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

NCT Number: NCT02394795

Protocol Approve Date: 05-Jan-2022

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

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

PROTOCOL

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

PARADIGM Study

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

Secondary sponsor	Takeda Pharmaceutical Company Limited
Protocol number	Panitumumab-3001
Version	Fifth Edition
Product name	Panitumumab
Creation date	Fifth 1, 2022

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1.0 CLINICAL STUDY PRINCIPLES AND CLINICAL STUDY MANAGEMENT INFORMATION

1.1 Clinical study principles

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol. This study will also be conducted as a "specified clinical trial" according to the Clinical Research Act (Act No. 16 of 2017)* and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- Clinical Research Act (Act No. 16 of 2017)*
- International Conference on Harmonisation E6 Good Clinical Practice (hereinafter referred to as ICH-GCP)
- All applicable laws and regulations, including, without limitation, data privacy laws and conflict of interest guidelines

: After approval by the Certified Review Board, the clinical study protocol, after amendment (second edition), will be 2017) used from the time of registration in the database established by the Ministry of Health, Labour and Welfare (jRCT: Japan Registry of Clinical Trials).

1.2 Clinical study administrative structure

This study will be conducted under the following administrative structure.

Clinical research steering committee:

Research steering committee chairman (person presiding over the study):

[redacted]

Research steering committee members:

[redacted]

[redacted]

Statistics Representative:

[redacted]

Certified Review Board:

[redacted]

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

Study site:

Institution where this clinical study will be conducted.

Investigator:

The person conducting a specified clinical trial and presiding over the study-related activities within the study site where the person is employed.

Subinvestigator:

A physician taking some of the responsibilities for study-related activities under the direction of the investigator at the study site where this person is employed.

Representative investigator:

An investigator who acts as the representative of all the investigators at multiple study sites when a multicenter study is conducted.

Supervisor at a study site:

A person managing and supervising the investigator at the study site where the investigator is employed.

Certified Review Board:

A committee engaged in reviewing and giving opinions about the conduct of clinical studies established in compliance with the Clinical Research Act.

Person engaged in coordination and management:

A person who can smoothly operate clinical studies based on knowledge and methods regarding the planned and efficient operational management of clinical studies.

Person engaged in presiding over the study:

A person presiding over the study who raises study funds for the clinical study, etc.

Study participant:

A person (including the deceased) to whom either of the following applies:

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

1.3 Secondary sponsor

Takeda Pharmaceutical Company Limited, [redacted]

Takeda Pharmaceutical Company Limited (hereinafter referred to as "Takeda") will take responsibility for drafting of the study and procurement of the study funds as well as all matters related to the conduct of this clinical study for which the representative investigator is responsible, in collaboration with the representative investigator. The method of supervising the consignee related to this clinical study will be described in a separately prepared procedure.

The expenses related to the operation of this clinical study* will be borne by Takeda.

*: According to the "business consignment contract," the expenses related to the activities of the research secretariat office, monitoring, registration/allocation, data management, statistical analysis, and audit will be paid to the consignee related to this clinical study. The expenses on which agreement has been reached with the study site will be paid to the study site on the basis of the separately prepared "Calculation criteria for study costs."

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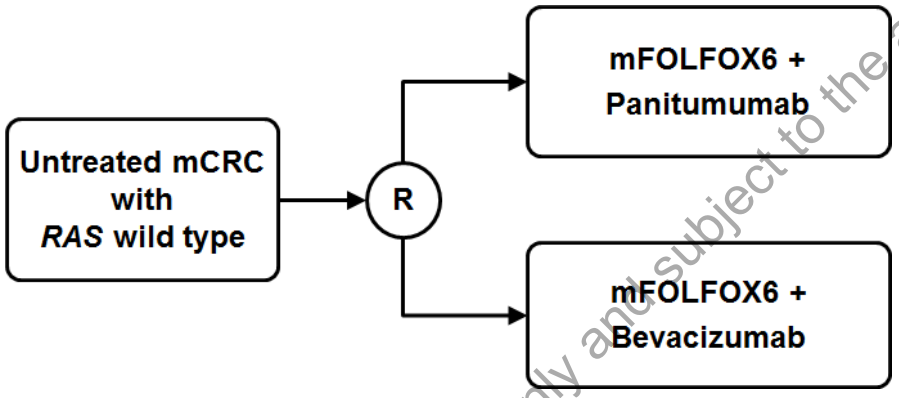
2.0 STUDY SUMMARY

	Test product: Panitumumab
Study title: A phase 3, randomized, controlled study of mFOLFOX6 + bevacizumab combination therapy versus mFOLFOX6 + panitumumab combination therapy in chemotherapy-naïve patients with *RAS* (*KRAS*/*NRAS*) wild-type, unresectable, advanced/recurrent colorectal cancer PARADIGM Study (PAnitumumab and *RAS*, DIagnostically-useful Gene Mutation for mCRC)	
Protocol number: Panitumumab-3001	
Clinical study design:  Untreated mCRC with *RAS* wild type, chemotherapy-naïve patients with *RAS* wild-type, unresectable, advanced/recurrent colorectal cancer; R, registration/randomization with allocation factors of study site, age at the time of entry (20 to 64 years/65 to 79 years), and liver metastasis (presence/absence).	
Objective: To verify the efficacy of mFOLFOX6 + panitumumab combination therapy and mFOLFOX6 + bevacizumab combination therapy in first-line treatment of chemotherapy-naïve patients with *RAS* wild-type, unresectable, advanced/recurrent colorectal cancer.	
Study population: chemotherapy-naïve patients with *RAS* wild-type, unresectable, advanced/recurrent colorectal cancer	
Planned number of participants: Number of randomized patients mFOLFOX6 + panitumumab arm: 400 mFOLFOX6 + bevacizumab arm: 400 Total: approximately 800 patients	**Number of study sites:** Approximately 200
Method of administration: The two groups will receive treatment for 2 weeks (14 days) as 1 course according to the dosage, schedule, and route of administration as follows.	

mFOLFOX6 + panitumumab group: 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: 2,400 mg/m^2/day 1-3 panitumumab: 6 mg/kg	mFOLFOX6 + bevacizumab group: mFOLFOX6 + bevacizumab 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: 2,400 mg/m^2/day 1-3 bevacizumab: 5 mg/kg
Duration of treatment (as a guide): 12 months (continue administration until the criteria for discontinuation of protocol treatment are met)	**Period of evaluation:** Approximately 95 months

Inclusion criteria at enrollment:

Patient's eligibility will be determined on the basis of the following criteria:

1. Patients who, in the opinion of the investigator* or the subinvestigator, are capable of understanding and complying with protocol requirements
   *: A person who takes part in conducting the study and presides over the study-related activities within a study site
2. Patients who sign and date a written informed consent form (ICF) prior to the initiation of any study procedures
3. Patients aged ≥20 and <80 years at the time of informed consent
4. Patients with unresectable adenocarcinoma originating in the large intestine (excluding carcinoma of the appendix and anal canal cancer)
5. Patients with lesion(s) that can be evaluated†
   †: It is not required that the lesion be measurable with the Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1)
6. Patients who have not received chemotherapy. Patients who experience relapse more than 24 weeks (168 days) after the final dose of perioperative adjuvant chemotherapy with fluoropyrimidine agents may be enrolled‡
   ‡: Patients who have received perioperative adjuvant chemotherapy that includes OXA cannot be enrolled.
7. Patients classified as *KRAS/NRAS* wild type§ by *KRAS/NRAS* testing**
   §: *KRAS/NRAS* test will be performed with the in vitro diagnostic that has been approved for marketing.
   **: All codons listed below are required to be wild type. If any codon is unmeasured or unmeasurable, it will not be defined as wild type.

KRAS	Exon	2	3	4
	Codon	12, 13	59, 61	117, 146

NRAS	Exon	2	3	4
	Codon	12, 13	59, 61	117, 146

8. Patients who satisfy the following criteria for major organ function in tests performed within 2 weeks (14 days) prior to enrollment
   (1) Neutrophil count $\geq 1.5\times10^3/\mu L$
   (2) Platelet count $\geq 10.0\times10^4/\mu L$
   (3) Hemoglobin ≥9.0 g/dL
   (4) Total blood bilirubin ≤2.0 mg/dL
   (5) AST ≤100 IU/L (≤200 IU/L if liver metastases are present)
   (6) ALT ≤100 IU/L (≤200 IU/L if liver metastases are present)
   (7) Serum creatinine ≤1.5 mg/dL
   (8) PT-INR <1.5 (<3.0 for patients treated with oral warfarin)
   (9) Urine protein: meet at least one of the following
      i. Urine protein (dip stick method) ≤1+
      ii. UPC (urine protein creatinine) ratio ≤1.0
      iii. Measurement of 24-hour urine protein ≤1,000 mg
9. Eastern Cooperative Oncology Group (ECOG) performance status (PS) has been determined to be 0 to 1
10. Life expectancy of ≥3 months (90 days) after enrollment

Exclusion criteria at enrollment:

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

1. Patients who have received radiotherapy within 4 weeks (28 days) prior to enrollment, except therapy received for pain relief of bone metastasis site
2. Patients with known brain metastasis or strongly suspected of brain metastasis
3. Patients with synchronous cancers or metachronous cancers with a disease-free period of ≤5 years (excluding colorectal cancer), excluding mucosal cancers cured or possibly cured by regional resection (esophageal, stomach, and cervical cancer; non-melanoma skin cancer; bladder cancer, etc.)
4. Patients with 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, are breast-feeding, or test positive for pregnancy
6. Patients with non-healing surgical wound(s) (excluding implanted venous reservoirs)
7. Patients with active hemorrhage requiring blood transfusion
8. Patients with disease requiring systemic steroids for treatment (excluding topical

steroids)

9. Patient with stent placement in colon
10. Patients who have received intestinal resection within 4 weeks (28 days) prior to enrollment or colostomy within 2 weeks (14 days) prior to enrollment
11. Patients with history of interstitial pulmonary disease or obvious and extensive computerized tomography (CT) findings of interstitial pulmonary disease (interstitial pneumonia, pulmonary fibrosis, etc.)
12. Patients with arterial thromboembolism, such as unstable angina pectoris, cardiac infarction, cerebral hemorrhage, or cerebral infarction, or who have had arterial thromboembolism within the 24 weeks (168 days) before registration
13. Patients with serious drug hypersensitivity
14. Patients with local or systemic active infection requiring treatment or fever indicating infection
15. Patients with heart failure or serious heart disease of ≥ class II by New York Heart Association
16. Patients with intestinal paralysis, gastrointestinal obstruction, or uncontrollable diarrhea (incapacitating symptoms despite adequate treatment)
17. Patients with poorly controlled hypertension
18. Patients with poorly controlled diabetes mellitus
19. Patients with active hepatitis B
20. Patients with known HIV infection
21. Patients with peripheral neuropathy (peripheral motor neuropathy and/or peripheral sensory neuropathy) of ≥ grade 2 by Common Terminology Criteria for Adverse Events (CTCAE, Japanese edition JCOG version 4.03)
22. Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study (such as patients who may be coerced to give consent)

Endpoints:

Primary endpoint:

The following item concerning all sites and a primary tumor occupying a left-sided site*

(hereinafter referred to as “left-side”)

Overall survival (OS)

*: Primary tumors occupying a left-sided site include the descending colon, sigmoid colon, and rectum.

Secondary endpoints:

Efficacy

The following items concerning all and left-sided sites

Progression-free survival (PFS)

Response rate (RR)

Duration of response (DOR)

Percentage of curative resection (complete excision, R0 resection)

Safety

Incidence of adverse events

Exploratory endpoints:

[redacted]

Statistical method:

The primary objective of this clinical study is to verify the OS prolongation in the panitumumab group as compared with the bevacizumab group. In order to meet the targeted number of events of 570 cases, 800 cases will be randomized in a ratio of 1:1 by using the minimization method with study sites, age (<65 or ≥65), and liver metastasis (presence/absence) as allocation factors. Details of the algorithm of the minimization method will be defined separately in the allocation specifications.

The primary endpoint, OS, will be analyzed in the "full analysis set."

A stratified log-rank test will be applied with allocation factors other than study sites as the stratum for OS intergroup comparison. Also, a stratified Cox model with allocation factors other than study sites as the stratum will be used to calculate the intergroup hazard ratio and its 95% confidence interval (two-sided) and the confidence interval corresponding to the level of significance at the time of analysis for summary index of difference in two groups. The Kaplan-Meier method will be used to calculate the median and its 95% confidence interval (two-sided) and the confidence interval corresponding to the level of significance at the time of analysis.

In this clinical study, one interim analysis is planned for OS, and interim analysis will also be performed for all and left-sided sites to evaluate the efficacy by using data at the time when 70% (399 events) of the overall targeted number of events have been observed. The level of significance for the interim analysis and final analysis will be set by using the O'Brien-Fleming type alpha-spending function.

Rationale for planned number of participants:

Table 6.a shows the OS (median) in clinical studies of mFOLFOX6 + bevacizumab combination therapy in chemotherapy-naïve patients with advanced/recurrent colorectal cancer. The OS (median) was reported to be between 21.0 and 30.9 months in the NO16966 Study, the HORIZON III Study, and the SOFT Study, and all studies were performed in patients with advanced/recurrent colorectal cancer not limited to *KRAS* wild type. The OS (median) of patients with *KRAS* wild-type cancer was

24.3 months in the PEAK Study, which was a randomized, controlled, phase 2 study of mFOLFOX6 + panitumumab combination therapy versus mFOLFOX6 + bevacizumab combination therapy as a first-line treatment of unresectable, advanced/recurrent colorectal cancer. Also, in the CALGB/SWOG80405 Study, [28] a phase 3 study of chemotherapy + cetuximab combination versus chemotherapy + bevacizumab combination therapy as a first-line treatment of unresectable, advanced/recurrent colorectal cancer, the OS (median) of the FOLFOX group was 26.9 months among patients with *KRAS* wild-type cancer.

Therefore, the OS (median) with mFOLFOX6 + bevacizumab combination therapy was assumed to be 29 months in the present study in patients with *RAS* wild-type, unresectable, advanced/recurrent colorectal cancer.

OS (median) with mFOLFOX6 + bevacizumab combination therapy reported so far

Study name	Phase	Number of patients	OS, median, months	*KRAS*
NO16966	3	349	21.0	Wild type / variant
HORIZON III	3	713	21.3	Wild type / variant
SOFT	3	159	30.9	Wild type / variant
PEAK	2	143	24.3	Wild type
PEAK	2	82	28.9	Wild type (including *NRAS*)
CALGB/SWOG80405 (FOLFOX group)	3	409	26.9	Wild type
CALGB/SWOG80405 (FOLFOX group)	3	192	29.0	Wild type (including *NRAS*)

The median OS among patients with *RAS* wild-type cancer in the FOLFIRI + cetuximab group and the FOLFIRI + bevacizumab group was 33.1 and 25.6 months, respectively, in the FIRE-3 Study (phase 3 study for comparing FOLFIRI + cetuximab with FOLFIRI + bevacizumab as a first-line treatment in patients with *KRAS* wild-type cancer with unresectable, advanced/recurrent colorectal cancer) of cetuximab, which has the same mechanism of action as panitumumab. The survival curve for each treatment group was almost overlapping up to 18 months, and showed tendency to change from then on. Also, the CALGB/SWOG80405 Study showed differences in the survival curve from the middle of the administration period, similar to that seen in the FIRE-3 Study.

Based on the above, in this clinical study, as the survival curve is presumed to show group differences after 18 months, piecewise exponential distribution will be assumed and it will be assumed that the survival rate after 18 months would be 75% and the survival rate after 48 months would be 22% for the bevacizumab group and 32% for the panitumumab group. In order to verify the OS prolongation in FOLFOX + panitumumab combination therapy compared with FOLFOX + bevacizumab combination therapy based on the log-rank test with a one-sided significance level of 2.5%, by assuming the enrollment period to be 24 months with a constant rate of patient registration and enrollment,

assuming the follow-up period to be 36 months from the enrollment of the last patient, and assuming the drop-out rate to be 5%, a total of 800 patients (400 patients per group) were to be enrolled. By accumulating a total of 570 death events, a detection power of approximately 80% will be ensured. Therefore, a total of 800 patients (400 patients per group) were scheduled to be enrolled.

[Detection power of main analysis of changed primary endpoint] (Added in the second version)
The number of patients with a left-sided site is presumed to be 600, and death events are assumed to be 400 assuming that the total number of patients is 760 (800, taking a 5% drop-out rate into account) and the total number of death events is 570. The main objective of the protocol, after modification, is to verify the OS prolongation by mFOLFOX6 + panitumumab combination therapy versus mFOLFOX6 + bevacizumab combination therapy either in all sites or for left-sided sites. The following is the detection power with the log-rank test and a one-sided significance level of 1.25% for both all and left-sided sites. For left-sided sites, the hazard ratio for mFOLFOX6 + bevacizumab combination therapy and mFOLFOX6 + panitumumab combination therapy is presumed to be 0.68, 0.70, 0.72, and 0.74, and the hazard of mFOLFOX6 + bevacizumab combination therapy is calculated based on the median survival time of the TRICOLORE Study (Table 1).
For a primary tumor with occupying site on the right side (primary tumors occupying a right-sided site include cecum, ascending colon, transverse colon. Hereinafter referred to as “right side”), the median survival time for the right side of the FIRE-3 Study is used (Table 2).

Efficacy of the treatment reported so far by primary tumor (*RAS* wild type, left side)

Study	CRYSTAL (Phase 3)		PRIME (Phase 3)		CALGB/SWOG 80405 (Phase 3)		FIRE-3 (Phase 3)		PEAK (Phase 2)	
Treatment group	FOLFIRI	FOLFIRI + Cmab	FOLFOX	FOLFOX + Pmab	FOLFOX/ FOLFIRI +Bmab	FOLFOX/ FOLFIRI +Cmab	FOLFIRI + Bmab	FOLFIRI + Cmab	FOLFOX + Pmab	FOLFOX + Bmab
No. of patients	138	142	159	169	152	173	149	157	53	54
OS, median, months	21.7	28.7	23.6	30.3	32.6	32.9	28.0	38.3	43.4	32.0
HR	0.65		0.73		0.77		0.63		0.84	
95% CI	0.50–0.86		0.57–0.93		0.59–0.99		0.48–0.85		0.22–3.27	
P value	0.02		not reported		0.04		0.002		not reported	

Table 1. OS in the median survival time of the TRICOLORE Study

TRICOLORE	
Treatment group	mFOLFOX6 or CAPEOX + bevacizumab combination therapy
No. of patients	243
OS, median, months	33.6

Table 2. OS in the median survival time of each group of the FIRE-3 Study (*RAS* wild type, right side)

	FIRE-3	
Treatment group	FOLFIRI + bevacizumab combination therapy	FOLFIRI + cetuximab combination therapy
No. of patients	50	38
OS, median, months	23.0	18.3

The log-rank test with a one-sided significance level of 1.25% will be conducted for both all and left-sided sites. The Monte Carlo simulation will be conducted, assuming an enrollment period of 24 months and assuming 800 patients for all and 600 for left-sided sites in case of a follow-up period of 36 months from enrollment of the last patient, accumulating a total of 570 death events for all and 400 for left-sided sites. As the result, the detection powers when "the log-rank test was significant in either all or left-sided sites" were as follows (Table 3).

Table 3. Result of Monte Carlo simulation

No. of patients	Level of significance	HR between the two groups in the left-sided site	Detection power
760 patients in all sites (380 patients/group) 600 patients in left-sided site (300 patients/group)	One-sided 1.25%, respectively*	0.68	91%
		0.70	86%
		0.72	79%
		0.74	71%

*: A significant group difference in either all or left-sided site will represent a significant difference between the mFOLFOX6 + bevacizumab combination therapy and mFOLFOX6 + panitumumab combination therapy.

[Level of significance and detection power of main analysis of changed primary endpoint] (Added in the third version)

Main analysis:

For the OS concerning left-sided sites, a stratified log-rank test will be performed with stratification according to allocation factors other than study site. If the analysis for left-sided sites shows a significant intergroup difference, then the stratified log-rank test for all sites will be performed with a hierarchical testing procedure.

Significance level for the main analysis:

The number of death events for left-sided sites for the final analysis planned for 2021 is assumed to be 420. The significance level for the final main analysis is discussed below.

In the previous (second) version of the protocol, which detailed plans to perform the interim analysis for both all sites and left-sided sites, the planned information time at interim analysis and the amount of alpha to be spent at interim analysis, as well as the computed planned nominal significance level for the final analysis were as follows:

Nominal significance level for all sites (second version):

Time of analysis	Fraction of total events	Nominal significance level (one-sided)
Interim analysis	71.2%	0.00308
Final analysis	100.0%	0.01154*

Nominal significance level for left-sided sites (second version):

Time of analysis	Fraction of total events	Nominal significance level (one-sided)
Interim analysis	70.5%	0.00293
Final analysis	100.0%	0.01159*

*: The nominal significance level planned for the final analysis based on the amount of alpha to be spent at the interim analysis planned in the second version of the protocol.

