumab in protocol treatment is classified and defined as follows:

Dose not changed	The dose of chemotherapy or panitumumab in protocol treatment was not changed even after onset of the adverse event. “Dose not changed” should be selected if another adverse event was the reason for discontinuation or dose reduction of OXA, 5-FU, or panitumumab in protocol treatment.
Dose reduced	The dose of OXA, 5-FU, or panitumumab in protocol treatment was reduced due to the adverse event.
Treatment suspended	Treatment with OXA, 5-FU, or panitumumab in protocol treatment was postponed due to the adverse event and resumed later.
Treatment discontinued	Treatment with OXA, 5-FU, or panitumumab in protocol treatment was discontinued due to the adverse event.
Not applicable	Treatment with OXA, 5-FU, or panitumumab in protocol treatment had already been completed or discontinued by the time of the onset of the adverse event.
Unknown	The clinical course after the event onset is unknown, for instance, because no contact with the subject can be made.

10.1.10 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

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 (no need for recording the date of death in this case)
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.
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 four weeks after discontinuation of protocol treatment.

10.2.1.2 Reporting of adverse events

At each visit, the investigator should assess the onset of subjective symptoms are present. 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 should follow up all subjects who developed adverse events irrespective of a causal relationship with protocol treatment until disappearance of symptoms or return of abnormal laboratory values to the value at initiation/dose reduction of protocol treatment, or until observed changes can be sufficiently explained for other events (persistent/irreversible adverse event, etc.).

All adverse events should be recorded in the case report form. The name of an adverse event, date of onset, date of disappearance, frequency, severity, causal relationship with protocol treatment (unrelated or related), action taken for protocol treatment (chemotherapy and panitumumab), outcome, and seriousness should be recorded.

Follow-up period of adverse events is until recovery of an adverse event, or the investigator judges that further follow-up would not be necessary.

When requested by the representative researcher, the investigator should check the additional necessary information and data and complete recording them in the case report form within the designated period.

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 judges that a serious adverse event has occurred based on the reporting by a subject, etc. and the result of various tests, imaging findings or definitive diagnosis, a report should be

submitted to the director of the study site and the representative researcher (see attached sheet for contact information) within one working day and a report should be made via the sponsor to the investigators of other sites jointly performing the clinical study. In addition, the investigator should submit a formal detailed report within 10 calendar days.

The following items are the requisite for reporting within one working day, and other items should be reported as best as possible.

- Study title
- Subject ID code
- Name of study site
- Name of investigator
- Name of serious adverse event, course (date of onset, reason for the judgment of "serious", protocol treatment given, causal relationship with protocol treatment, course, and outcome)
- Action taken for the serious adverse event (suspension of new enrollment, revision of the written informed consent, newly obtaining consent from other subjects)

10.2.3 Dissemination of a serious adverse event to study sites jointly performing the clinical study

When the head of study site receives a report of a serious adverse event from the investigator, he/she should obtain the opinions of the IRB such as the ethics review committee, add the following item to the report of the investigator, and disseminate it via the sponsor to the data monitoring committee and the study sites jointly performing the clinical study.

- Date of review by the IRB such as the ethics review committee, summary of review, result, and necessary actions, etc.

10.3 Follow-up of serious adverse events

The investigator 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 should submit a report specifying details of the change to the head of study site and the sponsor. When requested by the sponsor or the IRB 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.

11.0 COMMIITTEES ESTABLISHED FOR ADMINISTRATIVE STRUCTURE AND 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 steering committee members and biostatistician, and the sponsor or the person designated by the sponsor will act as the secretariat.

See the supplement for the research steering committee members.
The research steering committee will not be informed of the treatment allocation throughout the study period.

Details of the research steering committee will be specified in a separately prepared SOP.

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 person designated by the sponsor will act as the secretariat. See the supplement for the DMC member.

The DMC will notify a DMC advisory report on continuation/discontinuation of the study and change of the study plan according to the safety analysis results for evaluation 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.

12.0 DATA MANAGEMENT AND STORAGE OF RECORDS

Detailed procedures concerning data management will be specified in the data management plan. Adverse events, medical history, and concurrent conditions should be coded using the MedDRA. Drug names should be coded using the WHO Drug Dictionary.