With a protocol amendment, the final main analysis was changed to be performed for left-sided sites, and, if the analysis shows a significant difference, then the stratified log-rank test for all sites will be performed with a hierarchical testing procedure. The nominal significance level for the analysis on left-sided sites is calculated as follows:

$$(0.0125 - 0.00308) + 0.01159 = 0.02101$$

Thus, the nominal significance level is set to one-sided 2.101% (corresponding to two-sided 4.202%).
The rationale for this is as follows:
Although the protocol was amended to perform the final main analysis only for left-sided sites, the interim analysis was conducted for all sites and left-sided sites. Because it is difficult to explicitly calculate correlation between the test statistic for left-sided sites at final analysis and the test statistic for all sites at interim analysis, the conservative range "0.0125－0.00308" is used. To this value, the nominal significance level of 0.01159 that can be spent for left-sided sites is added, and the resultant value is employed as the significance level for the final main analysis.

<u>Detection power for the main analysis:</u>

When the log-rank test for left-sided sites is conducted with a one-sided significance level of 2.101% (two-sided 4.202%), the detection power is as follows:

The hazard ratio for the mFOLFOX6 + bevacizumab combination therapy group was assumed on the basis of the median survival in the TRICOLORE Study (33.6 months). The Monte Carlo simulation was used to calculate the detection power of the log-rank test for 420 death events for left-sided sites.

Table 2. Result of Monte Carlo simulation

No. of patients	Level of significance	HR between the two groups in the left-sided site	Detection power
604 Patients in left-sided site	One-sided 2.101%	0.70	91%
		0.72	87%
		0.74	80%
		0.76	71%

Study period:

Total study period: Approximately 95 months*

Enrollment period: Approximately 27 months*

Follow-up period: Approximately 56 months** after completion of enrollment

Statistical period: Approximately 12 months after completion of follow-up

*: After marketing approval of *KRAS*/*NRAS* test, enrollment will start when *KRAS*/*NRAS* can be measured at each site.

**: Follow-up period can be ended once target events for final analysis have been observed.

3.0 LIST OF ABBREVIATIONS

Abbreviation	Unabbreviated expression
5-FU	fluorouracil
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BBP	bevacizumab beyond first progression
BSC	best supportive care
CEA	carcinoembryonic antigen
COI	conflict of interest
CR	complete response
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
DCR	disease control rate
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EGFR	epidermal growth factor receptor
G-CSF	granulocyte colony stimulating factor
HB	hepatitis B
HBc	hepatitis B virus core antigen
HBs	hepatitis B surface
HBv	hepatitis B virus
HIV	human immunodeficiency virus
HR	hazard ratio
ICH-GCP	International Conference on Harmonisation E6 Good Clinical Practice
IDMC	independent data monitoring committee
ICF	informed consent form
IRI	irinotecan
JAPIC	Japan Pharmaceutical Information Center
JCOG	Japan Clinical Oncology Group
jRCT	Japan Registry of Clinical Trials
KRAS	Kirsten rat sarcoma-2 virus

Abbreviation	Unabbreviated expression
l-LV	levofolinate calcium
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NE	not all evaluated
NRAS	neuroblastoma rat sarcoma
OS	overall survival
OXA	oxaliplatin
PD	progressive disease
PFS	progression-free survival
PR	partial response
P.S.	performance status
PT-INR	prothrombin time–international normalized ratio
RAS	rat sarcoma
RECIST	Response Evaluation Criteria in Solid Tumors
RR	response rate
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
SoD	sum of diameters
SOP	standard operating procedures
TEAE	treatment-emergent adverse event
TTF	time to treatment failure
UPC	urine protein creatinine
VEGF	vascular endothelial growth factor

4.0 INTRODUCTION

4.1 Background

4.1.1 Etiology of colon cancer

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. Overall, colorectal cancer is the third leading cause of cancer death among men in Japan. In women, lung cancer (13.8%) was also the leading cause of cancer death, followed by gastric cancer (11.6%) and colon cancer (11.1%); deaths from colorectal cancer (colon cancer and rectal cancer combined) accounted for 14.9% of cancer deaths. Overall, colorectal cancer is the first leading cause of cancer death among women in Japan.

4.1.2 Standard treatment for colon cancer

The "Guidelines for Treatment of Colorectal Cancer (2014)" [2)] classifies 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 Stages 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 treatments for unresectable, advanced/recurrent colorectal cancer that have been demonstrated to be useful in clinical studies and are currently covered by national health insurance in Japan are presented below. Also, cetuximab and panitumumab should be used for indications limited to Kirsten rat sarcoma-2 virus wild type (hereinafter referred to as *KRAS*).

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

5. FOLFOXIRI therapy
   FOLFOXIRI therapy: combination chemotherapy with OXA, IRI, 5-FU, and *l*-LV
6. FL‡ or capecitabine + bevacizumab* or UFT + *l*-LV
   UFT: combination preparation of tegafur and uracil

   *: Combination with molecular-targeted drugs such as bevacizumab or anti-epidermal growth factor receptor (hereinafter referred to as EGFR) antibody is recommended, but if combination therapy is not indicated then monochemotherapy will be conducted

   †: Indication only for *KRAS* wild type

   ‡: Infusional 5-FU + *l*-LV

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

It is recommended that, in principle, a regimen not used in first-line treatment should be used for second-line treatment. More specifically, IRI-based regimens are recommended as a second-line treatment for 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 for 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 for patients who have received bevacizumab as a first-line treatment.

For third-line treatment, IRI + cetuximab or panitumumab combination therapy, cetuximab or panitumumab monotherapy, and regorafenib monotherapy, or symptomatic therapies, are currently recommended for patients with *KRAS* wild-type cancer.

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 the long term. [3)] On the basis of evidence showing that 5-FU combined with *l*-LV is superior to 5-FU monotherapy, the combination therapy of 5-FU and *l*-LV (hereinafter referred to as 5-FU/LV therapy) had been considered the standard chemotherapy for colorectal cancer for a long time. The type I topoisomerase inhibitor IRI and the third-generation 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)~9)] At present, continuous infusion of 5-FU/LV in combination with OXA (FOLFOX therapy) or 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 of final overall survival (hereinafter referred to as OS) was similar between the FOLFIRI-first and the FOLFOX-first arms (21.5 months vs 20.6 months), and therefore both of the therapies are used as the standard for unresectable colorectal cancer. The development of these therapies increased 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 mFOLFOX6) therapy, which include OXA at the approved dosage (85 mg/m^2) in Japan, are covered by national health insurance. The simpler and easier mFOLFOX6 therapy is more frequently used.

4.1.4 Efficacy and safety of panitumumab in patients with unresectable, advanced/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 a role in the pathogenesis and progression of tumors. Binding of epidermal growth factor, the major ligand of EGFR, to EGFR is considered to induce autophosphorylation 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. [11)]

4.1.4.2 Clinical study results for panitumumab in the US and Europe

As a clinical trial of panitumumab monotherapy for colorectal cancer, a phase 3 study was conducted to compare best supportive care (hereinafter referred to as BSC) versus BSC + panitumumab therapy in patients with unresectable, recurrent/advanced, EGFR-positive colorectal cancer that became resistant to fluoropyrimidine agents, OXA, and IRI (BSC group, 232 patients; BSC + panitumumab group, 231 patients). [12)] The median of the primary endpoint of progression-

free survival (hereinafter referred to as PFS) with BSC alone was 7.3 weeks, whereas with BSC + panitumumab therapy it was 8 weeks, which is significantly longer than that of BSC and shows the efficacy of panitumumab therapy (hazard ratio [HR], 0.54; two-sided 95% confidence interval [CI], 0.44 to 0.66, p<0.0001). The secondary endpoint of OS was not significantly different between the two groups (HR, 1.00; two-sided 95% CI, 0.82 to 1.22; p=0.81); however, this may be attributed to the 173 patients (75%) in the BSC group who received follow-up therapy with panitumumab.

With regard to clinical study of the combination of chemotherapy and panitumumab, a phase 3 clinical study (PRIME Study) has been reported, in which FOLFOX4 monotherapy was compared with FOLFOX4 therapy + panitumumab (given at a dose of 6 mg/kg every 2 weeks) as a first-line treatment in a total of 1,180 patients (590 in each group).[13)] The primary endpoint of median PFS in patients with *KRAS* wild-type cancer was 9.6 months in the FOLFOX4 + panitumumab group, which is significantly longer than the 8.0 months in the FOLFOX4 alone group (HR, 0.80; two-sided 95% CI, 0.66 to 0.97; p=0.02). Of grade 3/4 adverse events, panitumumab-related adverse events such as dermatologic toxicities, diarrhea, and hypomagnesemia occurred more frequently in the FOLFOX4 + panitumumab group, but there were no major differences in the incidence of other adverse events between the two groups. Grade 3 infusion reaction occurred in two patients (Table 4.a).

Table 4.a Grade 3/4 adverse events reported in patients with *KRAS* wild-type cancer 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
Diarrhea	59	18	29	9
Nerve disorder	52	16	51	16
Hypokalemia	32	10	15	5
Malaise	30	9	10	3
Stomatitis	28	9	2	<1
Hypomagnesemia	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 3 clinical study (Study 20050181) has been conducted, in which FOLFIRI monotherapy was compared with FOLFIRI therapy + panitumumab (given at a dose of 6 mg/kg every 2 weeks).[14)] The primary endpoints were PFS and OS in patients with *KRAS* wild-type cancer. In patients with *KRAS* wild-type cancer, PFS was 5.9 months and significantly longer in the FOLFIRI + panitumumab group than 3.9 months in the FOLFIRI alone group (HR, 0.73; two-sided 95% CI, 0.59 to 0.90; p=0.004). On the other hand, OS was 14.5 months in the FOLFIRI + panitumumab group and 12.5 months in the FOLFIRI alone group, with no statistically significant difference between the two groups (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 group as compared with 10% in the FOLFIRI alone group. Of grade 3/4 adverse events, the incidence of dermatologic toxicities was higher and the incidences of diarrhea and hypomagnesemia tended to be higher in the FOLFIRI + panitumumab group; however, there were no major differences in the incidence of toxicities including hematologic toxicities between the two groups, and the incidence of infusion reaction was not more than 1%.

Both the PRIME Study [13)] and Study 20050181 [14)] 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 1 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; ie, 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 six patients, and tolerance was ratified.

In a Japanese phase 2 clinical study of panitumumab monotherapy,[15)] 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 3 clinical study, was well tolerated, and the incidence of adverse events was similar to that observed in the US and Europe (Table 4.b). In addition, seven patients (13.5%) had partial response (hereinafter referred to as PR), and this Japanese study yielded an RR of 13.5% (two-sided 95% CI: 5.6 to 25.8), a time to treatment failure of 11.4 weeks (two-sided 95% CI: 8.4 to 15.0), a PFS of 8.0 weeks (two-sided 95% CI: 7.4 to 11.4), and an OS of 9.3 months (two-sided 95% CI: 7.1 to 12.8), similar to those observed in clinical studies in the US and Europe.

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

Table 4.b Common adverse events (≥20%) noted in a Japanese phase 2 clinical study of panitumumab monotherapy

Adverse events	Panitumumab monotherapy (n=52)			
	Any grade		Grade 3 or higher	
	n	%	n	%
Any adverse drug reaction	51	98	6	12
Skin disorder	51	98	3	6
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
Hypomagnesemia	17	33	0	-
Malaise	13	25	0	-
Stomatitis	12	23	0	-
Anorexia	11	21	1	2

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

In the post-marketing surveillance conducted for a fixed period where all the patients treated were registered, [16] the median treatment period (first day of treatment to the final day of treatment) for the 3,085 patients who were patient to safety evaluation was 113 days, incidence of adverse reaction was 84.1% (25.8% ≥ grade 3), of which the panitumumab monotherapy group with 1,254 patients was 80.1% (19.7% ≥ grade 3), and the panitumumab + chemotherapy combination group with 1,831 patients was 86.9% (30.0% ≥ grade 3). The occurrence status of intensively investigated adverse reaction items are listed in Table 4.c.

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

All patient surveillance	Panitumumab monotherapy group (n=1,254)				Panitumumab + chemotherapy combination group (n=1,831)			
	All grades		≥ Grade 3		All grades		≥ Grade 3	
Intensively investigated item	n	%	n	%	n	%	n	%
Skin & subcutaneous tissue disorders (SOC)	918	73.2	118	9.4	1,446	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.
*: Interstitial pneumonia subcommittee criteria

4.1.5 Efficacy and safety of bevacizumab in patients with unresectable, advanced/recurrent colorectal cancer

Bevacizumab is an IgG1 humanized monoclonal antibody that binds to vascular endothelial growth factor (hereinafter referred to as VEGF), a protein that plays a critical role in tumor angiogenesis. Bevacizumab inhibits the binding of VEGF to its receptor and thereby inhibits angiogenic signals.

A phase 3 study (Study AVF2107g) [17] was conducted to investigate the efficacy of bevacizumab used in combination with IFL therapy (combination chemotherapy with IRI and bolus intravenous infusion of 5-FU and LV), which is a first-line treatment of unresectable, advanced/recurrent colorectal cancer, by comparing IFL + bevacizumab combination therapy with IFL monotherapy. The RR, PFS (median), and OS (median) were 44.8% (p=0.004), 10.6 months (HR = 0.54, p<0.001), and 20.3 months (HR=0.66, p<0.001) in the IFL + bevacizumab group, as compared with 34.8%, 6.2 months, and 15.6 months in the IFL alone group. These results show the superiority of IFL + bevacizumab combination therapy in all endpoints. In addition, Study NO16966, [18] in which the combination of bevacizumab and FOLFOX therapy or CAPEOX therapy as a first-line treatment was investigated, also demonstrated that the primary endpoint of PFS was significantly prolonged in the bevacizumab combination therapy with FOLFOX/CAPEOX + bevacizumab group at 9.4 months versus the FOLFOX/CAPEOX alone group at 8.0 months (HR=0.83, p=0.0023). Common adverse events in the two studies are listed in Table 4.d.

Table 4.d Incidence of serious adverse events (≥ grade 3) reported with bevacizumab

Therapy	Study AVF2107g	Study NO16966	
	IFL + bevacizumab (n=392)	FOLFOX + bevacizumab (n=342)	CAPEOX + bevacizumab (n=353)
	No. (%)		
Venous thromboembolism	Grade 3: 35 (8.8) Grade 4: 15 (3.8)	32 (9.4)	22 (6.2)
Gastrointestinal perforation	8 (2.0)	1 (0.3)	3 (0.8)
Hemorrhage	Grade 3: 10 (2.6) Grade 4: 3 (0.8)	7 (2.0)	6 (1.7)
Complications due to delayed healing of wound	5 (8.3)	9 (2.6)	3 (0.8)

With regard to second-line treatment, a randomized controlled study (Study E3200) [19] was conducted to investigate the efficacy of FOLFOX4 + bevacizumab combination therapy as compared with FOLFOX4 monotherapy in patients who were resistant to IRI + 5-FU combination therapy. The OS (median) was 12.9 months in the FOLFOX4 + bevacizumab group, which was significantly prolonged in comparison with 10.8 months in the FOLFOX4 alone group (HR=0.75, p<0.0011). The PFS (median) was also significantly longer in the FOLFOX4 + bevacizumab group, at 7.3 months as compared with 4.7 months in the FOLFOX4 alone group (HR=0.61, p<0.0001). In addition, the usefulness of chemotherapy + continued bevacizumab therapy (bevacizumab beyond first progression: BBP) as a second-line treatment was investigated in patients with unresectable, advanced/recurrent colorectal cancer who had progressive disease (hereinafter referred to as PD) after bevacizumab combination chemotherapy (Study ML18147). [20] The OS (median) was significantly longer in the chemotherapy + BBP group at 11.2 months as compared with 9.8 months in the chemotherapy alone group (HR=0.81, p=0.0062), and the PFS was also significantly longer in the chemotherapy + BBP group at 5.7 months as compared with 4.1 months in the chemotherapy alone group (HR=0.68, p<0.0001). BBP did not increase serious adverse events.

Factors for predicting the therapeutic effect of bevacizumab (hereinafter referred to as biomarkers) have also been investigated. Study AVAGAST, [21] in which the usefulness of bevacizumab for advanced stomach cancer was investigated, reported that serum VEGF-A level and expression of neuropilin-1 in tumor tissue were candidates for predictive factors of the therapeutic effect of bevacizumab. However, no definite biomarker has been established yet.

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

In a phase 3 study (Study 20040408) of panitumumab monotherapy that investigated its efficacy as a third-line treatment in patients with unresectable, advanced/recurrent colorectal cancer who had received standard treatment, an exploratory biomarker analysis was performed. The results showed that the presence or absence of mutations in not only *KRAS* exon 2 but also in *KRAS* exons 3 and 4 or neuroblastoma rat sarcoma (hereinafter referred to as *NRAS*) exons 2, 3, and 4 may be predictive factors of the effect of panitumumab. [22)]

Among the patients enrolled in the PRIME Study, [23)] those who were determined to have wild-type *KRAS* exon 2 tumors by Therascreen® *KRAS* Mutation Kit were analyzed for the relationship between PFS and OS and the presence or absence of mutations in the genes of *KRAS* exons 3 (codon 61) and 4 (codons 117, 146), *NRAS* exons 2 (codons 12, 13), 3 (codon 61), and 4 (codons 117, 146), and *BRAF* exon 15 (codon 600) in the tumor. These mutations were analyzed with DNA sequencing by the Sanger method and WAVE-based SURVEYOR® Scan Kit.

In patients with *KRAS* wild-type and *NRAS* wild-type colorectal cancer (hereinafter referred to as *RAS* wild type), OS (median) was significantly prolonged by 5.6 months in the FOLFOX + panitumumab group at 25.8 months as compared with 20.2 months in the FOLFOX alone group (HR= 0.77, two-sided 95% CI: 0.64 to 0.94, p=0.009) (Figure 4.a). In patients with *RAS* mutation (*KRAS* or *NRAS* mutation), on the other hand, the median OS was significantly shorter in the FOLFOX + panitumumab group at 15.5 months as compared with 18.7 months in the FOLFOX alone group (HR=1.21, two-sided 95% CI: 1.01 to 1.45, p=0.04).

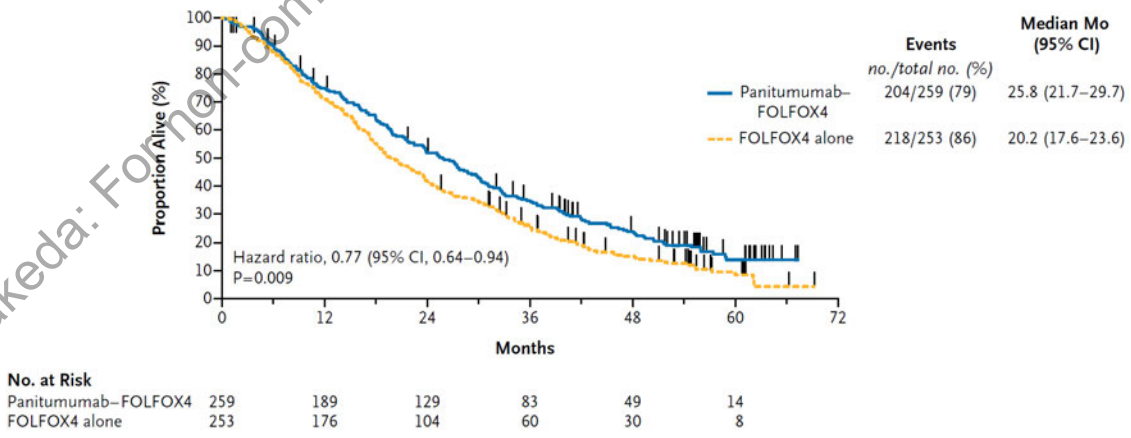


Figure 4.a Overall survival in patients with *RAS* wild-type cancer in the PRIME Study

The PEAK Study is a randomized phase 2 study to compare mFOLFOX6 + panitumumab combination therapy and mFOLFOX6 + bevacizumab combination therapy as a first-line treatment of unresectable, advanced/recurrent colorectal cancer. [24)]

DNA sequencing by the Sanger method and WAVE-based SURVEYOR Scan Kit were used to determine whether or not gene mutations existed. Patients with and without gene mutations in *KRAS* exon 2 (codons 12, 13), exon 3 (codons 59, 61), or 4 (codons 117, 146) and *NRAS* exon 2 (codons 12, 13), 3 (codons 59, 61), or 4 (codons 117, 146) were grouped into *RAS* mutation and *RAS* wild type, respectively. Additional analysis was performed for PFS and OS.