12.1 Case report form

The investigator should prepare the case report form for all subjects who have provided informed 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 and study collaborators with training for utilization of EDC. The case report form will be used to report the information collected during the study period to the sponsor. The case report form will be prepared in Japanese. Data will be directly entered into the case report form.

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

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

The data below will be directly recorded into the case report form.

- Severity and causal relationship of adverse event with “OXA”, “5-FU”, or “panitumumab” in protocol treatment

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

The sponsor or its designee should confirm the accuracy and completeness of the case report form during a visit to a study site. The sponsor or its designee should access to the medical records of study subjects and in-house records to ensure the accuracy of the case report form. The completed case report form is the property of the sponsor, and the investigator should not divulge the information to a third party other than the regulatory authority without a written permission of the sponsor.

12.2 Time limit for data input into the EDC

It is recommended that data obtained after informed consent be entered into the EDC 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 efforts be made to adhere to the time frame.

1) At enrollment: within two weeks after enrollment

2) During protocol treatment: within two weeks after discontinuation of each cycle of protocol treatment

3) At discontinuation of protocol treatment: within four weeks after discontinuation of protocol treatment

4) Imaging test results: within two weeks after evaluation of efficacy

5) Follow-up period: within two weeks after request for follow-up

6) Inquiry about data input into the EDC: within two weeks after inquiry

12.3 Storage of records

The investigator or the head of study site should store the following materials including those specified in Section 12.1 and study specific documents for use by the investigation or audit by the regulatory authority and the sponsor or their designee. 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 case report form (copy)/electronic copy of electronic case report form containing audit trail. The investigator and the head of study site should store the essential documents until five years after discontinuation or completion of the study. However, when the sponsor requires a longer storage period, the head of study site will discuss the period and methods of storage with the sponsor.

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

13.0 STATISTICAL ANALYSIS METHODS

13.1 Statistical and analytical plans

The statistician in charge should prepare and finalize the statistical analysis plan (SAP) before data fixation. Detailed definition of endpoints and analysis methods should be specified in the SAP to cope with the purpose of all studies.

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.

13.1.1 Analysis set

Two analysis sets, "full analysis set" and "safety population", are used in this study. "Full analysis set" is defined as "randomized subjects," and the "safety population" is defined as "the subjects who received at least one dose of protocol treatment after randomization."

The sponsor should confirm the definition of analysis sets and appropriateness of analytical handling rules of the subject data in the analysis sets before data fixation, add handling of problematic issues which have not been prescribed in the planning stage, and finalize the SAP.

13.1.2 Analysis of demographic and other baseline characteristics

The following analysis should be conducted in "full analysis set."

Concerning major subject background factors, frequency analysis should be conducted for numerical data and summary statistics should be calculated for quantitative data for each treatment group and collectively for all treatment groups.

13.1.3 Efficacy analysis

13.1.3.1 Primary endpoint and analysis method

[Primary endpoint]

Progression-Free Survival (PFS)

The PFS is the period from the day of randomization (Day 0) until the day of judgment of exacerbation from the day of randomization, or until death by all causes, whichever comes earlier.

Progression includes both PD based on diagnostic imaging according to RECIST Guidelines (ver 1.1) and progression of the underlying disease which cannot be confirmed on diagnostic imaging (clinical progression). If progression is diagnosed on the basis of diagnostic imaging, the date of the imaging test will be regarded as the date of progression, and the date of clinical judgment will be regarded as the date of progression in the case of clinical progression. Even when a condition is regarded as PD according to the criteria for efficacy evaluation, such as in the cases of extreme shrinkage of the tumor size, but "progression is obviously ruled out" from a clinical point of view, PD according to the efficacy evaluation criteria will be given priority and the condition will be regarded as progression (in this case, clinical judgment will be prioritized with respect to whether or not protocol treatment should be continued). When the condition is not regarded as PD according to the efficacy evaluation criteria but it is obviously deemed as progression from a clinical point of view, the clinical judgment will be prioritized and the condition will be regarded as progression. The study will be cut off for the surviving patients without a diagnosis of progression on the last day of clinical confirmation of the absence of progression (date of last confirmation of progression-free survival; Confirmation of the absence of progression on imaging test and sample

test is not essential. Clinical confirmation of the absence of progression at outpatient clinic will suffice. Reporting by telephone only will not be accepted). Even in the cases of protocol treatment discontinuation for such reasons as toxicity and patients' withdrawal in which other treatment has been given in the after-care, events and cutoff will be handled in the same manner. In other words, the timing of discontinuation of treatment or the date of the start of after care will not be regarded as the cut-off dates.
[Main analysis]

Perform the following analysis for the “full analysis set”.