The median of PFS, the primary endpoint, was 10.9 months in the mFOLFOX6 + panitumumab group and 10.1 months in the mFOLFOX6 + bevacizumab group (HR=0.87, two-sided 95% CI: 0.65 to 1.17, p=0.353); these are not significantly different. In patients with *RAS* wild-type cancer, however, the median PFS was 13.0 months in the mFOLFOX6 + panitumumab group and 9.5 months in the mFOLFOX6 + bevacizumab group (HR=0.65, two-sided 95% CI: 0.44 to 0.96, p=0.029), which shows that the PFS was significantly prolonged in the mFOLFOX6 + panitumumab group. In *RAS*-mutant patients, on the other hand, the median PFS was not significantly different between the two groups, at 7.8 months for the mFOLFOX6 + panitumumab group and 8.9 months for the mFOLFOX6 + bevacizumab group (HR=1.39, two-sided 95% CI: 0.73 to 2.64, p=0.32).

The median of OS was 34.2 months (incidence of events: 37%) in the mFOLFOX6 + panitumumab group, which is significantly longer than the 24.3 months (55%) in the mFOLFOX6 + bevacizumab group (HR=0.62, two-sided 95% CI: 0.44 to 0.89, p= 0.009). In patients with *RAS* wild-type cancer, moreover, it was 41.3 and 28.9 months (HR=0.63, two-sided 95% CI: 0.39 to 1.02, p=0.058), respectively, which shows that the outcome tended to be more favorable in the mFOLFOX6 + panitumumab arm (Figure 4.b).

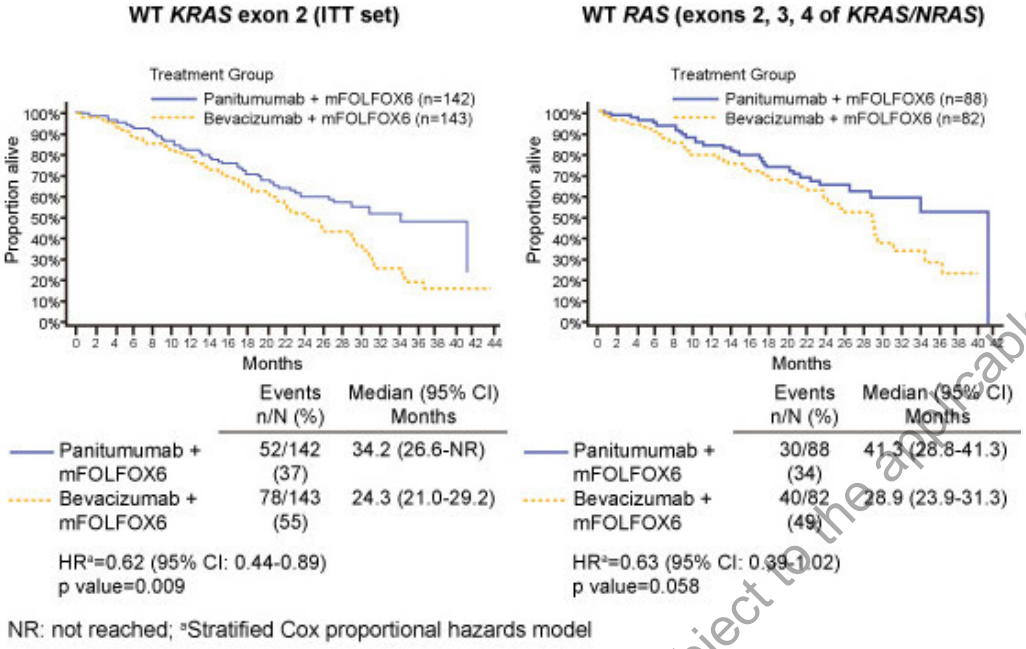


Figure 4.b Overall survival in panitumumab and bevacizumab arms in the PEAK Study

In conclusion, in terms of both PFS and OS, mFOLFOX6 + panitumumab combination therapy has been shown to be superior to mFOLFOX6 + bevacizumab combination therapy as a first-line treatment of colorectal cancer with wild-type *KRAS* (exons 2, 3, and 4) and wild-type *NRAS* (exons 2, 3, and 4).

In addition to the above studies, several post hoc analyses have shown that that anti-EGFR antibody drugs are ineffective in patients with *KRAS* (exons 3 and 4) and *NRAS* (exons 2, 3, and 4) mutations. [25)]

It has been recognized that evaluation of the presence or absence of *RAS* (*KRAS/NRAS,* hereinafter referred to as *RAS*) mutations other than *KRAS* exon 2 should be added. The Japanese Society of Medical Oncology has published "Guidance for measuring *RAS* (*KRAS/NRAS*) mutations in colorectal cancer patients." [26)]

4.2 Rationale for the proposed study

As of November 2014, it is unclear which molecular target drug, bevacizumab or anti-EGFR antibody, should be used in first-line treatment of chemotherapy-naïve, unresectable, advanced/recurrent colorectal cancer, and several controlled studies are currently ongoing and being analyzed.

The PEAK Study, conducted by Schwartzberg et al., [24)] had results similar to those described above: for patients with *RAS* wild type, including *KRAS/NRAS* wild types besides *KRAS* exon 2,

mFOLFOX6 + panitumumab combination therapy was shown to be superior in both PFS and OS in comparison to mFOLFOX6 + bevacizumab combination therapy as a first-line treatment for unresectable, advanced/recurrent colorectal cancer. The FIRE-3 Study, conducted by Heinemann et al., [27] is a phase 3 study directly comparing FOLFIRI + cetuximab and FOLFIRI + bevacizumab as first-line treatment for patients with *KRAS* exon 2 wild-type, unresectable, advanced/recurrent colorectal cancer. In patients with *KRAS* exon 2 wild-type cancer, the FOLFIRI + cetuximab combination group showed statistical significance in prolongation with a median OS 3.7 months longer than that in the FOLFIRI + bevacizumab combination group. Further, when limited to patients with *RAS* wild-type cancer through retrospective analysis, the cetuximab combination significantly improved the median OS by 7.5 months in comparison to the bevacizumab combination group. The CALGB/SWOG 80405 Study is a large-scale, phase 3 study directly comparing cetuximab and bevacizumab for combination therapy with mFOLFOX6 or FOLFIRI. In the CALGB/SWOG 80405 Study report for the American Society of Clinical Oncology 2014 meeting, [28] unlike the PEAK Study and FIRE-3 Study, no difference was shown in OS and PFS between the EGFR antibody plus chemotherapy group and the bevacizumab plus chemotherapy group, even in patients with *KRAS* wild-type cancer. Further, at the European Society for Medical Oncology 2014 meeting, a retrospective analysis result of patients with *RAS* wild type in the same study was described, [29] and the median OS was 32.0 months for the cetuximab combination group for all chemotherapy and 31.2 months for the bevacizumab combination group for all chemotherapy; thus, no significant difference was shown (HR=0.9, two-sided 95% CI: 0.7 to 1.1, p=0.40). FOLFOX was selected for chemotherapy in 70% of the patients participating in the CALGB/SWOG80405 study. In the analysis of each chemotherapy in the FOLFOX group, the median OS was 32.5 months in the cetuximab combination group and 29.0 months in the bevacizumab combination group. This slight difference is not statistically significant (HR=0.86, two-sided 95% CI: 0.6 to 1.1, p=0.2).

From the above results, consensus has not been reached about whether to choose bevacizumab or anti-EGFR antibody as a molecular-targeted drug for combination therapy in the first-line treatment of *RAS* wild-type, unresectable, advanced/recurrent colorectal cancer. Also, results from these studies (PEAK Study, FIRE-3 Study, and CALGB/SWOG80405 study) were based on results from post hoc analyses of prospective studies, and as of November 2014, a prospective comparative study limited to *RAS* wild type has not been conducted.

With this background, in order to determine the molecular-targeted drug to be used in combination with mFOLFOX6 therapy, we considered it necessary to prospectively verify that mFOLFOX6 + panitumumab combination therapy prolongs OS as compared with mFOLFOX6 + bevacizumab combination therapy for first-line treatment in patients with *RAS* wild-type, unresectable, advanced/recurrent colorectal cancer. Therefore, we planned this study.

5.0 OBJECTIVE AND ENDPOINTS OF THE STUDY

5.1 Objective

To verify that mFOLFOX6 + panitumumab combination therapy prolongs OS as compared with mFOLFOX6 + bevacizumab combination therapy in first-line treatment of chemotherapy-naïve patients with *RAS* wild-type, unresectable, advanced/recurrent colorectal cancer.

5.2 Definition of endpoints

5.2.1 Primary endpoint

The following item concerning all and left-sided sites:

Overall survival (OS)

5.2.2 Secondary endpoints

The following items concerning all and left-sided sites:

Efficacy

Progression-free survival (PFS)

Response rate (RR)

Duration of response (DOR)

Curative resection (complete resection, hereinafter referred to as R0) rate

Safety

Percentage of patients with adverse events

5.2.3 Exploratory endpoint

[redacted]

5.3 Rationale for the endpoints

5.3.1 Primary endpoint

The OS was selected as the primary endpoint because it is considered to be the most important efficacy measure in the first-line treatment of unresectable, advanced/recurrent colorectal cancer. Given that retrospective analyses and meta-analyses of several large-scale clinical studies in recent years showed that treatment sensitivity and prognosis vary according to differences in the location of the primary site in unresectable, advanced/recurrent colorectal cancer, it was decided to evaluate the endpoint for all and left-sided sites separately.

5.3.2 Secondary endpoints

The PFS, RR, and DOR were selected as secondary endpoints because they reflect the antitumor efficacy. The percentage of patients treated with R0 resection after chemotherapy was also selected as the secondary endpoint because it is suggested that R0 resection following chemotherapy may contribute to prolonged survival of patients with unresectable colorectal cancer.

In addition, the percentage of patients with adverse events was selected as a secondary endpoint, because safety is also an important factor in treatment selection.

It was decided to evaluate the secondary endpoints for all and left-sided sites, as will be done for the primary endpoint.

5.4 Additional research

In an exploratory manner according to the Ethical Guideline for Clinical Research, blood and tumor tissue samples will be used for additional research to assess biomarkers that may be predicting factors for the therapeutic effect of the tested treatments. Details will be determined in a separately prepared protocol. The additional research will be conducted at a study site that has been approved by the site director on the basis of approval of the ethics review board, etc. Also, among the participants in this study, patients will only participate in the additional research if consent has been confirmed with an ICF relevant to the additional research.

6.0 CLINICAL STUDY DESIGN

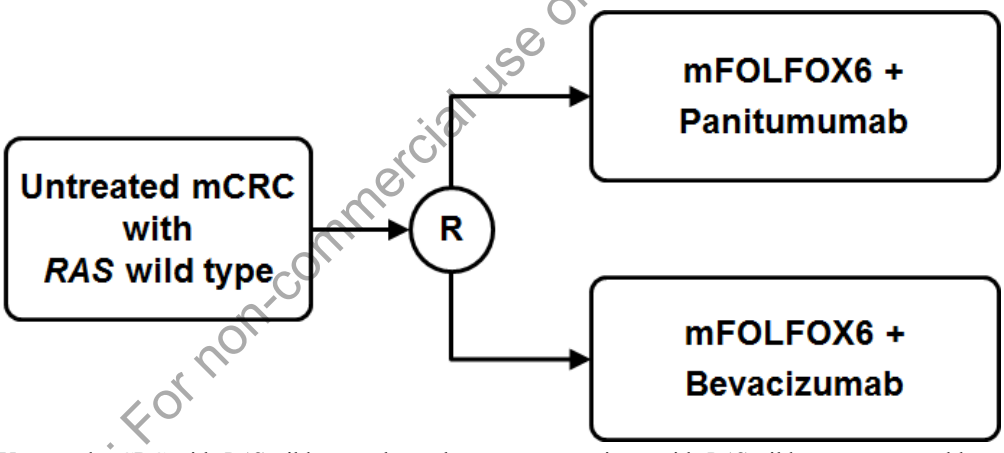
6.1 Clinical study design

This study is a phase 3, randomized, controlled study to verify that mFOLFOX6 + panitumumab combination therapy prolongs OS versus mFOLFOX6 + bevacizumab combination therapy in first-line treatment of chemotherapy-naïve patients with *RAS* wild-type, unresectable, advanced/recurrent colorectal cancer. Patients who are judged eligible for the study on the basis of the inclusion and exclusion criteria will be randomized to either the mFOLFOX6 + panitumumab arm or mFOLFOX6 + bevacizumab arm in a 1:1 ratio at the time of registration. See Section "8.0 PROTOCOL TREATMENT" for details of treatment.

For randomization, a minimization method will be performed with the allocation factors of study site, age (20 to 64 years/65 to 79 years), and presence/absence of liver metastasis.

Protocol study of both treatment groups will be started within 14 days (2 weeks) after enrollment.

Protocol treatment will be continued until the criteria in Section "8.7 Criteria for discontinuation of protocol treatment for individual " are met. Treatment may be performed for inpatients or outpatients.



Untreated mCRC with *RAS* wild-type, chemotherapy-naïve patients with *RAS* wild-type, unresectable, advanced/recurrent colorectal cancer; R, registration and randomization with allocation factors of study site, age at the time of entry (20 to 64 years/65 to 79 years), and liver metastasis (presence/absence).

Figure 6.a Outline of study design

6.2 Rationale for study design

6.2.1 Study population

To verify the superiority of mFOLFOX6 + panitumumab combination therapy over mFOLFOX6 + bevacizumab combination therapy in prolonging OS in first-line treatment, chemotherapy-naïve patients with unresectable, advanced/recurrent colorectal cancer will be included in the study. The patients should also be *RAS* wild type, because the above-mentioned analysis results in the PRIME [23)] and PEAK [24)] studies suggest that panitumumab may be the most effective in these patients.

KRAS/NRAS tests will be performed with an in vitro diagnostic that has been approved for marketing.

6.2.2 Treatment regimens and planned number of patients

6.2.2.1 Reason for selecting mFOLFOX6 +bevacizumab combination therapy and mFOLFOX6 + panitumumab combination therapy as the treatment regimens

As described in Section 4.1.2, the following regimens are shown in the "Guidelines for Treatment of Colorectal Cancer (2014)" as first-line treatments for patients with unresectable, advanced/recurrent colorectal cancer.

1. FOLFOX therapy + bevacizumab or CAPEOX therapy + bevacizumab
2. FOLFIRI therapy + bevacizumab
3. FOLFOX therapy + cetuximab or panitumumab
4. FOLFIRI therapy + cetuximab or panitumumab
5. FOLFOXIRI therapy
6. FL or capecitabine + bevacizumab or UFT + LV

In Japan, FOLFOX-based therapy is more frequently selected as first-line treatment for unresectable, advanced/recurrent colorectal cancer than FOLFIRI-based therapy, and bevacizumab is widely used for *KRAS* wild-type colorectal cancer as well. As a result, FOLFOX + bevacizumab combination therapy is the most common first-line treatment in Japan (in-house document). On the other hand, the phase 2 PEAK Study [24)] suggested that panitumumab may be superior to bevacizumab in prolonging OS when used in combination with FOLFOX-based chemotherapy for *RAS* wild-type colorectal cancer. As of November 2014, however, no phase 3

study has been conducted to compare the two combination therapies, and this is an important clinical issue to be addressed. Therefore, the present study is designed to assess the superiority of mFOLFOX6 + panitumumab combination therapy as compared with mFOLFOX6 + bevacizumab combination therapy, the most widely used first-line treatment for unresectable, advanced/recurrent colorectal cancer for *RAS* wild type.

6.2.2.2 Rationale for planned number of patients

The planned number of randomized patients is set at 400 per group, for a total of 800 patients. The rationale is described below.

Table 6.a shows the OS (median) in clinical studies of mFOLFOX6 + bevacizumab combination therapy in chemotherapy-naïve patients with advanced/recurrent colorectal cancer. The OS was reported to be between 21.0 and 30.9 months in the NO16966 Study, HORIZON III Study, and SOFT Study, and all studies were performed in patients with advanced/recurrent colorectal cancer not limited to *KRAS* wild type. The OS (median) of patients with *KRAS* wild-type cancer was 24.3 months in the PEAK Study, which was a randomized controlled phase 2 study of mFOLFOX6 + panitumumab combination therapy versus mFOLFOX6 + bevacizumab combination therapy as a first-line treatment of unresectable, advanced/recurrent colorectal cancer. Also, in the CALGB/SWOG80405 Study, [28] a phase 3 study of chemotherapy + cetuximab combination or chemotherapy + bevacizumab combination therapy as a first-line treatment of unresectable, advanced/recurrent colorectal cancer, the OS of the FOLFOX group was 26.9 and 29.0 months among patients with *KRAS* and *RAS* wild-type cancer, respectively.
Therefore, the OS with mFOLFOX6 + bevacizumab combination therapy was assumed to be 29 months in the present study in patients with *RAS* wild-type, unresectable, advanced/recurrent colorectal cancer.

Table 6.a Overall survival (OS) (median) with mFOLFOX6 + bevacizumab combination therapy reported so far

Study name	Phase	Number of patients	OS (median), months	*KRAS*
NO16966	3	349	21.0	Wild type/variant
HORIZON III	3	713	21.3	Wild type/variant
SOFT	3	159	30.9	Wild type/variant
PEAK	2	143	24.3	Wild type
PEAK	2	82	28.9	Wild type (including *NRAS*)
CALGB/SWOG80405 (FOLFOX group)	3	409	26.9	Wild type
CALGB/SWOG80405 (FOLFOX group)	3	192	29.0	Wild type (including *NRAS*)

The median OS among patients with *RAS* wild-type cancer in the FOLFIRI + cetuximab group and FOLFIRI + bevacizumab group was 33.1 and 25.6 months, respectively, in the FIRE-3 Study (phase 3 study for comparing FOLFIRI + cetuximab with FOLFIRI + bevacizumab as a first-line treatment in patients with *KRAS* wild-type cancer with unresectable, advanced/recurrent colorectal cancer) of cetuximab, which has the same mechanism of action as panitumumab. The survival curve for each treatment group was almost overlapping up to 18 months, and showed a tendency to diverge from then on. The CALGB/SWOG80405 Study also showed differences in the survival curve from the middle of the administration period, similar to those seen in the FIRE-3 Study.

On the basis of the above data, the survival curve in this study is presumed to show group differences after 18 months, piecewise exponential distribution will be assumed with a survival rate after 18 months of 75%, and the survival rate after 48 months is assumed to be 22% for the bevacizumab group and 32% for the panitumumab group.

In order to verify the OS prolongation with FOLFOX + panitumumab combination therapy compared with FOLFOX + bevacizumab combination therapy on the basis of the log-rank test with a one-sided significance level of 2.5%, assuming the enrollment period to be 24 months and a constant rate of patient registration and enrollment, the follow-up period to be 36 months from the enrollment of the last patient, and the drop-out rate to be 5%, a total of 800 patients (400 patients per group) were to be enrolled. By accumulating a total of 570 death events, a detection power of approximately 80% will be ensured. Therefore, a total of 800 patients (400 patients per group) were scheduled to be enrolled.

The number of patients was calculated by assuming a median OS of 29 months in the bevacizumab group, but ensuring the scheduled number of events during the follow-up period may become difficult when OS is improved in both the bevacizumab group and the panitumumab group. The number of patients may be calculated again to ensure the required number of events, depending on the level of OS in the two groups reported by periodic monitoring report under blinded conditions.

[Detection power of the main analysis of changed primary endpoint] (Added in the second version)
The number of patients with a left-sided site is presumed to be 600 and the number of death events is assumed to be 400 when it is assumed that the total number of patients is 760 (800, taking the 5% drop-out rate into account) and the total number of death events is 570. The main objective of the protocol after modification is to verify the OS prolongation by mFOLFOX6 + panitumumab combination therapy in comparison with mFOLFOX6 + bevacizumab combination therapy either in all or left-sided sites. The following is the detection power when the log-rank test with a one-sided significance level of 1.25% is conducted for both all and left-sided sites.

For left-sided sites, the HR in mFOLFOX6 + bevacizumab combination therapy and mFOLFOX6 + panitumumab combination therapy is presumed to be 0.68, 0.70, 0.72, and 0.74, and the hazard of mFOLFOX6 + bevacizumab combination therapy is calculated based on the median survival time of the TRICOLORE Study (Table 1).

For the right side, the median survival time for the right side of the FIRE-3 Study is used (Table 2).