For each treatment group, calculate the progression-free survival rate at a given time point and its 95% confidence interval (two-sided) by Kaplan-Meier method, and calculate the quartile of PFS and its 95% confidence interval (two-sided). At the same time, draw a Kaplan-Meier chart for the progression-free survival rate. If the median value of observed PFS is 9 months or more in each group, the treatment regimen concerned will be regarded as being of worth of further investigation.

Moreover, for the sake of reference, calculate the hazard ratio of Group B to Group A and its 95% confidence interval (two-sided) on the basis of the stratified Cox regression model and apply the log-rank test.

13.1.3.2 Secondary endpoints and analysis method

[Secondary endpoints]

Overall survival（OS）

OS is defined as the period from the day of randomization (Day 0) until death by all causes.
[Analysis method]

For OS, perform the same analysis as that for the primary endpoint for the "full analysis set."

・Response rate（RR）

RR is defined as the percentage of subjects who have shown complete response or partial response as the best overall response in RECIST ver 1.1 after randomization. The overall response will be complete response, followed by partial response, stable disease, progression, and nonevaluable in this order.

[Analysis method]

In "full analysis set," RR and two-sided 95% confidence interval will be calculated for each group. At the same time, the inter-group difference of RR (Group B－Group A) and the two-sided 95% confidence interval will be calculated.

・Time to treatment failure（TTF）

TTF is defined as the period from the date of randomization (counted as Day 0) to the date of judgment of discontinuation of protocol treatment, the date of judgment of progression, or the date of death for all causes, whichever has come earliest.

[Analysis method]

For TTF, perform the same analysis as that for the primary endpoint for the "full analysis set."

13.1.3.3 Other efficacy endpoints

See "5.2 Endpoints".

13.1.3.4 Data conversion method and handling of missing data

The subjects who have not experienced any events at the end of study on the data cutoff date in the analyses of PFS and OS will be handled as the cutoff cases.

For the cutoff cases, the last day of available image evaluation results prior to the data cutoff date for image test will be regarded as the timing of cutoff in the analysis of PFS, and the data cutoff date or the date of last confirmation of survival, whichever comes earlier, will be regarded as the timing of cutoff in the analysis of OS. Date of last confirmation of progression-free survival on which absence of clinical progression has been confirmed.

Details about the method of conversion of other data and handling of missing data will be specified separately in the SPA.

13.1.3.5 Level of significance, confidence coefficient

- Level of significance: 5%
- Confidence coefficient: 95% (two-sided estimation)

13.1.4 Safety analysis

Perform the following analyses in the “safety population”.

13.1.4.1 Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAE) are the adverse events which developed after initiation of protocol treatment after randomization.

For TEAE, perform the following analyses for each treatment group. Code TEAE using the MedDRA to summarize them by Preferred Term (PT) and System Organ Class (SOC).

- Frequency tabulation of all TEAE
- Frequency tabulation of TEAE for which the causal relationship with any of the protocol treatments was judged as “related”
- Frequency tabulation of all TEAE by severity
- Frequency tabulation of TEAE by severity for which the causal relationship with any of protocol treatment was judged as “related”
- Table of TEAE by frequency with the action taken for any of protocol treatment was handled as “discontinuation”
- Frequency tabulation of serious TEAE
- Frequency tabulation of TEAE of peripheral nerve disorders (secondary endpoint)

Peripheral nerve disorders will be defined as the events classified with the preferred term of "peripheral neuropathy" according to the Standardised MedDRA Queries, and skin disorders will be defined as the events classified with the System Organ Class of "Skin and subcutaneous tissue disorders" or the events classified as with the Preferred Term of "paronychia." The interstitial pneumonia will be the events of the Preferred Terms of the MedDRA Standard Search Formula.

13.1.5 Predetermined subgroup analysis

In this study, the following subgroup analysis will be conducted.

- Subgroup analysis based on *NRAS* test

13.2 Criteria for interim analysis and premature discontinuation

Interim analysis will not be conducted.

13.3 Determination of the planned number of subjects

This study will be designed as a phase II randomized screening comparison study which does not use direct comparison for primary analysis[22].

In the phase III study (PRIME Study) in which FOLFOX4 therapy was combined with bi-weekly administration of panitumumab 6 mg/kg as a first-line therapy, the median PFS in the patients of *KRAS* wild-type as the primary endpoint was reported as 9.6 months[12]. Moreover, in PEAK study[23] in which panitumumab and bevacizumab were compared as the drugs to be administered in combination with mFOLFOX6 therapy, the median PFS in the mFOLFOX6 therapy + panitumumab group was reported as 10.9 months. The percentage of the cases in which any events occurred or the study was cut off within 3 months in PRIME Study and PEAK Study was approximately 10% of all cases.

The subjects of this study will be the patients who receive mFOLFOX6 + panitumumab combination therapy for 3 months, and can continue OXA administration. Since the PFS 40% point in PRIME Study and PEAK Study was approximately 13 months, the median PFS in Group A in this study is expected to be approximately 10 months, which is obtained by subtracting 3 months from the 40% point. The median PFS in Group B is assumed to be comparable to that in Group A.

In the primary analysis, a test based on the method of Brookmeyer-Crowley[24] will be conducted for the null hypothesis, "true median PFS will be lower than the threshold median PFS for judgment as ineffective", separately in Group A and Group B on the basis of the observed median PFS. When the threshold median PFS is regarded as 6 months, true median PFS as 10 months, enrollment period as 12 months, follow-up period as 12 months, one-sided significance level as 5%, and power of test as 80%, the number of subjects required in Group A and Group B will become 54 subjects each. Considering the cases of discontinuation, the target number of subjects to be randomised was set at 60 patients for each group (120 patients in total).

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. During site visit monitoring, the data recorded in EDC are checked against source documents. Source documents are the original documents, data and records. The investigator and the head of study site will ensure that the sponsor or its designee and the IRB such as the ethics review committee have access to the source documents.

The sponsor or its designee will access the records including the subject code list, medical records, signed and dated original consent forms to confirm that the study is appropriately conducted in compliance with the protocol. The investigator and other persons involved in the study will spare sufficient time to facilitate monitoring procedures during visits to the study site.

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.

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

See separately prepared monitoring plan for the frequency and procedures of site visit monitoring.

14.2 Protocol deviations

The investigator should record all deviations from the protocol. When a deviation is disclosed, the investigator will immediately notify the head of study site and the sponsor in writing. Revision of the protocol should be discussed with the sponsor when necessary, and when the protocol is revised, the revised protocol should be submitted to the head of study site and approved by the IRB such as the ethics review committee.

14.3 Quality assurance and regulatory agency inspections

The sponsor or its designee 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 the site of collecting laboratory test samples and other sites to be used during the study. This study may also be audited by overseas regulatory authorities (e.g., Food and Drug Administration [FDA], Medicines and Healthcare Products Regulatory Agency [MHRA]). The study site will immediately notify the sponsor when the study site is contacted by the regulatory authority

concerning an audit. The investigator and the head of study site should ensure that the auditor has access to all the source documents listed in Section 14.1.

15.0 ETHICAL CONDUCT OF A STUDY

This study will be conducted in compliance with the protocol and ethical principles based on the Declaration of Helsinki to preserve the interest of study participants (subjects). Each investigator should conduct a study based on the regulatory requirements and in compliance with the "Responsibilities of the investigator" in Attachment A.

15.1 Conflict of interests

Prior to the study, the investigator should obtain the review/approval by the IRB such as the COI committee that this study has no conflict of interests (COI)[25)-29)].

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

15.2 Approval by the institutional review board including the ethics review committee

The institutional review board (IRB) including the ethics review committee is constituted according to local regulations applicable to the study site. The sponsor or its designee should obtain the document listing the name and title of each IRB member. When the IRB members are directly participating in this study, a document should be obtained that they are not taking part in deliberation and voting.

The sponsor or its designee should provide related documents to the IRB 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 IRB or the IRB of each study site such as the ethics review committee to obtain approval. The sponsor or its designee should obtain written approval of the protocol and the informed consent form from the IRB such as the ethics review committee prior to initiation of protocol treatment. The IRB's approval document should contain the study title, protocol number, and date of preparation/revision of the concerned study, as well as version numbers and approval dates of other reviewed documents (e.g., informed consent form). The sponsor should notify the study site and the investigator 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 and the investigator receive the notification.