Efficacy of the treatment reported so far by primary tumor (RAS wild type, left side)

Study	CRYSTAL (phase 3)		PRIME (phase 3)		CALGB/SWOG 80405 (phase 3)		FIRE-3 (phase 3)		PEAK (phase 2)	
Treatment group	FOLFIRI	FOLFIRI + Cmab	FOLFOX	FOLFOX + Pmab	FOLFOX/FOLFIRI + Bmab	FOLFOX/FOLFIRI + Cmab	FOLFIRI + Bmab	FOLFIRI + Cmab	FOLFOX + Pmab	FOLFOX + Bmab
No. of patients	138	142	159	169	152	173	149	157	53	54
OS (months, median)	21.7	28.7	23.6	30.3	32.6	32.9	28.0	38.3	43.4	32.0
HR	0.65		0.73		0.77		0.63		0.84	
95% CI	0.50–0.86		0.57–0.93		0.59–0.99		0.48–0.85		0.22–3.27	
P value	0.02		not reported		0.04		0.002		not reported	

Table 1. Median overall survival time of the TRICOLORE Study

TRICOLORE	
Treatment group	mFOLFOX6 or CAPEOX + bevacizumab combination therapy
No. of patients	243
OS, median, months	33.6

Table 2. Median overall survival time of each group of the FIRE-3 Study (RAS wild type, right side)

	FIRE-3	
Treatment group	FOLFIRI + bevacizumab combination therapy	FOLFIRI + cetuximab combination therapy
No. of patients	50	38
OS, median, months	23.0	18.3

The log-rank test with a one-sided significance level of 1.25% will be conducted for both all and left-sided sites. A Monte Carlo simulation was conducted, assuming an enrollment period of 24 months and numbers of 800 patients for all and 600 for left-sided sites, allowing for a follow-up period of 36 months from enrollment of the last patient, accumulating a total of 570 death events for all and 400 for left-sided sites. As the result, the detection powers when "the log-rank test was significant in either all or left-sided sites was significant" were as follows (Table 3).

Table 3. Results of Monte Carlo simulation

No. of patients	Level of significance	HR between the two groups in the left-sided site	Detection power
760 patients in all sites (380 patients/group) 600 patients in left-sided site (300 patients/group)	One-sided 1.25%*	0.68	91%
		0.70	86%
		0.72	79%
		0.74	71%

*: A significant group difference in either all or left-sided sites will represent a significant difference between the mFOLFOX6 + bevacizumab combination therapy and mFOLFOX6 + panitumumab combination therapy.

[Level of significance and detection power of main analysis of changed primary endpoint] (Added in the third version)

The protocol was amended (approved by the clinical research steering committee on March 17, 2020) to change the main analysis as follows:

Main analysis:

For the OS concerning left-sided sites, a stratified log-rank test will be performed with stratification according to allocation factors other than study site. If the analysis for left-sided sites shows a significant intergroup difference, then the stratified log-rank test for all sites will be performed with a hierarchical testing procedure.

Significance level for the main analysis:

The number of death events for left-sided sites for the final analysis planned for 2021 is assumed to be 420. The significance level for the final main analysis is discussed below.

In the previous (second) version of the protocol, which detailed plans to perform the interim analysis for both all sites and left-sided sites, the planned information time at interim analysis and the amount of alpha to be spent at interim analysis, as well as the computed planned nominal significance level for the final analysis, were as follows:

Nominal significance level for all sites (second version):

Time of analysis	Fraction of total events	Nominal significance level (one-sided)
Interim analysis	71.2%	0.00308
Final analysis	100.0%	0.01154*

Nominal significance level for left-sided sites (second version):

Time of analysis	Fraction of total events	Nominal significance level (one-sided)
Interim analysis	70.5%	0.00293
Final analysis	100.0%	0.01159*

*: The nominal significance level planned for the final analysis is based on the amount of alpha to be spent at the interim analysis planned in the second version of the protocol.

With a protocol amendment, the final main analysis was changed to be performed for left-sided sites, and, if the analysis shows a significant difference, then the stratified log-rank test for all sites will be performed with a hierarchical testing procedure. The nominal significance level for the analysis on left-sided sites is calculated as follows:

$$(0.0125 - 0.00308) + 0.01159 = 0.02101$$

Thus, the nominal significance level is set to one-sided 2.101% (corresponding to two-sided 4.202%). The rationale for this is as follows: Although the protocol was amended to perform the final main analysis only for left-sided sites, the interim analysis was conducted for all sites and left-sided sites. Given that it is difficult to explicitly calculate correlation between the test statistic for left-sided sites at final analysis and the test statistic for all sites at interim analysis, the conservative range of 0.0125–0.00308 is used. To this value, the nominal significance level of 0.01159 that can be spent for left-sided sites is added, and the resultant value is employed as the significance level for the final main analysis.

Detection power for the main analysis:

When the log-rank test for left-sided sites is conducted with a one-sided significance level of 2.101% (two-sided 4.202%), the detection power is as follows: The HR for the mFOLFOX6 + bevacizumab combination therapy group was assumed on the basis of the median survival in the TRICOLORE Study (33.6 months). A Monte Carlo simulation was used to calculate the detection power of the log-rank test for 420 death events for left-sided sites.

Table 2. Result of Monte Carlo simulation

No. of patients	Level of significance	HR between the two groups in the left-sided site	Detection power
604 Patients in left-sided site	One-sided 2.101%	0.70	91%
		0.72	87%
		0.74	80%
		0.76	71%

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

6.3.1 Criteria for discontinuation of entire clinical study

The person presiding over the study, the representative investigator, and Takeda will hold discussions, and this study will immediately be discontinued if at least one of the following criteria becomes applicable:

- When new information or other evaluation on the safety or efficacy of protocol treatment becomes available that shows a change in the known risk/benefit profile of the concerned compound and risks/benefits are no longer tolerable for patient participation in the study
- When suspension or discontinuation of the clinical study is notified by the independent data monitoring committee and/or the steering committee
- Occurrence of serious violation of the Clinical Research Act or ICH-GCP that endangers safety of patients
- When study-specific criteria for clinical study discontinuation are met (e.g., when the clinical study meets predetermined criteria for usefulness and unusefulness)

6.3.2 Criteria for discontinuation of clinical study at a study site

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

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

In the event that the person presiding over the study, the representative investigator, Takeda, or the Certified Review Board decides to suspend or discontinue the entire clinical study or clinical study at a study site, the person presiding over the study, the representative investigator, and Takeda will discuss the procedure according to the Clinical Research Act, and the discussion results will be notified by the research secretariat office. The procedure will be followed by applicable study sites during the course of clinical study suspension or discontinuation.

6.4 Procedures for protocol amendment

When protocol amendment is required, the person presiding over the study, the representative investigator, and Takeda will assess the propriety of the amendment.

The protocol will be amended only when the following purposes are applicable, and when an amendment is made, the contents of the amendment will be inquired of the representative investigator, and the research secretariat office will notify the contents to all study site investigators. An amendment will not be made if there is only a minor change that does not fall under the above items. Then, investigators should confirm the content of the amendment of the protocol and submit a letter of agreement to the research secretariat office to prove agreement with the protocol amendment.

1. Change or addition of objective
2. Change or addition of efficacy, safety evaluation method
3. Addition of test (frequency, items) or change in test method that may increase the burden of the patient
4. Dose alteration (including addition of treatment group)
5. Critical change or addition to inclusion/exclusion criteria
6. Change in planned number of patients
7. Change of plan or description of content resulting from occurrence of serious adverse event, etc.
8. Following discussion by the person presiding over the study, the representative investigator, and Takeda, it is determined that the proposed change is a critical change

Upon receipt of the above notification, investigators at the study sites must obtain approval from the supervisor in accordance with the regulations at each site.

7.0 SELECTION OF STUDY PARTICIPANTS AND ENROLLMENT

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

7.1 Inclusion criteria at enrollment

Patient's eligibility will be determined on the basis of the following criteria:

1. Patients who, in the opinion of the investigator* or the subinvestigator, are capable of understanding and complying with protocol requirements.

   *: A person who takes part in conducting the study and presides over the study-related activities within a study site.
2. Patients who sign and date a written ICF prior to the initiation of any study procedures
3. Patients aged ≥20 and <80 years at the time of informed consent
4. Patients with unresectable adenocarcinoma originating in the large intestine (excluding carcinoma of the appendix and anal canal cancer)
5. Patients with lesion(s) that can be evaluated†

   †: It is not required that the lesion be measurable with the Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1).
6. Patients who have not received chemotherapy. Patients who experience relapse more than 24 weeks (168 days) after the final dose of perioperative adjuvant chemotherapy with fluoropyrimidine agents may be enrolled.‡

   ‡: Patients who have received perioperative adjuvant chemotherapy that includes OXA cannot be enrolled.
7. Patients classified as *KRAS/NRAS* wild type§ by *KRAS/NRAS* testing.**

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

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

KRAS	Exon	2	3	4
	Codon	12, 13	59, 61	117, 146
NRAS	Exon	2	3	4
	Codon	12, 13	59, 61	117, 146

8. Patients who satisfy the following criteria for major organ function in tests performed within 2 weeks (14 days) prior to enrollment
   (1) Neutrophil count $\geq 1.5\times10^3/\mu L$
   (2) Platelet count $\geq 10.0\times10^4/\mu L$
   (3) Hemoglobin ≥9.0 g/dL
   (4) Total blood bilirubin ≤2.0 mg/dL
   (5) AST ≤100 IU/L (≤ 200 IU/L if liver metastases are present)

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

(7) Serum creatinine ≤1.5 mg/dL

(8) PT-INR <1.5 (<3.0 for patients treated with oral warfarin)

(9) Urine protein: meet at least one of the following

(i) Urine protein (dip stick method) ≤1+

(ii) UPC (urine protein creatinine) ratio ≤1.0

(iii) Measurement of 24-hour urine protein ≤1,000 mg

9. Eastern Cooperative Oncology Group (ECOG) performance status (PS) has been determined to be 0 to 1.
10. Life expectancy of ≥3 months (90 days) after enrollment.

7.2 Exclusion criteria at enrollment

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

1. Patients who have received radiotherapy within 4 weeks (28 days) prior to enrollment, except therapy received for pain relief of bone metastasis site
2. Patients with known brain metastasis or strongly suspected of brain metastasis
3. Patients with synchronous cancers or metachronous cancers with a disease-free period of ≤5 years (excluding colorectal cancer), excluding mucosal cancers cured or possibly cured by regional resection (esophageal, stomach, and cervical cancer; non-melanoma skin cancer; bladder cancer, etc.)
4. Patients with 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, are breast-feeding, or test positive for pregnancy
6. Patients with non-healing surgical wound(s) (excluding implanted venous reservoirs)
7. Patients with active hemorrhage requiring blood transfusion
8. Patients with disease requiring systemic steroids for treatment (excluding topical steroids)
9. Patient with stent placement in colon
10. Patients who have received intestinal resection within 4 weeks (28 days) prior to enrollment or colostomy within 2 weeks (14 days) prior to enrollment
11. Patients with history or obvious and extensive computerized tomography (CT) findings of interstitial pulmonary disease (interstitial pneumonia, pulmonary fibrosis, etc.)
12. Patients with arterial thromboembolism such as unstable angina pectoris, cardiac infarction, cerebral hemorrhage, or cerebral infarction, or have had arterial thromboembolism within the 24 weeks (168 days) before registration
13. Patients with serious drug hypersensitivity

14. Patients with local or systemic active infection requiring treatment or fever indicating infection
15. Patients with heart failure or serious heart disease of ≥ class II by New York Heart Association
16. Patients with intestinal paralysis, gastrointestinal obstruction, or uncontrollable diarrhea (incapacitating symptoms despite adequate treatment)
17. Patients with poorly controlled hypertension
18. Patients with poorly controlled diabetes mellitus
19. Patients with active hepatitis B
20. Patients with known HIV infection
21. Patients with peripheral neuropathy (peripheral motor neuropathy and/or peripheral sensory neuropathy) of ≥ grade 2 by Common Terminology Criteria for Adverse Events (CTCAE, Japanese edition JCOG version 4.03)
22. Other patients judged by the investigator or subinvestigator to be ineligible for enrollment in the study (such as patients who may be coerced to give consent)

7.3 Procedures for registration and allocation of drugs

7.3.1 Procedures for registration and initiation of protocol treatment

In this study, there are two steps for registration, the preregistration and the formal registration. The investigator or subinvestigator will register patients according to the following procedure.

1. The investigator, subinvestigator, or study collaborator should preregister the patient, who has been given written information on informed consent, by entering the identification code and date of informed consent discussion into the web-based case registration system (https://edmsweb28.eps.co.jp/paradigm_study/).*

   *: A study collaborator may enter data into the web-based case registration system by instruction of the investigator or the subinvestigator.

2. After preregistration, the investigator, subinvestigator, or study collaborator should enter the necessary items into the web-based case registration system (formal registration) for a patient who has given consent.
3. After formal registration, eligibility of a prospective participant is judged by the web-based case registration system and a protocol study group will be assigned if the patient is eligible.
4. The investigator, subinvestigator, and study collaborator will check the registration result and assigned protocol study group on the web-based case registration system. The registration

result and assigned protocol study group will be sent via email from the web-based case registration system to the investigator, subinvestigator, and study collaborator.

5. The investigator or the subinvestigator should start the allocated protocol treatment within 2 weeks (14 days) of formal registration (including the same day of week as the day of enrollment). However, if protocol treatment cannot be initiated within 4 weeks of formal registration, or it is predicted that the initiation of protocol will be more than 4 weeks after registration, this must be reported to the study office before protocol treatment initiation. See the attached Sheet 1 for study office contacts.

7.3.2 Contacts for enrollment procedure

See the attached Sheet 1.

7.3.3 Preparation and storage of allocation procedures

The statistics representative, or person designated by the statistics representative, should prepare the allocation procedures and manage allocation information of patients. The minimization method should be used for allocation of protocol treatment using the allocation factors of 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 independent from the statistics representative or person designated by the statistics representative.

8.0 PROTOCOL TREATMENT

The protocol treatment, contraindicated drugs/therapies, and recommended supportive care/ combination therapies in this study are explained in this section.

8.1 Definition of protocol treatment

Even if any of the criteria for suspension or discontinuation of each drug is met, treatment with other drugs will be continued unless any of the criteria for discontinuation of protocol treatment is met. However, neither OXA, bevacizumab, OXA + panitumumab, nor OXA + bevacizumab should be administered alone, and in such a case the protocol treatment will be discontinued.

8.2 Drugs used in protocol treatment

The drugs used for this study should be commercial drugs used by the study site. See the latest package insert for details and handling of each drug.

8.2.1 mFOLFOX6 + panitumumab combination therapy

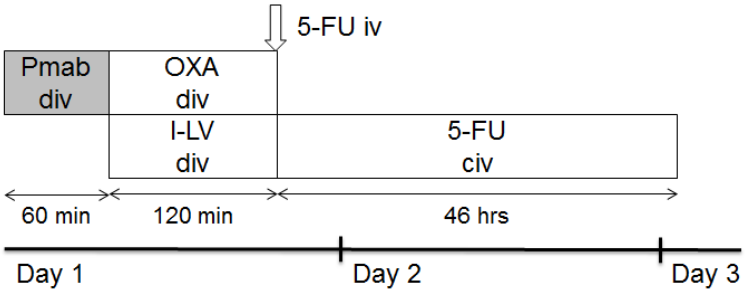
The treatment regimen shown below should be administered once every 2 weeks (14 days) (with one treatment as one course), until any of the criteria specified in Section "8.7 Criteria for discontinuation of protocol treatment for individual " is met. For administration of each drug, see Section "8.4 Criteria for administration" and Section "8.5 Criteria for protocol treatment change."

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)	2,400 mg/m^2	civ 46 hr	Day 1-3

div, intravenous drip infusion; iv, intravenous infusion; civ, continuous intravenous infusion.

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



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

Figure 8.a mFOLFOX6 + panitumumab combination therapy

8.2.2 mFOLFOX6 + bevacizumab combination therapy

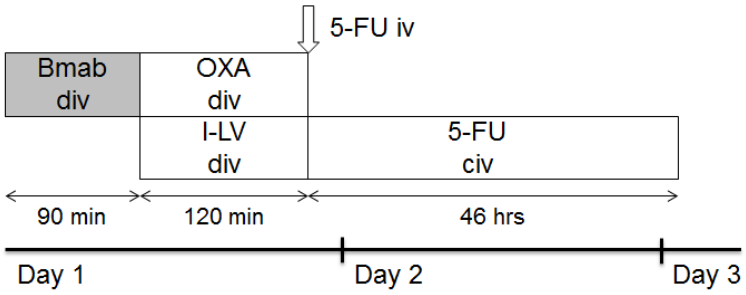
The treatment regimen shown below should be administered once every 2 weeks (14 days) (with one treatment as one course) until any of the criteria specified in Section "8.7 Criteria for discontinuation of protocol treatment for individual " is met. For administration of each drug, see Section "8.4 Criteria for administration" and Section "8.5 Criteria for protocol treatment change."

Table 8.b Treatment regimen of mFOLFOX6 + bevacizumab combination therapy

Drug	Dose	Method of administration (recommended)	Date of administration
Bevacizumab	5 mg/kg	div 30–90 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)	2,400 mg/m^2	civ 46 hr	Day 1–3

div, intravenous drip infusion; iv, intravenous infusion; civ, continuous intravenous infusion.

*: The method of administration specified at each study site will be employed.



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

Figure 8.b mFOLFOX6 + bevacizumab 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 data center will announce the body surface area, which is calculated by 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. If more than 10% change in body weight is observed further after the recalculation, the same method should be taken.

Panitumumab or bevacizumab	: 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 administration

In principle, the day (day 15) that is 2 weeks after the day of treatment (day 1) in the previous course will be day 1 of the subsequent course. Postponement or acceleration due to holidays is allowed. See “Table 9.b Allowance range for protocol treatment and laboratory tests.”

It should be confirmed that all of the criteria for initiation of protocol treatment (Table 8.c to *: See footnote for Table 8.e.

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 course and serve as the reference point for the subsequent schedule.

When the criteria for administration are not satisfied only for panitumumab or bevacizumab, mFOLFOX6 therapy or 5-FU + *l*-LV therapy will be administered. The subsequent course of treatment with panitumumab or bevacizumab will be administered in time with mFOLFOX6 therapy or 5-FU + *l*-LV therapy. (In principle, panitumumab monotherapy is not allowed during mFOLFOX6 therapy). However, when mFOLFOX6 cannot be continued for any reason and if panitumumab monotherapy is considered appropriate according to the judgment of the investigator or the subinvestigator, panitumumab monotherapy will be allowed, but bevacizumab monotherapy will not be allowed.

Protocol treatment should be discontinued when the subsequent course of treatment has not been started 28 days after it was scheduled to start (on day 43 with the date of starting the previous course as day 1). Postponement due to holidays is allowed.

Table 8.c Criteria for initiation of treatment course

Item	Criteria for initiation
Neutrophil count	$\geq 1.2\times10^3/\mu L$
Platelet count	$\geq 7.5\times10^4/\mu L$
Total bilirubin	≤2.0 mg/dL
AST	≤100 IU/L
ALT	(≤200 IU/L with liver metastasis)
Serum creatinine	≤1.5 mg/dL
Infection	Absence of fever (≥38 °C) indicating infection
Nausea, vomiting, diarrhea, stomatitis	≤ Grade 1
Initiation of treatment may be postponed at the discretion of the investigator or the subinvestigator due to adverse events not listed above.	

Table 8.d Criteria for initiation of treatment with panitumumab

Item	Criteria for initiation
Skin symptom (eg, rash acneiform, dry skin, paronychia)	≤ Grade 2
infusion reaction (infusion-related reaction)*	≤ Grade 1
Dose reduction/suspension is allowed as necessary, at the discretion of the investigator or the subinvestigator, because of adverse events not listed above.	

*: See footnote for Table 8.e.

Table 8.e Criteria for initiation of treatment with bevacizumab

Item	Criteria for initiation
Proteinuria	At least one of the following is satisfied: (i) Urine protein (dip stick method) ≤2+ (ii) UPC ≤2.0 (iii) Urine protein ≤ 2,000 mg by measurement of 24-hr urine protein
Thromboembolism	≤ Grade 2*
Hemorrhage	≤ Grade 1
Dose suspension is allowed as necessary, at the discretion of the investigator or the subinvestigator, as a result of adverse events not listed above.	

UPC, urine protein creatinine ratio.

*: In the event of grade 2 thromboembolism, bevacizumab should be suspended for the first episode. After the start of anticoagulation therapy, PT-INR should be confirmed to be within the therapeutic range (≥1.5, <3.0). Bevacizumab may be resumed when all of the criteria described below are satisfied in the subsequent course of treatment. From the second episode onwards of grade 2 thromboembolism (after the start of anticoagulation therapy), although suspension of bevacizumab is not mandatory it may be administered after confirming that PT-INR is within the therapeutic range (≥1.5, <3.0) and all of the criteria described below are satisfied. PT-INR should be measured when bevacizumab is resumed. After resumption of bevacizumab, PT-INR will be measured as appropriate, but it will not be mandatory.

1. No subjective or objective symptom of thrombosis
2. No evidence of exacerbation of thrombosis
3. No serious hemorrhage during treatment with bevacizumab
4. Clinically low risk of hemorrhage (no tumor invasion to the macrovascular system)

8.5 Criteria for protocol treatment change

8.5.1 Criteria for dose reduction/suspension of mFOLFOX6

The criteria for dose reduction/suspension and the doses of OXA and 5-FU (bolus/infusional) are shown in Table 8.f and Table 8.g, respectively. The dose of *l*-LV should not be changed.