The study site should comply with all the requirements specified by the IRB such as the ethics review committee. The requirements include notifications to the IRB 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 IRB such as the ethics review committee, and study completion report. The sponsor or its designee should obtain written approval of the abovementioned items and all related materials from the IRB such as the ethics review committee.

15.3 Written information and subject's consent

The informed consent from contains specific requirements of the Declaration of Helsinki and all applicable laws and regulations. The informed consent from 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 from 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.

The investigator is responsible for preparation, content, and IRB approval of the informed consent form. The informed consent form should be approved by IRB before use.

The informed consent from should be written in a language easily understood by subjects. The investigator is responsible for providing detailed explanation of the informed consent from to subjects. Information should be provided orally and in writing as best as possible by the method deemed appropriate by the IRB.

The investigator 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 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 should also sign or write name/affix seal, and date the consent form prior to subject participation.

The investigator should store the original consent form which was signed or contains name/affixed seal. The investigator 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 name seal affixed should be provided to the subject.

The investigator should take the same procedures as those for obtaining the initial consent to newly obtain consent from the concerned subject when the informed consent from 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.

To confirm that this study is performed in compliance with the protocol, 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, representative regulatory authority, auditor designated by the sponsor, and the IRB. The investigator should obtain approval of subjects concerning access to the original medical records by a monitor and the representative regulatory authority, etc. when obtaining consent from a subject (see Section 15.3).

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

15.5 Advantages and disadvantages to subjects

15.5.1 Advantage to subjects

This study is performed as part of routine clinical practice, and no advantage is expected by participation in this study.

15.5.2 Disadvantage to subjects

This study is performed in the scope of ordinary medical examination, and no disadvantage is expected by participation in this study.

15.6 Publication, disclosure, and clinical trial registration policy

15.6.1 Publication and disclosure

The investigator should 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 regulatory authorities 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.

The sponsor may make public the data and information obtained from the study (including the data and information provided by the investigator) based on the agreement with the representative researcher.

The investigator should obtain the prior written consent of the sponsor when making public the information obtained in this study at a specialized academic meeting, etc.

15.6.2 Clinical trial 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 at least to the Clinical Trials.gov and public web site (UMIN-CTR) to comply with the applicable laws/regulations and guidelines. The city and country where a study is performed, and the subject recruitment state should be registered as well as the contact information of Takeda Pharmaceutical Company Limited. to enable general access.

15.6.3 Clinical trial results disclosure

Takeda Pharmaceutical Company Limited. will post the results of a clinical study at the Clinical Trials.gov and public web site (UMIN-CTR) as specified by the applicable laws and regulations irrespective of results.

15.7 Attribution of study results and intellectual property rights

The study results generated in this study belong to Takeda Pharmaceutical Company Limited. 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 permission from the representative researcher and the research steering committee.

15.8 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.

16.0 REFERENCES

1 The Editorial Board of Cancer Statistics in Japan. Cancer Statistics in Japan 2013. Foundation for Promotion of Cancer Research: 2013.

2 Japanese Society for Cancer of the Colon and Rectum (JSCCR). JSCCR Guidelines 2014 for the Treatment of Colorectal Cancer.

3 Moertel CG. Chemotherapy for colorectal cancer. N Engl J Med. 1994;330(16):1136-42.

4 Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med. 2000;343(13):905-14.

5 Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet. 2000;355(9209):1041-7.

6 de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000;18(16):2938-47.

7 Rothenberg ML, Oza AM, Bigelow RH, Berlin JD, Marshall JL, Ramanathan RK, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. J Clin Oncol. 2003;21(11):2059-69.

8 Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol. 2004;22(1):23-30.

9 Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004;22(2):229-37.

10 National Comprehensive CancerNetwork. Clinical Practice Guidelines in Oncology. Colon Cancer verslon 3, 2013

11 Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007;25(13):1658-64.

12 Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol. 2010;28(31):4697-705.

13 Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol. 2010;28(31):4706-13.

14 Muro K, Yoshino T, Doi T, Shirao K, Takiuchi H, Hamamoto Y, et al. A phase 2 clinical trial of panitumumab monotherapy in Japanese patients with metastatic colorectal cancer. Jpn J Clin Oncol. 2009;39(5):321-6.

15 Boku N, Sugihara K, Kitagawa Y, Hatake K, Gemma A, Yamazaki N, et al. Panitumumab in Japanese Patients with Unresectable Colorectal Cancer: A Post-marketing Surveillance Study of 3085 Patients. Jpn J Clin Oncol. 2014;44(3):214-223.

16 Hochster HS, Hart LL, Ramanathan RK, Hainsworth JD, Hedrick EE, Childs BH. Safety and efficacy of oxaliplatin/fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer (mCRC): Final analysis of the TREE-Study. J Clin Oncol 2006;24(18S) 3510.

17 Summary of product characteristics, December 2003: Sanofi-Synthelabo.

18 Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, et al. OPTIMOX1:A Randomized Study of FOLFOX4 or FOLFOX7 With Oxaliplatin in a Stop-and-Go Fashion in Advanced Colorectal Cancer—A GERCOR Study. J Clin Oncol 2006;24(3):394-400.

19 Maindrault-Goebel F, et al. Final results of OPTIMOX2, a large randomized phase Ⅱ study of maintenance herapy or chemotherapy–free intervals(CFI) after FOLFOX in patients with metastatic colorectal cancer(MRC) : A GERCOR study. ASCO Meeting Abstructs, Jun 2007;25:4013.

20 Saif MW, Reardon J. Management of oxaliplatin-induced peripheral neuropathy. Therapeutics and Clinical Risk Management 2005;1(4):249–258.

21 Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007;25(12):1539-44.

22 Buyse M. Randomized designs for early trials of new cancer treatments - an overview. Drug Inf J 2000; 34: 387-396.

23 Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, et al. PEAK: A Randomized, Multicenter Phase II Study of Panitumumab Plus Modified Fluorouracil, Leucovorin, and Oxaliplatin (mFOLFOX6) or Bevacizumab Plus mFOLFOX6 in Patients With Previously Untreated, Unresectable, Wild-Type KRAS Exon 2 Metastatic Colorectal Cancer. J Clin Oncol. 2014.

24 Brookmeyer R and Crowley, JJ. A confidence interval for the median survival time. Biometrics 1982; 38: 29-41.

25 Report of the Working Group on Conflict of Interest (Ministry of Education, Culture, Sports, Science and Technology dated November 1, 2002)

26 Guidelines for determining the conflict of interest polity for clinical researches (Review group for ethical aspects of clinical researches and conflict of interest, March 2006)

27 Guidelines on the Management of Conflict of Interest (COI) in Health and Labour Sciences Research (March 31, 2008)

28 Guidelines for management of COI in medical reserach (COI Committee of Japan Association of Medical Sciences, February 2011)

29 Common guidelines for conflict of interest (COI) in clinical research (Japanese Society of Internal Medicine, Japan Society of Hepatology, Japanese Circulation Society, Japan Endocrine Society, Japan Diabetes Society, Japanese Respiratory Society, Japanese Society of Hematology, Japanese Society of Allergology, Japanese Association for Infectious Diseases, August 2011)

Appendix A Responsibilities of the investigator

1 To appropriately conduct the clinical study in compliance with the protocol and in consideration of the human rights, safety and welfare of subjects.

2 To request COI committee of each study site to review and approve that there is no COI issues with this study.

3 When assigning a part of important duties related to this study to subinvestigators or study collaborators, prepare a list of assigned duties and persons, submit it in advance to the head of study site, and to obtain approval.

4 To prepare the informed consent form and revise it as necessary.

5 To check the contents of the study contract.

6 To provide sufficient information on the protocol, drug and duties of each person to subinvestigators and study collaborators, and to provide them with guidance and supervision.

7 To select subjects who satisfy the protocol, give explanation using written information, and obtain consent in writing.

8 To be responsible for all medical judgments related to the study.

9 To ensure together with the head 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.

10 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 then prepare the record.

11 When emergency report of serious adverse events, etc. is required, immediately report it in writing to the head of the study site and the sponsor.

12 To prepare accurate and complete EDC and submit it to the sponsor with an electronic signature.

13 To inspect and check the contents of EDC prepared by subinvestigators, or transcribed by study collaborators from the source data, and submit it to the sponsor with an electronic signature.

14 To discuss a revision of the protocol, etc. when proposed by the sponsor.

15 To report the study completion in writing to the head of study site.