Table 8.f Criteria for dose reduction/suspension of OXA and 5-FU

Item	Grade	Dose adjustment of OXA and 5-FU for next course
Neutropenia, thrombopenia	4	Suspend both OXA and 5-FU (bolus/infusional). Upon resumption, confirm initiation criteria are satisfied, administer dose decreased by 1 level
Grade 3 neutropenia or thrombopenia that persists for more than 7 days	≥3	
Febrile neutropenia, infection, nausea, vomiting, diarrhea, fatigue	≥3	
Sensory nerve disorder*	≥3	Suspension of OXA
	2	Suspension or dose reduction of OXA by 1 level
Pulmonary fibrosis (interstitial pneumonia)	≥2	Discontinue protocol treatment
Allergic reaction†	≥3	Discontinuation of OXA (no resumption)
Dose reduction/suspension is allowed as necessary, at the discretion of the investigator or the subinvestigator, as a result of adverse events not listed above.		

*: OXA may be resumed when nerve disorder has improved after suspension.

†: If allergic reaction is observed, immediately discontinue administration of OXA. The course may be resumed at the discretion of the study site. If it is an allergic reaction of grade 2 and under, careful administration will be allowed after appropriate supportive therapy has been given or infusion speed has been decreased, etc., upon administration of subsequent course.

Table 8.g Doses of OXA and 5-FU

Dose reduction level	OXA	5-FU (iv)	5-FU (civ)
Initial dose	85 mg/m^2	400 mg/m^2	2,400 mg/m^2
−1	65 mg/m^2	200 mg/m^2	2,000 mg/m^2
−2	50 mg/m^2	0 mg/m^2 (discontinuation)	1,600 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 Criteria for dose reduction/suspension of panitumumab

The criteria for dose reduction/suspension and the dose of panitumumab are shown in Table 8.h and Table 8.i, respectively.

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

Item	Grade	Dose adjustment of panitumumab for next course
Skin disorder	≥3	Dose reduction by 1 level after suspension However, treatment is allowed without dose reduction when it recovers to grade 2 or less within 6 weeks (42 days).
Hypomagnesemia*		
Pulmonary fibrosis (interstitial pneumonia)	≥2	Discontinue protocol treatment
Infusion reaction (reaction from injection)†,‡	≥3	Discontinuation (no resumption)
Dose reduction/suspension is allowed as necessary, at the discretion of the investigator or the subinvestigator, as a result of 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 hypomagnesemia.

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

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

Table 8.i Dose of panitumumab

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

8.5.3 Criteria for discontinuation of bevacizumab

The dose of bevacizumab is fixed at 5 mg/kg and should not be reduced. However, treatment with bevacizumab should be discontinued when any of the events shown in Table 8.j is observed.

Table 8.j Criteria for discontinuation of bevacizumab

Item	Grade	Bevacizumab
Thromboembolism	≥3	Discontinuation (no resumption)
Hemorrhage	≥3	
Perforation of the digestive tract	-	
Treatment may be discontinued when the investigator or the subinvestigator decides that treatment should be discontinued because of adverse events not listed above		

8.6 Criteria for dose increase of protocol treatment

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

8.7 Criteria for discontinuation of protocol treatment for individual patients

The number of doses is not specified either for the mFOLFOX6 + panitumumab group or for the mFOLFOX6 + bevacizumab group. However, protocol treatment should be discontinued when any of the criteria for discontinuation of protocol treatment listed below is met. The date of discontinuation of protocol treatment is defined as the date when the investigator or the subinvestigator decides on discontinuation of protocol treatment. The investigator or the subinvestigator should record the main reason for discontinuation of protocol treatment in the case report form (hereinafter referred to as CRF) according to the classification described below. See Section "9.3 Records of patients who discontinued before randomization" for patients withdrawn from the study before randomization.

1. Lack of efficacy (exacerbation)
   When PD is evident in the clinical or imaging evaluation
2. Adverse event
   Discontinuation of treatment because of an adverse event, in the opinion of the investigator or the subinvestigator, or according to the protocol treatment discontinuation criteria.

   However, death during protocol treatment will be classified in Section "4. Death during protocol treatment" and not in this item.

   Protocol treatment is postponed because of an adverse event for 44 days or more after the day of starting the last course. However, postponement due to holidays is allowed.
3. Voluntary discontinuation
   A patient wishes to discontinue study participation. The reason for discontinuation should be recorded in the CRF when it is clarified.
   Note: Attempts should be made as best as possible to clarify the reason for voluntary discontinuation. (Discontinuation due to adverse event or lack of efficacy should not be classified as "voluntary discontinuation.")
4. Death during protocol treatment

   A patient dies before investigators decide to discontinue protocol treatment. Date of death, reason of death (protocol treatment–related, primary disease, others) should be described in the CRF.

5. When surgery aimed at curative resection (complete resection: R0 resection) of colorectal cancer is scheduled
   Note: "When surgery is scheduled" means the day when the surgery date is decided.
6. Significant deviation from the protocol
   When study continuation may cause intolerable risk to the health of a patient because the patient was found not to satisfy the inclusion criteria specified in the protocol after initiation of protocol treatment or the protocol has not been observed.
7. Lost to follow-up
   When patient fails to make visits and cannot be contacted. The attempts that were made to contact the patient should be recorded in the source documents.
8. Discontinuation of entire study
   When discontinuation of the clinical study is decided by the person presiding over the study, the representative investigator, Takeda, or the Certified Review Board. See "6.3.1 Criteria for discontinuation of entire clinical study" for details.
9. Pregnancy
   When a female patient is found to be pregnant.
   Note: Study participation should immediately be discontinued when pregnancy becomes known. See Section "9.2.14 Pregnancy" for procedures.
10. Other
    When the investigator or the subinvestigator decides that protocol treatment should be discontinued for other reasons. Details should be described in the CRF.

8.8 Procedures for discontinuation or withdrawal of a patient

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

8.9 Contraindicated drugs/therapies

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

- Chemotherapy for primary disease other than protocol treatment
- Hormone therapy for primary disease
- Immunotherapy for primary disease
  - Cellular immunotherapy
  - Vaccine therapy
  - Cytokine therapy (except for G-CSF)
  - Biological response modifiers therapy
  - Antibody therapy
  - Gene therapy
- Other antibody therapy
  However, treatment for the pain relief of bone metastasis is permitted
- Radiotherapy for primary disease
  Treatment for pain relief of a bone metastasis site is allowed
- Hyperthermia therapy for primary disease
- Study drug and unapproved drug

8.10 Recommended supportive care and combination medications

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

- Neutropenia
  Granulocyte colony stimulating factor (hereinafter referred to as G-CSF) should be administered 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 by 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 the subsequent course. Careful administration of panitumumab or bevacizumab by slowing the infusion speed may be considered.

- Hypertension
  Measures may be taken to maintain systolic blood pressure of <140 mm Hg and diastolic blood pressure of <90 mm Hg.
- Pulmonary fibrosis (interstitial pneumonia)
  If pulmonary fibrosis occurs, it should be treated according to the severity (e.g., steroid pulse therapy).
- Hepatitis B
  Refer to JSH Guidelines for the Management of Hepatitis B virus infection (http://www.jsh.or.jp/doc/guidelines/HBV_GL_ver2.201406.pdf) and take appropriate action and monitoring.
- Others
  Drugs for treatment of adverse events may be coadministered at the discretion of the investigator or the subinvestigator. Symptomatic therapies that have been continued from before the start of this study are allowed.

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

- Skin disorder
  - Tetracycline antibiotic (e.g., oral minocycline)
  - External salicylic acid petrolatum (10%)
  - External steroid therapy, e.g.,

    Face: hydrocortisone butyrate (0.1%)

    Trunk: difluprednate (0.05%)
  - Moisturizer (eg, heparin analog lotion)
  - Sunscreen (example): not containing 4-aminobenzoic acid, SPF (sun protection factor) ≥30, PA (protection grade of UVA) ≥++. Apply before going out to block ultraviolet rays (UVA and UVB).

  Dermatopathy prevention with humectants, suntan lotions, antibiotics, or external steroid preparations may be carried out by methods employed at each study site.
- Electrolyte abnormality (e.g., hypomagnesemia, hypocalcemia)
  - 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 (e.g., 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) as a result of 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 Section "9.1 Study calendar.")

8.12 Recommended follow-up therapy

8.12.1 Recommended second-line treatment

- mFOLFOX6 + panitumumab group: Combination of bevacizumab with IRI-based chemotherapy is strongly recommended.
- mFOLFOX6 + bevacizumab group: combination of bevacizumab or anti-EGFR antibody with IRI-based chemotherapy is strongly recommended.

8.12.2 Recommended third-line or subsequent treatment

All approved drugs (regorafenib, trifluridine/tipiracil hydrochloride, etc.) should be used appropriately as much as possible.

9.0 PROTOCOL, EVALUATION ITEMS, AND PROCEDURES FOR OBSERVATIONS

9.1 Study calendar

The investigator or the subinvestigator should collect data according to "Table 9.a Study calendar." The same investigator or the subinvestigator should perform tests/observations/evaluation of patients if possible. For the allowance range of protocol treatment and various laboratory tests, see "Table 9.b Allowance range for protocol treatment and laboratory tests."

Table 9.a Study calendar

Item	At enrollment	During protocol treatment	Discontinuation of protocol treatment[a]	Follow-up period[b]
Obtaining ICF	●[c]			
Patient background	●			
RAS status	●			
Clinical findings (including adverse events)	●	●[d]	●	
Height/body weight	●[e]	○[f]		
ECOG PS	●[e]	●[d]	●	
Protocol treatment		●		
Laboratory tests				
Hematology, serum chemistry, urinalysis	●[e]	●[g]	●	
Immunological tests (HBs antigen)	●[h]			
Tumor markers		●[i,j]	●	
Imaging tests (thoracoabdominal-pelvic CT/MRI)	●[k]	●[i]	○[l]	
Follow-up treatment				●
Survival survey				●

●: Mandatory, ○: Perform as necessary

[a]: Perform within 28 days of discontinuation or earlier date than start of follow-up treatment.

[b]: Perform every 6 months as a guide, with protocol discontinuation date as starting point.

[c]: Consent must be obtained before enrollment. Further, consent should be obtained after *RAS* status has been identified.

[d]: Perform before administration on treatment day of each course.

[e]: Perform within 2 weeks (14 days) prior to enrollment (including the same day of week as the day of enrollment). Results of tests performed before obtaining consent may be used if it is within 2 weeks prior to enrollment. Height can be used even if it was measured before 2 weeks prior to enrollment as long as it had been measured at study site.
[f]: Measurement is not mandatory during protocol treatment period. Even if measured, it is unnecessary to record in the CRF. However, if transition in decrease of body weight is judged to be a clinical problem by the investigator or the subinvestigator, it will be an adverse event.
[g]: Perform 2 days before each course prior to administration on treatment day.
[h]: Test results from up to 1 year before obtaining consent may be used. However, follow JSH Guidelines for the Management of hepatitis B virus infection for the measurement of HBs antibody, HBc antibody, and HBv DNA.
[i]: Measure once every 8 weeks (56 days) with day 1 of first course as starting point. However, reduce the frequency to once every 12 weeks (84 days) when 2 years have passed since initiation of protocol treatment.
[j]: If it has been performed within 28 days before treatment day, the test for the first course may be omitted.
[k]: Perform within 4 weeks (28 days) before enrollment (including the same day of week as the day of enrollment). Results from tests performed before obtaining consent may be used if they are within 4 weeks before enrollment.
[l]: If discontinued because of results of imaging tests (PD), imaging test will not be mandatory.

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

<table>
<tr><th>Performed items</th><th>Protocol specification</th><th>Allowance range</th></tr>
<tr><td>Clinical laboratory test values</td><td>Before administration</td><td>From −2 days to before administration</td></tr>
<tr><td>Protocol treatment</td><td>From treatment day (day 1) of previous course to 2 weeks later (day 15)</td><td>±3 days</td></tr>
<tr><td>Tumor markers (at enrollment)</td><td>From 28 days before initial dose to treatment day</td><td rowspan="2">Same as protocol specification</td></tr>
<tr><td>Imaging tests (at enrollment)</td><td>From 28 days before enrollment to the enrollment day</td></tr>
<tr><td rowspan="2">Tumor markers and imaging tests (during protocol treatment)</td><td>Protocol treatment ≤2 years: 8 weeks (56 days)</td><td rowspan="2">±2 weeks (14 days)</td></tr>
<tr><td>Protocol treatment >2 years: 12 weeks (84 days)</td></tr>
</table>

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

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

9.2.1 Informed consent procedure

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

To anonymize the participant, a unique participant ID code will be assigned to each patient at the time of obtaining consent. The participant ID code will be used throughout the study period and will not be changed.

The method for obtaining consent is described in Section "7.3 Procedures for registration and allocation of drugs."

9.2.2 Registration and allocation of protocol treatment

For procedures for registration and allocation of drugs and preparation and storage of allocation procedures, see Section "7.2 Exclusion criteria at enrollment."

9.2.3 Patient demographics

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

1. Information on primary organ
2. Solitary/multiple
3. Primary tumor site (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectosigmoid, rectum)
   The definitions of primary lesion location (left-sided/right-sided/other) are as shown below.
   - ✓ Left-sided: Single lesion or multiple lesions in the descending colon, sigmoid colon, rectosigmoid region, or rectum
   - ✓ Right-sided: Single lesion or multiple lesions in the cecum, ascending colon, or transverse colon
   - ✓ Other: Multiple primary lesions in both the right side and the left side.
4. Information on metastasis
5. Number of organs with metastasis (0, 1, ≥2)*
   *: Does not include primary tumor/regional lymph node. Other lymph nodes in several sites will be counted as one organ. For example, if metastasis is observed in a cervical lymph node and a thoracic lymph node, it will be counted as one organ.
6. Organ with metastasis (liver, lung, peritoneum, lymph node,* bone, adrenal gland, skin, and others†)
   *: Does not include primary tumor/regional lymph node. Other lymph nodes in several sites will be counted as one organ. For example, if metastasis is observed in a cervical lymph node and a thoracic lymph node, it will be counted as one organ.
   †: Name of organ to be recorded in CRF.
7. History of treatment

8. History of surgery in primary tumor site/palliative metastasis site and history of colostomy/ bypass surgery
9. For patients with history of surgery, the date of surgery
   However, endoscopic surgery, which is not considered a history of surgery, should not be entered into the CRF
10. History of radiotherapy (radical irradiation)
11. For patients with history of radiotherapy, the date of final dose
    However, irradiation for pain relief (palliative irradiation) in a bone metastasis site, which is not considered radiotherapy, should not be entered into the CRF
12. History of preoperative and/or postoperative adjuvant chemotherapy
    For patients with a history of adjuvant chemotherapy, record the type of preoperative and/or postoperative adjuvant chemotherapy, date of final treatment, and most recent date of relapse
13. *RAS* assay
    Histological type will be evaluated on the basis of histological findings in the "Japanese Classification of Colorectal Carcinoma."
14. Histological type (primary) of sample used in *RAS* assay
15. Collection site (primary tumor/metastasis site) of sample used in *RAS* assay
16. Type of sample used in *RAS* assay
    a. Biopsy sample
    b. Surgical sample
17. Collection date of sample used in *RAS* assay
18. Method of *RAS* assay
19. Results of *RAS* assay (wild type/mutant type/not measured or unable to determine)

    The following test results of codons should all be recorded in the CRF

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

9.2.4 Concurrent medical condition

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

- Notable concurrent medical conditions: hypertension, diabetes mellitus, and others*

  *: When judged by the investigator or the subinvestigator that evaluation in this study may be affected.

9.2.5 Clinical findings (including adverse events)

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

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

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

See Section "10.0 Adverse events" for definition of adverse event.

9.2.6 Height, body weight

Body weight at enrollment should be measured within 2 weeks (14 days) before enrollment (including the same day of the week as the day of enrollment) and recorded in the CRF. Height measured at the study site in the past may be used.

9.2.7 Eastern Cooperative Oncology Group Performance Status

ECOG PS will be assessed according to "Table 9.c. Eastern Cooperative Oncology Group Performance Status" at enrollment or within 2 weeks (14 days) prior to enrollment (including same day of the week as the day of enrollment). Before initiation of each course, PS will be determined on treatment day before administration. PS at discontinuation will be determined as much as possible within 4 weeks (28 days) after discontinuation or before next treatment, whichever date is earlier.

Table 9.c Eastern Cooperative Oncology Group Performance Status

P.S.	Definition
0	Fully active, able to carry on all predisease 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

P.S.	Definition
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

9.2.8 Protocol treatment implementation status

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

- When dosage of drug used in protocol treatment is adjusted (Number of adjustments/reduction/suspension/discontinuation)
- If drug used in protocol is adjusted, the dosage should be recorded

9.2.9 Laboratory tests

Laboratory tests should be conducted at each study site.

Laboratory tests at enrollment will be conducted within 2 weeks (14 days) prior to enrollment (including same day of the week as the day of enrollment). Tests before initiation of each course will be conducted before administration on treatment day. Tests at discontinuation will be conducted as much as possible within 4 weeks (28 days) after discontinuation or before next treatment, whichever date is earlier.

Test items and notes are listed in Table 9.d to Table 9.f.

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

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

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

Hematology	Serum chemistry	Tumor marker	Urinalysis
Neutrophil count	Total bilirubin	None	One of the
Platelet count	ALT		following: urine
Hemoglobin content	AST		protein (dipstick
Immunology	Creatinine		method), UPC ratio,
HBs antigen*	PT-INR		and 24-hour urine
	Mg		protein
	Albumin		
	Na		
	K		
	Ca		

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

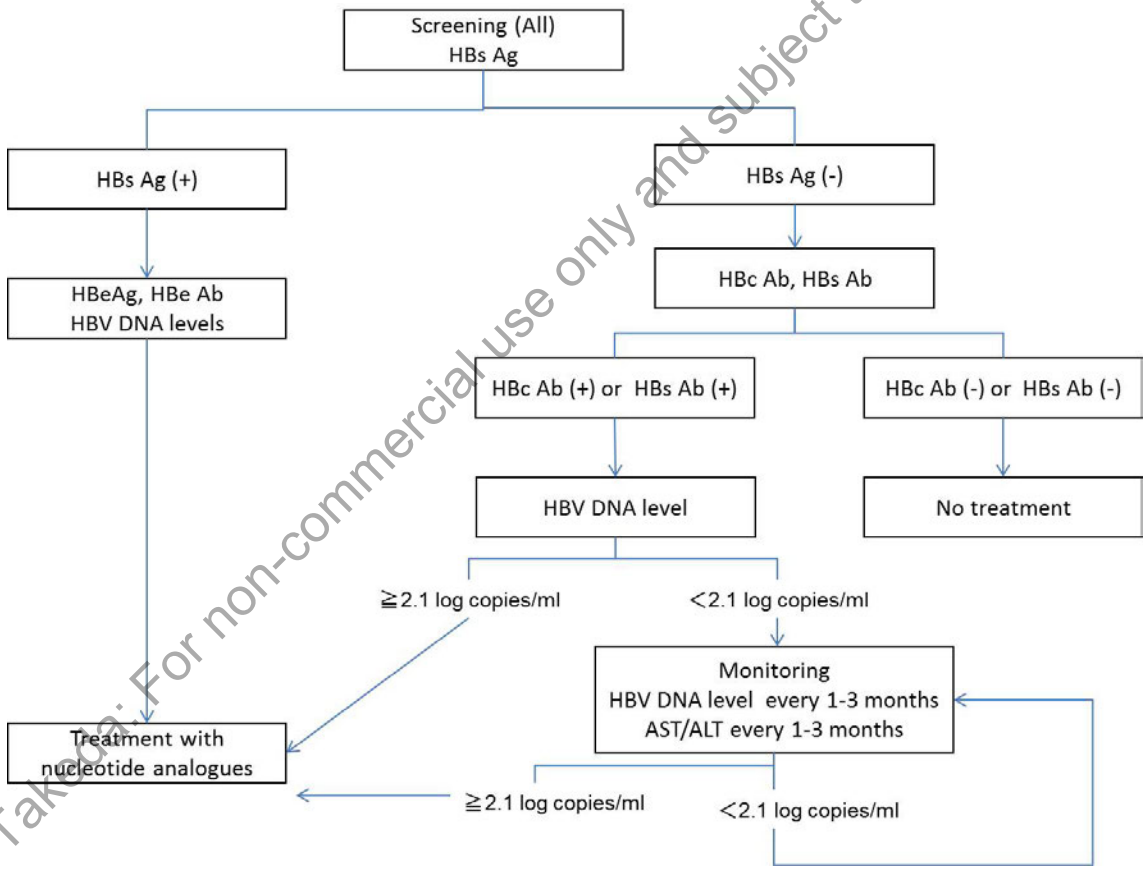


Figure 9.a JSH Guidelines for the management of hepatitis B virus infection

Hepatitis B due to HBv reactivation occurs in some patients who are HBsAg-positive or HBsAg-negative during or after intensive chemotherapy for hematological malignancies, and some cases become fulminant; therefore, caution is required. In addition, the risk of HBv reactivation should be taken into account in routine chemotherapy for

hematological malignancies or solid tumors and in immunosuppressive therapy for autoimmune diseases, such as rheumatic diseases and collagen diseases. With conventional chemotherapy and immunosuppressive therapy, the frequency of HBv reactivation, onset of hepatitis, and fulminant hepatitis is not clear, and there is not enough evidence for guidelines. In addition, the preventive effect of nucleic acid analog administration on fulminant disease is not completely guaranteed.

Notes:

1. HBv carriers and patients with a history of HBv infection should be screened before immunosuppressive therapy or chemotherapy. First, HBsAg is measured to determine whether the patient is an HBv carrier. If the patient is negative for HBs antigen, then HBc antibody and HBs antibody should be measured to confirm whether the patient has a history of infection. The measurement of HBs antigen HBc antibody and HBs antibody should be performed by a highly sensitive method. In addition, HBv reactivation has been reported in patients who are positive for HBs antibody alone (HBs antigen negative and HBc antibody negative). Therefore, it is desirable to take measures in accordance with the Guideline unless the history of vaccination is clear.
2. Patients who are HBsAg-positive should be referred to a hepatologist. It is desirable to consult a hepatologist when administering nucleic acid analog in all cases.
3. In cases of retreatment without HBc antibody or HBs antibody measurement at the start of initial chemotherapy and cases in which immunosuppressive therapy has already been started, the antibody titer may have decreased, and close examination by HBv DNA quantitative test, etc., is desirable.
4. Patients with a history of HBv infection will be screened for HBv DNA by real-time polymerase chain reaction.
5.
    a. Use of rituximab/steroid, fludarabine-based chemotherapy, and hematopoietic stem cell transplantation is associated with a high risk of HBv reactivation in patients with a history of infection, and caution should be exercised. Monitor HBv DNA monthly during treatment and for at least 12 months after stopping treatment. Long-term monitoring after hematopoietic stem cell transplantation is necessary.
    b. There is a risk of HBv reactivation, albeit infrequent, when usual chemotherapy and molecular-targeted drugs with immune effects are used concomitantly. Monitoring of HBv DNA levels should be performed approximately every 1 to 3 months, and the interval and duration should depend on the type of treatment. Careful measures are desirable for hematological malignancies.
    c. Immunosuppressive therapy with corticosteroids, immunosuppressants, or molecular-targeted agents with immunosuppressive or immunomodulatory properties may also result in HBv

reactivation. Monthly monitoring of HBv DNA levels is recommended after initiation of immunosuppressive therapy and for at least 6 months after any change in therapy. After 6 months, the interval and period will be decided in consideration of the contents of treatment.

6. It is desirable to start administration as soon as possible before the start of immunosuppressive therapy/chemotherapy. However, in HBsAg-positive patients with a high viral load, cases of death due to fulminant hepatitis have been reported even during prophylactic administration of nucleos(t)ide analogs, and it is desirable to reduce the viral load before the start of immunosuppressive therapy/chemotherapy.
7. Administration should be started immediately when HBv DNA is 2.1 log copies/mL or more during or after immunosuppressive therapy/chemotherapy. For patients receiving immunosuppressive therapy or chemotherapy, it is recommended that immunosuppressants or antineoplastic drugs with immunosuppressive effects should not be discontinued immediately and that the patient should be referred to a hepatologist for treatment.
8. The use of entecavir as a nucleoside analog is recommended.
9. Termination of nucleoside analog therapy may be considered if the following conditions are met: Patients who are positive for HBs antigen at screening meet the criteria for termination of nucleic acid analog treatment for chronic hepatitis B. In patients who are positive for HBc antibody or HBs antibody at screening, (1) treatment should be continued for at least 12 months after completion of immunosuppressive therapy or chemotherapy; (2) ALT (GPT) is normalized during this extension period (except in cases of ALT abnormalities other than HBv); and (3) test results for HBv DNA remain negative during this extension period.
10. Patients will be closely monitored, including HBv DNA monitoring, for at least 12 months after the end of nucleic acid analog treatment. The method of follow-up is based on the precautions for use of each nucleoside analog. Resume treatment as soon as HBv DNA ≥2.1 log copies/mL during follow-up.

Table 9.e Laboratory tests performed before the start of each course of treatment

Hematology	Serum chemistry	Tumor marker	Urinalysis
Neutrophil count*	Total bilirubin*	CEA[‡, §]	One of the following: urine protein (dipstick method), UPC ratio, and 24-hour urine protein*
Platelet count*	ALT*		
Hemoglobin content*	AST*		
	Creatinine*		
	PT-INR*,[†]		
	Mg*		
	Albumin*		
	Na*		
	K*		
	Ca*		

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

[†]: Measurement before the start of each course of treatment is not mandatory. However, in the event of grade 2 thromboembolism, bevacizumab should be suspended for the first episode. After the start of anticoagulation therapy, it should be confirmed that PT-INR is within the therapeutic range (≥1.5, <3.0). Bevacizumab may be resumed when all of the criteria described below are satisfied in the subsequent course of treatment. From the second episode onward of grade 2 thromboembolism (after the start of anticoagulation therapy), suspension of bevacizumab is not mandatory; it may be administered after confirming that PT-INR is within the therapeutic range (≥1.5, <3.0) and all of the criteria described below are satisfied. PT-INR should be measured when bevacizumab is resumed. After resumption of bevacizumab, PT-INR will be measured as appropriate, but it will not be mandatory.

(1) No subjective or objective symptom of thrombosis
(2) No evidence of exacerbation of thrombosis
(3) No serious hemorrhage during treatment with bevacizumab
(4) Clinically low risk of hemorrhage (no tumor invasion to the macrovascular system)

[‡]: If it has been conducted within 28 days before treatment day, it may be omitted.

[§]: With day 1 of first course as starting point, measure once every 8 weeks (56 days). However, when 2 years have passed since initiation of protocol treatment, once every 12 weeks (84 days).

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

Hematology	Serum chemistry	Tumor marker	Urinalysis
Neutrophil count	Total bilirubin	CEA[†]	One of the following: urine protein (dipstick method), UPC ratio, and 24-hour urine protein
Platelet count	ALT		
Hemoglobin content	AST		
	Creatinine		
	PT-INR*		
	Mg		
	Albumin		
	Na		
	K		
	Ca		

*: Optional tests

[†]: If ≥28 days has not passed since the last measurement, the test can be omitted

9.2.10 Imaging test (thoracoabdominal-pelvic CT/MRI)

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

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

After initiation of protocol treatment, imaging test will be performed every 8 weeks (56 days) with protocol treatment initiation date (day 1) of the first course as the starting point. However, when 2 years have passed since initiation of protocol treatment, it will be performed once every 12 weeks (84 days) (See "Table 9.a Study calendar").

Thoracoabdominal-pelvic CT (in principle, contrast CT with a slice width of 10 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 entered into the CRF. If necessary, a brain MRI/CT and a neck CT may be performed.

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

The investigator or the subinvestigator should evaluate the test results according to the RECIST v1.1 [redacted] and enter the determined results into the CRF.

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

9.2.11 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 (in case of fractional excision, the last surgery date will be entered), site of surgery, and postoperative assessment of residual tumor should be recorded into the CRF. The residual tumor is assessed according to the table shown below, and the histological results of resection specimens should be

recorded into the CRF as much as possible. On the day the scheduled date of surgery aimed at curative resection of colorectal cancer is decided, protocol treatment will be discontinued.

When surgery aimed at curative resection is performed in more than one session, the number of sessions should be entered into the CRF. As for the postoperative determined results of residual tumor, data obtained before initiation of subsequent treatment or within 6 months from discontinuation of protocol treatment, whichever is earlier, should be entered into the CRF.

Table 9.g Histological changes

Grade	Criteria
Grade 0 (no change)	Denaturation and necrosis, such as by treatment, is not recognized in cancer cells
Grade 1a (very slight change)	Less than about one-third of the cancer shows degeneration or necrosis
Grade 1b (slight change)	More than one-third but less than two-thirds of the cancer shows degeneration, necrosis, or melting
Grade 2 (moderate change)	More than two-thirds of the cancer is markedly modified by necrosis, melting, or disappearance
Grade 3 (marked change)	The entire cancer is marked by necrosis, melting, or disappearance, or the entire cancer has been replaced by a granuloma-like tissue or patchy fibrosis

Table 9.h 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

*: When radio frequency ablation, microwave coagulation therapy, etc., has been used in combination, classify as R2.

9.2.12 Follow-up treatment

When follow-up treatment is performed after discontinuation of protocol treatment, the following information on follow-up treatment should be collected every 6 months, in principle, after discontinuation of protocol treatment. Information on the follow-up treatment should be collected until a patient dies or the period of evaluation of the study is terminated.

- Secondary treatment

  - Drug name
  - Initiation date, end date
- Third-line or subsequent treatment
  - Drug name
  - Initiation date

9.2.13 Survival survey

After discontinuation of protocol treatment, every patient will be followed up to confirm survival of patients every 6 months in principle after discontinuation of protocol treatment. The following information on survival should be collected. The survey should be continued until the patient dies or the period of study evaluation is terminated.

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

9.2.14 Pregnancy

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

For every female patient allocated in the panitumumab group and reported to have become pregnant, the investigator or subinvestigator should follow the patient up to delivery, including result of premature delivery, with consent from the patient, and report to the research secretariat office using the specified follow-up form. Evaluation after delivery will also be conducted.

9.3 Records of patients who discontinued before randomization

Every patient who signed the ICF and then dropped out before randomization should be registered in the web-based registration center, and a CRF should be prepared for them.

The following items are to be described in the CRF.

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

For patients who drop out of the study before randomization, the main reason for drop-out should be entered into the CRF according to the following categories:

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

The participant ID code of a patient withdrawn from the study before randomization should not be reused.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse events

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

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

10.1.2 Items to be considered concerning adverse events

Generally unfavorable findings are shown below:

- Newly diagnosed disease or unexpected aggravation of existing symptom (intermittent event of the existing symptom is not considered an adverse event)
- Requiring action or medical practice
- Requiring invasive diagnostic treatment
- Requiring discontinuation of protocol treatment (mFOLFOX6 + bevacizumab or mFOLFOX6 + panitumumab combination treatment) or concomitant drugs under use, or adjustment in dosage
- Considered unfavorable by the investigator or the subinvestigator

Diagnosis name and signs/symptoms:

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

Laboratory test values and ECG findings:

Abnormal laboratory values and ECG findings are recorded as adverse events when the investigator or the subinvestigator judges the course to be clinically problematic (in other words, when certain action or medical practice is required, or the investigator or the subinvestigator

judges the change to have exceeded the normal physiological variation range of the patient). Retest and/or continued monitoring of abnormality are not considered medical practice. Also, repeated or additional conduct of noninvasive test for verification, evaluation, and monitoring of abnormality are not considered medical practice.

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

Existing symptoms (diseases and/or symptoms that have been present from before initiation of protocol treatment):

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

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

Change of severity of adverse events:

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

Previously planned surgery or treatment:

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

Nonurgent surgery or treatment:

Nonurgent surgery or treatment that does not induce a change in the condition of a patient (cosmetic surgery, etc.) is not considered an adverse event. However, it should be recorded in the

source documents. Complications due to a nonurgent surgery should be reported as an adverse event.

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

Panitumumab overdose:

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

Furthermore, the overdose of panitumumab is defined as follows.

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

10.1.3 Serious adverse events

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

1. Results in death during protocol treatment,* including all deaths irrespective of a causal relationship with protocol treatment
   *: Period from initiation of protocol treatment up to 4 weeks (28 days) after discontinuation of protocol treatment or initiation of next treatment.
2. Results in death after discontinuation† of protocol treatment for which a causal relationship with protocol treatment cannot be denied. However, death obviously due to the underlying disease is not applicable
   †: From 29 days after discontinuation of protocol treatment or from initiation of next treatment
3. Is life-threatening
   The term “life-threatening” refers to an event in which the patient 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 more severe.
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. Serious adverse events also include other medically important events that cause a risk to the patient, even if not immediately life-threatening and not resulting in death or hospitalization, or that require action or treatment to prevent the results in items 1 to 6 above

10.1.4 Special interest adverse event

Adverse events listed in "Table 10.a Takeda medically significant adverse event list" will be handled as "special interest adverse event" irrespective of severity determined by the investigator or the subinvestigator. Further, any adverse events listed in Table 10.a that have been determined as serious by the investigator or the subinvestigator will be handled as serious adverse event.

Table 10.a Takeda medically significant adverse event list

Acute respiratory failure/acute respiratory distress syndrome	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 events is classified into five grades (grades 1–5) as follows based on the Common Terminology Criteria for Adverse Events (hereafter referred to as CTCAE, Japanese

edition JCOG version 4.03), of National Cancer Institute, USA. Furthermore, the grade for adverse events not listed in CTCAE will be classified according to the following criteria.

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

Grade 1	Mild; asymptomatic or slightly symptomatic; only clinical or test findings; or requiring no treatment
Grade 2	Moderate; requiring the least treatment or local or noninvasive 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

";" stands for "or."

*: Activities of daily living except for self-care activities include meal preparation, shopping for daily necessities and clothing, making phone calls, 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 (mFOLFOX6 + bevacizumab or mFOLFOX6 + panitumumab combination therapy) and adverse events, and causal relationship between adverse events in the mFOLFOX6 + panitumumab group and panitumumab (information on causal relationship with panitumumab will be collected only when causal relationship is "related" with protocol treatment) is classified and defined as described below. Information on causal relationship with adverse event is not collected for any drugs other than protocol treatment.

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

10.1.7 Action taken for protocol treatment

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

10.1.8 Outcome

Outcome of adverse events is classified as follows.

Category	Criteria for judgment
Recovered	• Disappearance or recovery of symptoms and findings • Laboratory values returned to normal or baseline
Improved	• Severity was improved by one or more grades • Symptoms or findings mostly disappeared • Laboratory values improved but have not returned to normal or baseline • The patient died from a cause other than the adverse event concerned while the event was resolving
Not recovered	• No change in symptoms, findings, or laboratory data • The symptoms, findings, or laboratory data on the final day of observable period were aggravated in comparison with the date of onset • Irreversible congenital anomaly • The patient died and the concerned adverse event was not a direct cause of death but the concerned adverse event remained not recovered
Recovered with sequelae	• Disability that disturbs daily life
Death	• Direct relationship between death and the concerned adverse event; "direct relationship" means that the concerned adverse event was the cause of death or the concerned adverse event was clearly responsible for death • Outcome of an adverse event that was not determined (judged, presumed) a direct cause of death observed in the same patient is not considered as death
Unknown	• Follow-up specified in the protocol after the date of onset was not possible due to change of hospitals or relocation, etc.

10.2 Procedures

10.2.1 Collection and reporting of adverse events

10.2.1.1 Period for collection of adverse events

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

10.2.1.2 Reporting of adverse events

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

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

All adverse events should be entered into the CRF: the name of the adverse event, severity, seriousness, causal relationship with protocol treatment (unrelated or related). Further, if a patient in the panitumumab group has causal relationship "related" to protocol treatment, causal relationship with panitumumab (unrelated or related) should be recorded. Also, for the last course, action taken and outcome concerning protocol treatment should be recorded.

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

10.2.2 Collection and reporting of serious adverse events

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

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

The investigator or the subinvestigator should also report to the research secretariat office (see the attached Sheet 1 for contact information) within 72 hours of recognition of the onset of an event. The investigator should also submit a report on diseases associated with the drug to the research secretariat office within 10 calendar days.

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

- Name of the adverse event (including known/unknown events*)
- Brief description of the adverse event and the reason why it was determined to be serious
- Study title
- Participant ID code
- Name of study site
- Name of investigator or subinvestigator
- Name of protocol treatment being conducted
- Determined causal relationship

*: The investigator or subinvestigator will determine whether adverse events are known or unknown according to the latest package insert of the drug used in the protocol treatment.

The representative investigator receiving a report from the research secretariat office will hear the opinions of the Certified Review Board, and also provide information to the investigator at each study site through the research secretariat office according to the Clinical Research Act. The investigator will provide information to the supervisor at the study site as necessary. When receiving a report of an unknown serious adverse event, Takeda will add the following item to the report from the investigator and disseminate them to the independent monitoring committee.

10.2.3 Follow-up of serious adverse events

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

When a change such as alteration of outcome was made to the report of a serious adverse event, the investigator or the subinvestigator should submit a report specifying details of the change to

the supervisor at the study site and the research secretariat office. When requested by the research secretariat office or the Certified Review Board, related data of the study site (e.g., ECG, laboratory test values, summary of discharge report, result of autopsy, etc.) should be provided.

10.2.4 Reporting of additional information concerning adverse events

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

10.2.5 Reporting of serious adverse events, etc., to regulatory authorities

Takeda should report, according to regulations, unexpected serious adverse drug reactions and other serious adverse events that are subject to emergency reporting to regulatory authorities.

From the time point of first acknowledging the event or receiving additional information, Takeda or research secretariat office should comply with regulatory required time frame for reporting, and make an emergency report concerning unexpected serious adverse drug reactions and expected serious adverse drug reactions to regulatory authorities. Also, Takeda should in the same way make an emergency report of other critical safety information that may have a major effect on the study drug risk-benefit, continuation of study drug administration, and continuation of this clinical study.

11.0 COMMITTEES ESTABLISHED FOR THIS STUDY

11.1 Research steering committee

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

The research steering committee will consist of the person presiding over the study, the representative investigator, the research steering committee members, the statistics representative, and Takeda. Takeda or its designee will act as the secretariat. The research steering committee will not be informed of the content of treatment allocation throughout the study period.

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

11.2 Independent data monitoring committee

The independent data monitoring committee (hereinafter referred to as IDMC) will be established according to the ICH E6 (1.25), and Takeda or its designee will serve as the secretariat of the IDMC.

The objective of IDMC is to evaluate the progress of this clinical study, safety data, and endpoints of clinical efficacy on a regular basis and propose continuation, alteration, or discontinuation of this study to Takeda.

The IDMC will prepare an IDMC advisory report on continuation/discontinuation of the study and a change of the study plan according to the efficacy analysis results as well as the safety analysis results for reference, which will be submitted to Takeda. The person presiding over the study, the representative investigator, and Takeda will hold discussions and determine whether to continue, discontinue, or change the study based on the results.

Takeda will prepare the IDMC procedures (IDMC charter) specifying details such as the objective, roles, and responsibilities of the IDMC and management procedures. IDMC members are listed in attached Sheet 1.

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 with MedDRA.

12.1 Case report form

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

Takeda or its designee should provide study sites with access authorization to the electronic data capture (hereinafter referred to as EDC). Takeda or its designee should provide the investigator, subinvestigators, and study collaborators with training for utilization of EDC. The CRF will be used to report the information collected during the study period to Takeda. The CRF will be prepared in Japanese. Data will be directly entered in preparing the CRF. However, written CRFs will be collected when the sixth or a subsequent line of treatment is performed in the collection in Section "9.2.12 Follow-up treatment."

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

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

The data below will be directly recorded into the CRF:

- Seriousness, severity, and causal relationship of adverse event with protocol treatment
  - Further, for the panitumumab group, causal relationship with panitumumab

When the investigator or the subinvestigator makes a change or correction in the data entered into the CRF after fixation of the clinical database, a record (data clarification form) of change or correction in the CRF, provided by Takeda, 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 their name, or affix a seal, and date it.

The monitor should confirm that the CRF has been prepared appropriately. The monitor should have access to the medical records of study participants and in-house records to ensure the accuracy of the CRF as necessary. The completed CRF is the property of Takeda, and the

investigator, subinvestigator, or study collaborator should not disclose the information to a third party without written permission from Takeda.

12.2 Time limit for data input into the electronic data capture

The research secretariat office or monitor should request the investigator, subinvestigator, or study collaborator to promptly enter EDC during the period from enrollment of the patient to the end of the follow-up.

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

1. At enrollment: within 2 weeks (14 days) after enrollment
2. During protocol treatment: within 2 weeks (14 days) after initiation of each course of protocol treatment
3. At discontinuation of protocol treatment: within 4 weeks (28 days) after discontinuation of protocol treatment
4. Imaging test results: within 2 weeks (14 days) after evaluation of efficacy
5. Follow-up period: within 2 weeks (14 days) after request for follow-up
6. Inquiry about data input items of EDC: within 2 weeks (14 days) from inquiry

12.3 Storage of records

The investigator should store the following materials, including those specified in Section 14.1, and study-specific documents to be used by the person designated by the representative investigator for investigation and audit. The materials include a list of patient screenings, medical records, signed and dated original consent forms, and a record of change and correction of the CRF (copy or electronic copy) containing the audit trail. Also, the investigator should store the essential documents for 5 years after completion of the study. However, when the representative investigator and Takeda require a longer storage period, the investigator will discuss the period and methods of storage with the representative investigator and Takeda.

Further, the investigator will store the essential documents until the representative investigator or Takeda notifies that storage is no longer necessary.

13.0 STATISTICAL ANALYSIS METHODS

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

13.1 Statistical and analytical plans

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

Data review should be performed before data fixation. Data review is performed to evaluate the accuracy and completeness of the study data, patient 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 the main efficacy analysis set, and is defined as "randomized patients who received at least one dose of protocol treatment and satisfied main enrollment criteria." Detailed definition of analysis sets is separately specified in the SAP.

The analysis personnel should finalize the definition of analysis sets and appropriateness of analytical handling rules of the participant data in the analysis sets before data fixation, in discussion with the statistics representative.

13.1.2 Analysis of demographic and other baseline characteristics

Descriptive summary should be provided for demographic and other baseline characteristics for each treatment group for all and for left-sided sites.

13.1.3 Efficacy analysis

13.1.3.1 Primary endpoint and analysis method

[Primary endpoint]

Overall survival (OS)

OS is the period from the day of randomization (day 1) until death by all causes. For surviving patients, the period is terminated on the final day of confirming survival or data cut-off date, whichever occurs earlier.

[Main analysis]

The following analysis will be performed using the full analysis set.
For the OS concerning left-sided sites, a stratified log-rank test will be performed with stratification according to allocation factors other than study site. The significance levels used for this analysis are described in Section "13.1.3.5 Level of significance, confidence coefficient."

Show the survival curve by the Kaplan-Meier method until occurrence of an event for each group and calculate the quantile of survival period, point estimation of survival rate at a given time point and its confidence interval, and the confidence interval corresponding to the level of significance at the time of analysis for each treatment group. For reference, the 95% confidence interval (two-sided) will be calculated.

Also, calculate the intergroup HR and its confidence interval (two-sided) with a stratified Cox model with allocation factors other than sites as the stratum, and the confidence interval corresponding to the level of significance at the time of analysis. For reference, the 95% confidence interval (two-sided) will also be calculated and the log-rank test and Cox model calculation without stratification will also be conducted.

This analysis will use a hierarchical testing procedure in which only if the analysis for left-sided sites shows a significant intergroup difference, the same analysis for all sites will be performed. Thus, if the analysis for left-sided sites shows a significant intergroup difference, then the same analysis for all sites will be performed.

[Adjustment by covariate]

For the full analysis set, if deviation is observed in an important covariate, apply the Cox model and adjust confounding element and calculate HR and 95% confidence interval (two-sided) between treatment groups.

13.1.3.2 Secondary endpoints and analysis method

[Secondary endpoints]

Progression-free survival (PFS)
PFS is the period from the day of randomization (day 1) until the day of documented PD or the day of death due to all causes, whichever comes earlier. For surviving patients without documented PD, the period will be cut off on the final day when no progression is confirmed

(final day of confirming PFS). Confirmation of progression-free status by imaging test or sample test is not mandatory, and clinical confirmation by outpatient medical examination, etc., will be allowed. Contact only by telephone will not be allowed. If information on aggression and progression-free status is received from medical institutions to which the patient is transferred or referred, a medical examination information form stating rationale for diagnosis must be obtained and retained. In this case also, contact only by telephone will not be allowed. For surviving patients without documented PD for whom curative resection is indicated during protocol treatment, the period will be cut off on the final day when specified preoperative diagnostic imaging reveals no PD (final day of confirming PFS).

[Analysis method]

The analyses below will be performed in patients with evaluable lesion in the full analysis set of all and of left-sided sites.

Show the survival curve up to the onset of an event by Kaplan-Meier method by treatment group, and calculate point estimation of survival rate and its 95% confidence interval (two-sided) by treatment group at quantile of survival period and the specified time point. The stratified log-rank test will be applied to the analysis with allocation factors other than study sites as the stratum, and the intergroup HR and its 95% confidence interval (two-sided) will be calculated with the stratified Cox model with allocation factors other than study sites as the stratum. For reference, the log-rank test and the Cox model calculation without stratification will also be conducted.

- Response rate (RR)
  Percentage of patients whose best overall response is either CR or PR

  [Analysis method]

  For patients with evaluable lesion in the full analysis set, perform frequency tabulation in each treatment group for all and for left-sided sites, respectively, to calculate the point estimation value and 95% confidence interval (two-sided). Apply the Cochran-Mantel-Haenszel test by using the allocation factors other than study sites as a stratum and calculate the point estimation value of intergroup difference (mFOLFOX6 + panitumumab group minus the mFOLFOX6 + bevacizumab group) and its 95% confidence interval (two-sided).

- Duration of response (DOR)
  DOR is the period from the day when either CR or PR is first confirmed until the day of documented PD or the day of death due to all causes, whichever occurs earlier. For surviving patients without documented PD, the period will be cut off on the final day when specified diagnostic imaging reveals no PD (final day of confirming PFS). For surviving patients without documented PD for whom curative resection is indicated during protocol treatment, the period

will be cut off on the final day when specified preoperative diagnostic imaging reveals no PD (final day of confirming PFS).

[Analysis method]

Show the Kaplan-Meier survival curve until the onset of event by treatment group for the patients who showed response among the full analysis set of all and of left-sided sites, respectively, and calculate the point estimation value of survival rate and its 95% confidence interval (two-sided) for each treatment group at the quantile of survival period and specified time points.

- Percentage of curative resection
  Percentage of patients treated with curative resection (complete resection: R0 resection)

  [Analysis method]

  Perform frequency tabulation for each group in the full analysis set to calculate the point estimation value and 95% confidence interval (two-sided) of all and of left-sided sites, and calculate the point estimation value and 95% confidence interval (two-sided) of intergroup difference (mFOLFOX6 + panitumumab group minus the mFOLFOX6 + bevacizumab group).

13.1.3.3 Exploratory endpoints

[redacted]

13.1.3.4 Data conversion method and handling of missing data

Details are separately determined in the SAP.

13.1.3.5 Level of significance, confidence coefficient

Primary endpoint:

- Level of significance:

  2.101% (two-sided 4.202%) for left-sided sites

  2.5% (two-sided 5.0%) for all sites

- Confidence coefficient:

  95.798% (two-sided) for left-sided sites*

  95% (two-sided) for all sites*

*; Errors were found at the time of finalization of the statistical analysis plan and were corrected at the time of revision to the clinical study protocol (5th edition)

Secondary endpoints and other efficacy endpoints:

The significance level is not determined. Refer to the significance level: 5% (two-sided).

13.1.4 Subgroup Analyses

[redacted]

13.1.5 Safety analysis

Perform the following analyses in the safety population.

13.1.5.1 Treatment-emergent adverse events

Treatment-emergent adverse events (TEAEs) are adverse events that developed during the protocol treatment period after initiation of protocol treatment.

Perform the following TEAE analyses for each treatment group. Code TEAEs with MedDRA and summarize by preferred term and system organ class (SOC).

- Frequency tabulation of all TEAEs
- Frequency tabulation of TEAEs for which the causal relationship with protocol treatment was "related"
- Frequency tabulation of all TEAEs by severity
- Frequency tabulation of TEAEs by severity for which the causal relationship with protocol treatment was "related"
- Frequency tabulation of TEAEs for which action taken for protocol treatment was "discontinuation"
- Frequency tabulation of serious TEAEs

13.2 Criteria for interim analysis and premature discontinuation

The purpose of interim analysis is to determine whether or not to continue the prespecified follow-up period of mFOLFOX6 + panitumumab combination therapy in a comprehensive manner in terms of efficacy and safety as compared with mFOLFOX6 + bevacizumab combination therapy. In relation to the number of events observed, interim analysis during enrollment period will not be conducted.

One interim analysis is planned for OS in this study to evaluate the efficacy for all and left-sided sites, respectively, when approximately 70% of the overall targeted number of events are observed (399 events are expected for all sites and 280 events are expected for left-sided sites).

To maintain the type 1 error of the entire study within 2.5%, significance level of interim and final analyses will be calculated by using O'Brien-Fleming type alpha-spending function, and a significance level of 1.25% will be used for both all and left-sided sites.

The analysis personnel will prepare an interim analysis plan that determines details of interim analysis prior to interim analysis.

13.3 Determination of the planned number of participants

See Section "6.2.2.2 Rationale for planned number of patients."

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring of study sites

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

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

14.1.1 Central monitoring

Central monitoring will be performed to check that the study is safely conducted in accordance with the protocol and that data are accurately collected on the basis of the data collected by EDC. The results of central monitoring will be evaluated by the research steering committee and feedback will be given to study sites as necessary.

Detailed procedures for central monitoring will be determined in the separately prepared procedures.

14.1.2 Site visit monitoring

Site visit monitoring is conducted to confirm that the study is carried out safely and in compliance with the protocol, and the data are accurately collected by checking the data entered into the EDC against source documents. Source documents are the original documents, data, and records. The investigator and the supervisor at the study site will ensure that the monitor and the Certified Review Board have access to the source documents.

The monitor will access the records, including the list of patient screenings, medical records, and signed and dated original consent forms, to confirm that this study is appropriately conducted in compliance with the protocol and to confirm consistency between the CRF and the related source documents. The investigator, the subinvestigator, and other personnel involved in the study will ensure sufficient time to facilitate monitoring procedures during visits to the study site.

Prior to site visit monitoring, study sites are randomly selected to perform source document verification for the enrolled patients.

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

14.1.3 Deviations from the Clinical Research Act, ICH-GCP, and protocol (non-compliance)

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

When acknowledging that the Clinical Research Act, ICH-GCP, and protocol are not met (hereinafter referred to as "non-compliance"), the investigator or subinvestigator should immediately report it to the supervisor at the study site and notify the research secretariat office. They should provide information on non-compliance to the investigator at each study site and the supervisor at the study site through the research secretariat office.

The representative investigator receiving a report from the research secretariat office will hear the opinions of the Certified Review Board according to the Clinical Research Act when he/she determines it to be serious non-compliance.

14.2 Quality assurance

The auditor and the Certified Review Board will audit the study site when necessary. In such a case, the auditor designated by the representative investigator and Takeda should contact the study site in advance to determine the date of the audit. The auditor may request a visit to other sites that will be used during the study. The investigator and the supervisor at the study site should ensure that the auditor has access to study-related source documents.

15.0 ETHICAL CONDUCT OF CLINICAL STUDY

This study will be conducted with the highest respect for the individual participants (i.e., patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the Clinical Research Act, and the ICH-GCP. The investigator at each site will conduct this study according to the regulatory requirements [redacted]

15.1 Application to the Certified Review Board

Through the conduct of this clinical study, approval by the Certified Review Board and permission for the conduct of the study by the supervisor in each study site should be obtained according to the clinical study protocol and using the written information for patients.

15.2 Conflict of interests

This study will be conducted with support from a sponsor.

Prior to conduct of the study, the investigator should appropriately manage, according to the Clinical Research Act, that this study has no conflict of interests (hereinafter referred to as COI) in companies involved in protocol treatment.

15.3 Written information and patient's consent

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

1. Clinical study and ICF
2. Disease and medical condition
3. Method of treatment for disease
4. Name of study and explanation that approval has been obtained from the director of study site for conducting the study

5. Name of research steering committee chairman, study site, and investigator
6. Objective of study and meaning
7. Method of study (including purpose of use of samples/information collected from patient) and study duration
8. The estimated number of patients participating in the study
9. The reason for being selected as participant
10. Burden for the patient and foreseeable risk and benefits
11. Consent for participation
12. Even if consent for carrying out or continuing the study has been given, this can be withdrawn at any time
13. Explanation that the patient can disagree on or withdraw consent for carrying out or continuing the study without loss of benefits
14. Method of information disclosure
15. Explanation that, upon request, the patient can obtain and have access to material concerning protocol and method of study and on the method of obtainment and access within the scope where protection of personal information of other patients and the assurance of originality of the study is not hindered
16. Handling of personal information (including method of anonymity)
17. Method of storage and destruction of sample/information
18. Status related to funding of study, etc.; study site–related conflict of interest and personal benefits related to the study, etc.; and study staff–related conflict of interest
19. Intellectual property rights
20. Possibility that the data will be used for future studies
21. Correspondence to inquiries from patients and persons concerned
22. Expenses
23. Items on other methods of treatment
24. Correspondence to health care provided after study has been conducted
25. Compensation for injuries related to the study and what injuries are covered
26. Issues to be followed
27. Notification of new information and study discontinuation
28. Explanation that participant's privacy will be preserved and monitoring personnel, audit personnel, and ethics review committee members will only have access to information or samples related to participants within the scope of necessity
29. Explanation that informed consent cannot be obtained from anyone but the patient

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

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

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

The investigator or the subinvestigator should store the original consent form that was signed or contains name/affixed seal. The investigator or the subinvestigator should document in the patient's medical record the date when the patient signed or wrote name/affixed seal on the consent form. A copy of the consent form with signature or name typed with seal affixed should be provided to the patient.

If the ICF is revised, the investigator or the subinvestigator should repeat the same procedures taken for obtaining the initial consent. The date of obtaining new consent should be recorded in the patient's medical record, and a copy of the revised consent form should be provided to the patient.

15.4 Patient confidentiality

The person engaged in this clinical study or the person who has been engaged in this clinical study should comply with the principles of protection of the patient's right against invasion of privacy. The participant ID code in this study is used to connect the clinical study database and related study documents of Takeda with the source data of patients. The limited information of patients such as sex, age, and date of birth may be used within the scope of all applicable laws and regulations for identification of patients and confirmation of accuracy of participant ID code.

In compliance with the Clinical Research Act and the ICH-GCP, the investigator should provide monitoring and audit personnel with 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 the monitor, auditor, and the Certified Review Board. The investigator or the subinvestigator should obtain approval from patient concerning access to the original medical records by a monitor when obtaining consent from a patient (see Section 15.3).

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

15.5 Contacts for inquiries from patients and concerned people

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

15.6 Advantages and disadvantages to participants

15.6.1 Advantage to participants

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

15.6.2 Disadvantage to participants

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

15.7 Attribution of study results and access rights

15.7.1 Attribution of study results

The study results and data obtained from this study belong to Takeda. The intellectual property rights regarding the pharmaceutical products manufactured and/or distributed by Takeda also belong to Takeda. Data generated from this study may be made available for secondary use (e.g.,

meta-analysis) without any link to personally identifying information, only after discussion among and approval by the person presiding over the study, the research representative, and the research steering committee.

15.7.2 Data access rights

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

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

15.8.1 Reporting of results, publication, and disclosure

The investigator should report to the supervisor of the study site a written summary of results of this study, and provide Takeda with all the results and data obtained from this study. Only Takeda may disclose the study information to other investigators or subinvestigators during the study period except for a case required by laws and regulations.

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

Takeda may publish the data and information obtained from this study (including the data and information provided by the investigator) on the basis of the agreement with the personnel presiding over the study and the representative investigator.

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

Takeda should report to the supervisor of the study site that final publication of the study result has been made.

15.8.2 Clinical study registration

The representative investigator and Takeda will ensure timely publication of information about the clinical study and registration of all clinical research in patients under way all over the world, at least to the ClinicalTrials.gov and public website (JAPIC) to comply with the applicable laws/regulations and guidelines. The city and country where a study is performed and the patient

recruitment status should be registered, as well as the contact information of Takeda, to enable general access.

The representative investigator will perform registration in the database established by the Ministry of Health, Labour and Welfare (jRCT: Japan Registry of Clinical Trials) according to the Clinical Research Act after approval by the Certified Review Board.

15.8.3 Clinical trial results disclosure

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

The representative investigator will perform registration in the database established by the Ministry of Health, Labour and Welfare (jRCT: Japan Registry of Clinical Trials) according to the Clinical Research Act after reporting to the Certified Review Board.

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

The investigator should appropriately retain the material/information related to this study for at least 5 years from completion of the study.

15.9 Insurance and compensation for injury

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

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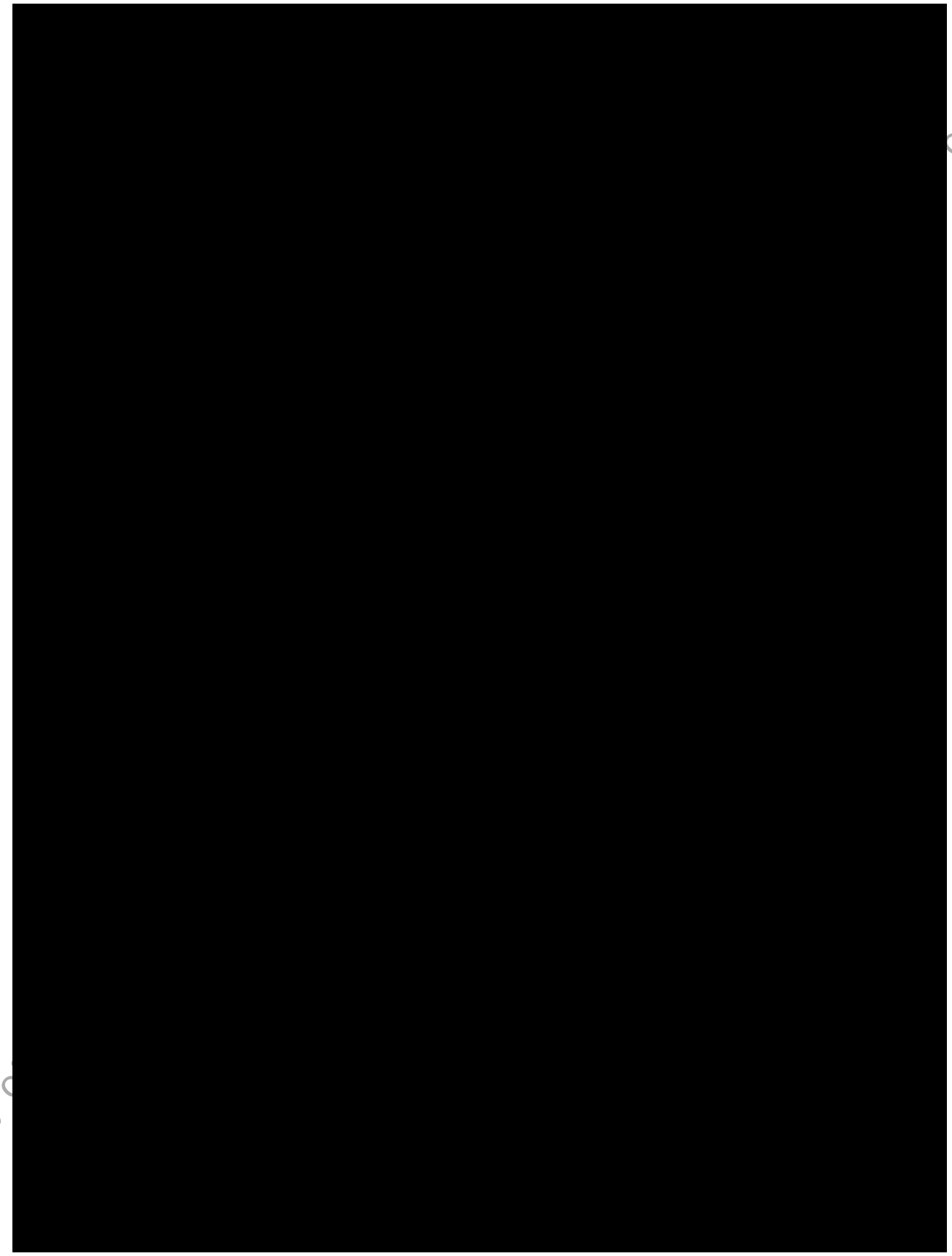

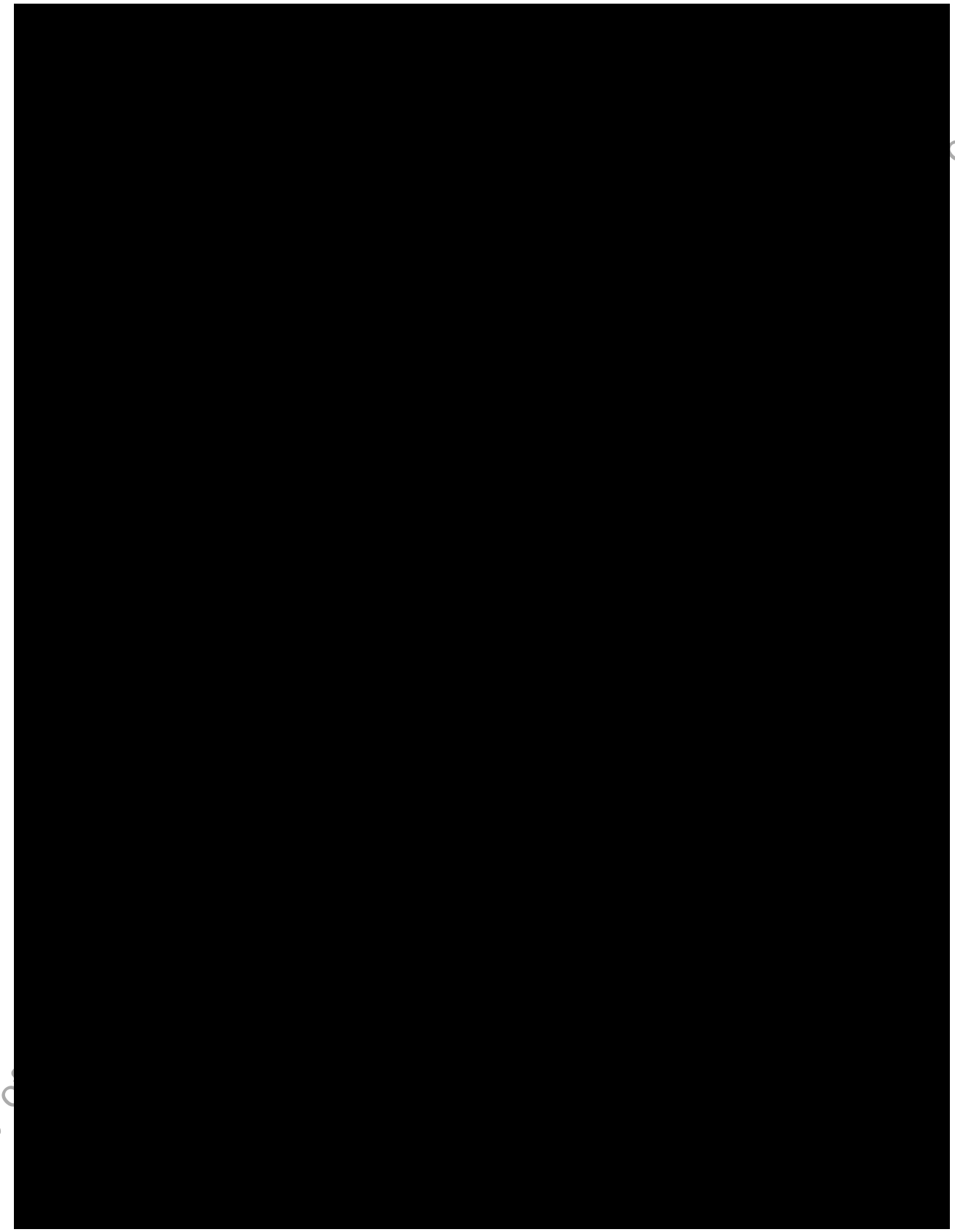

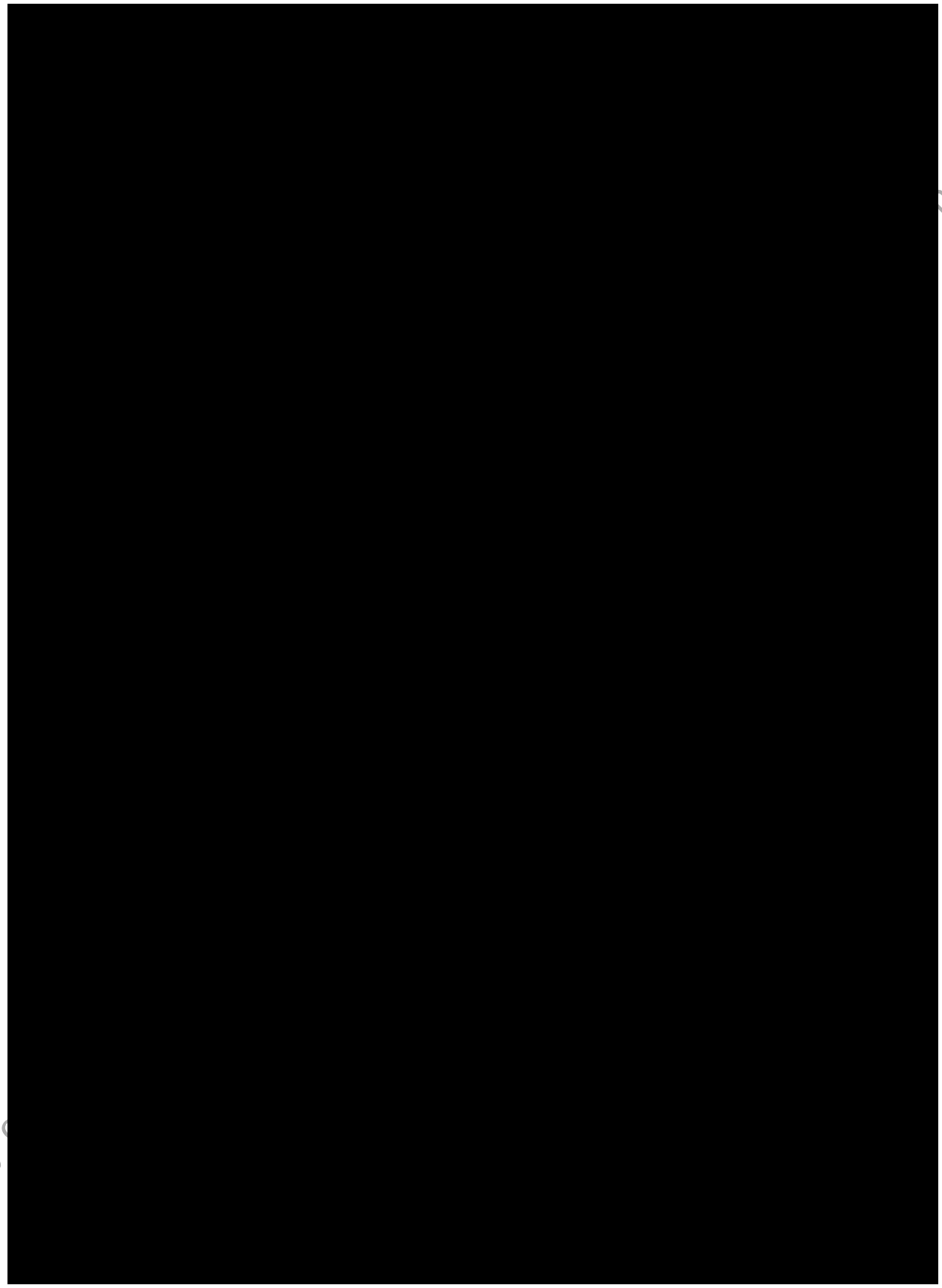

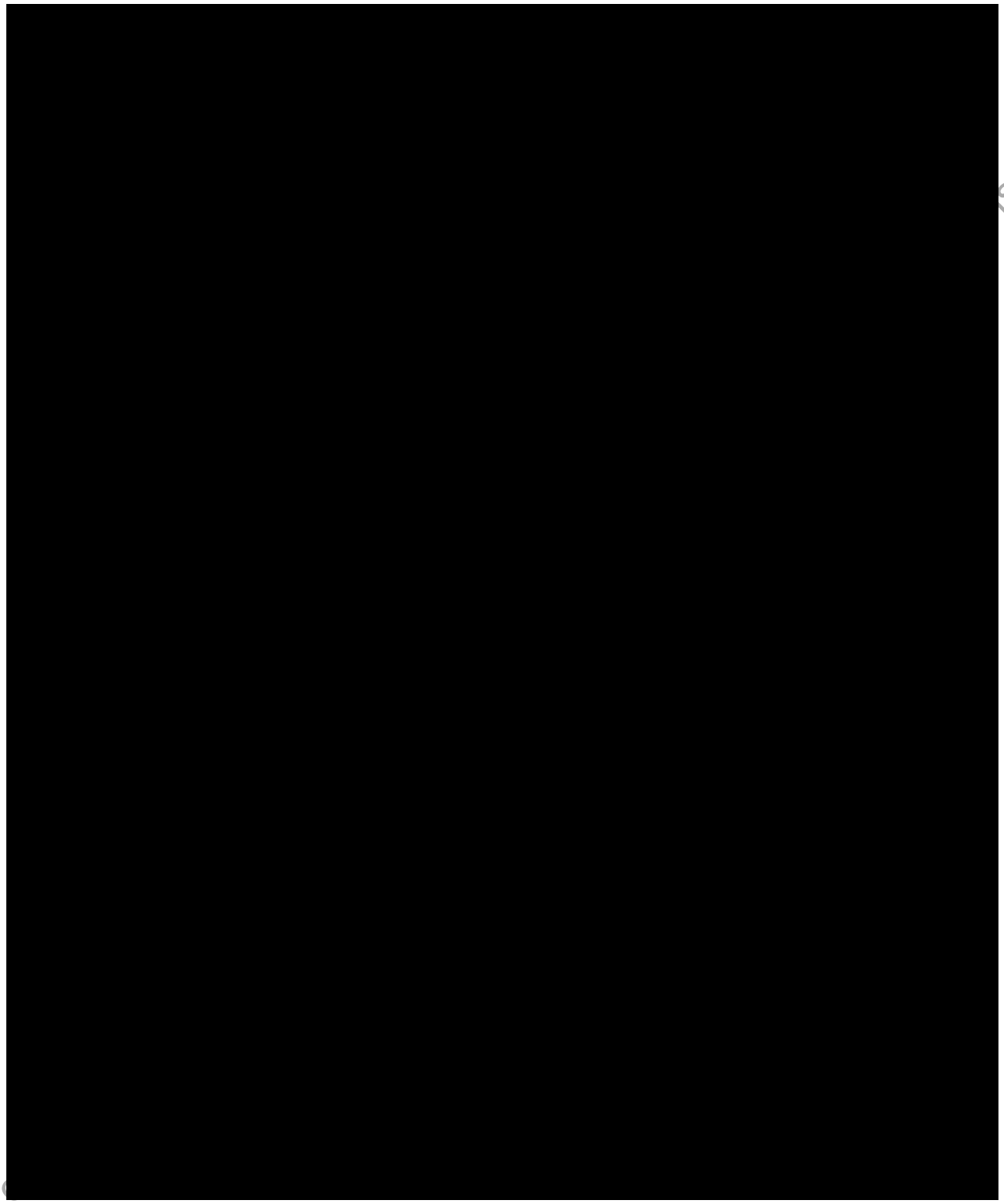

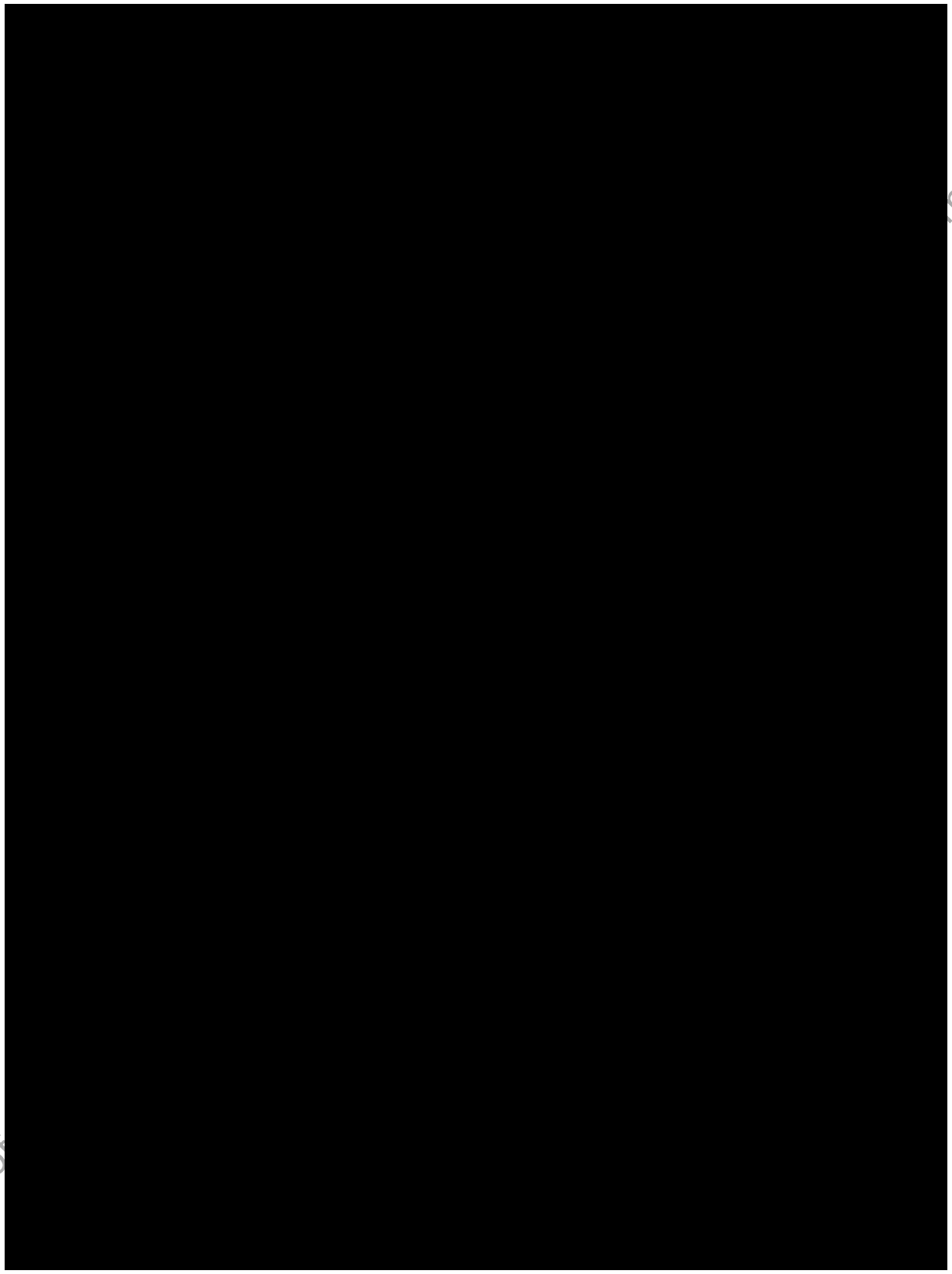

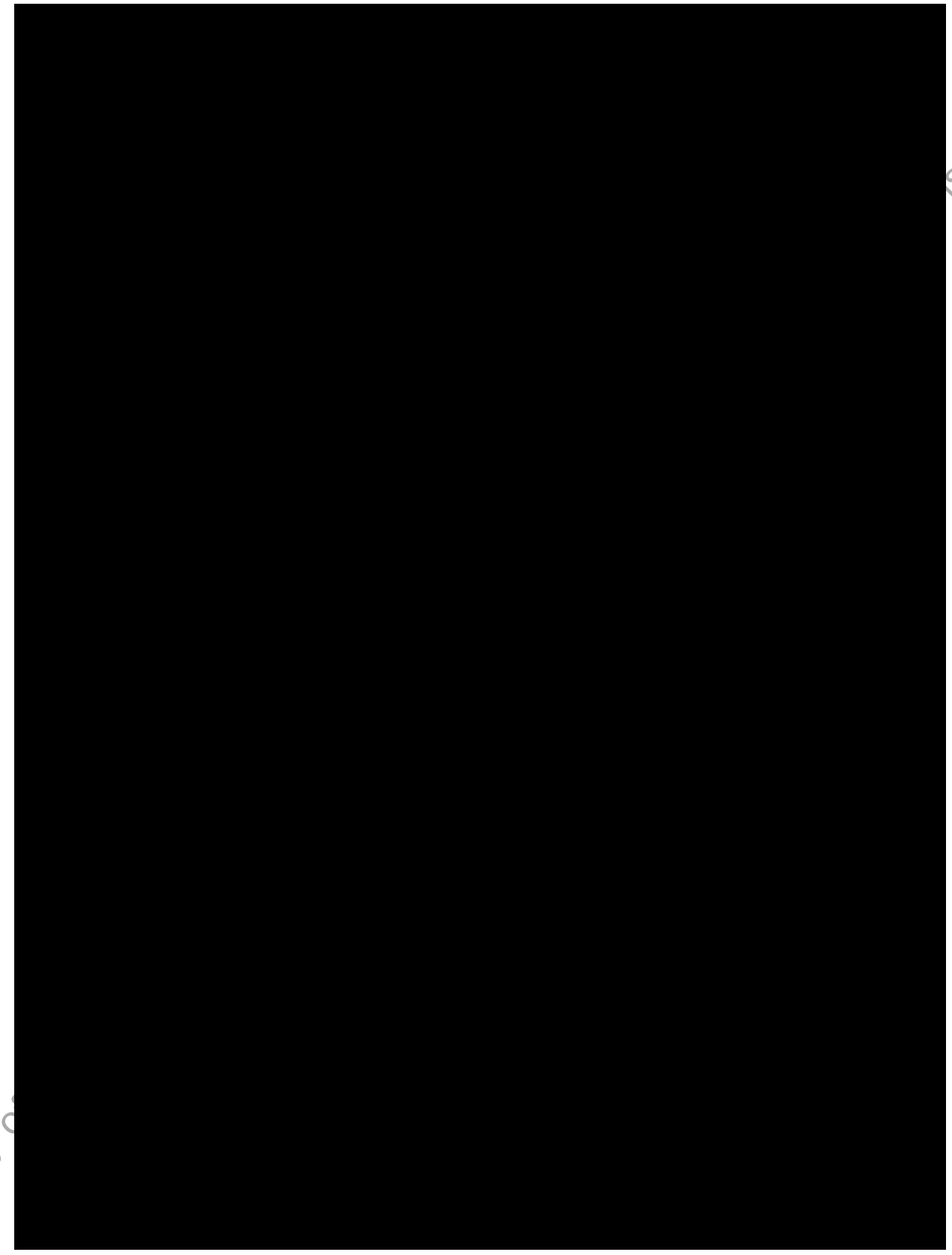

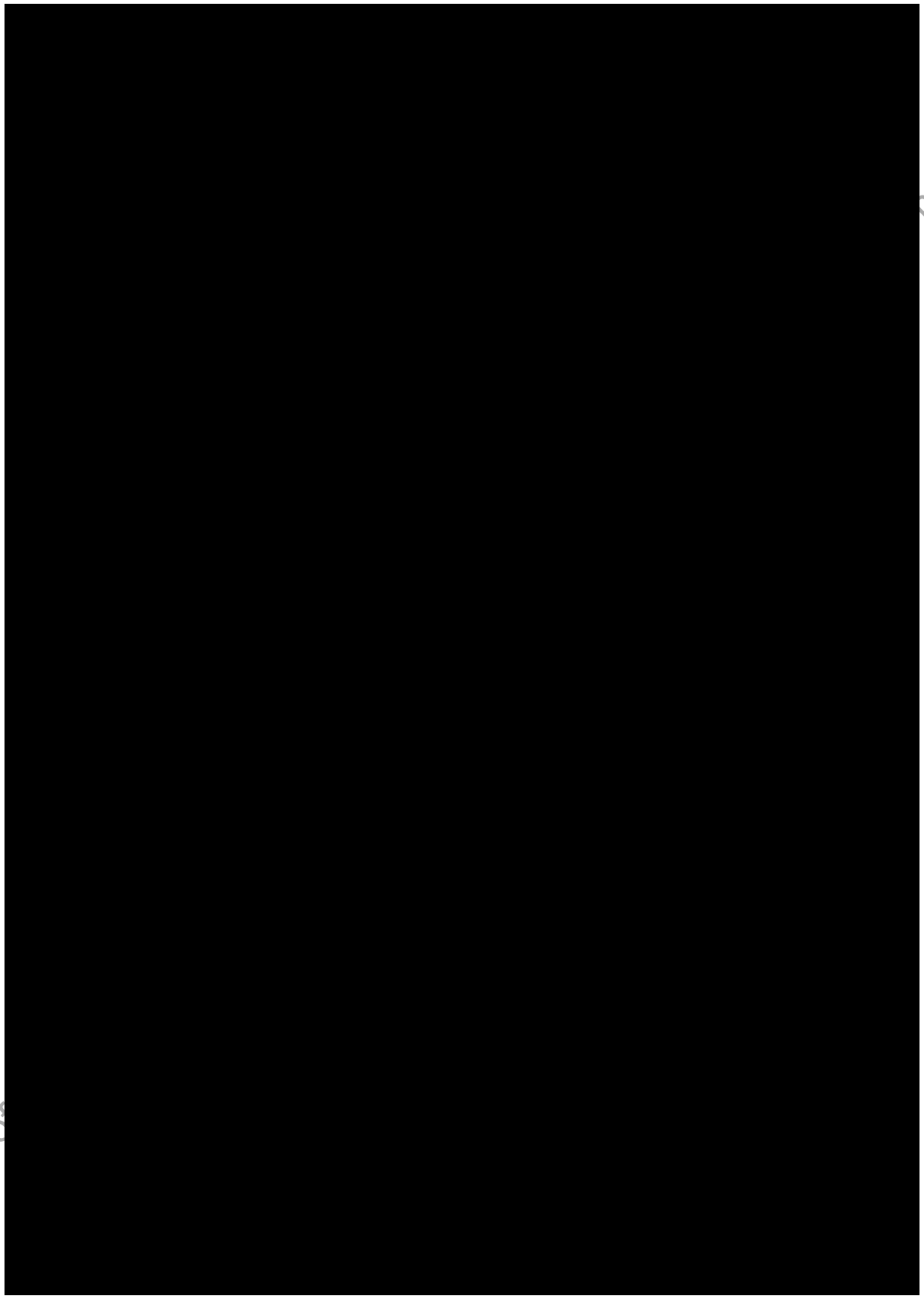

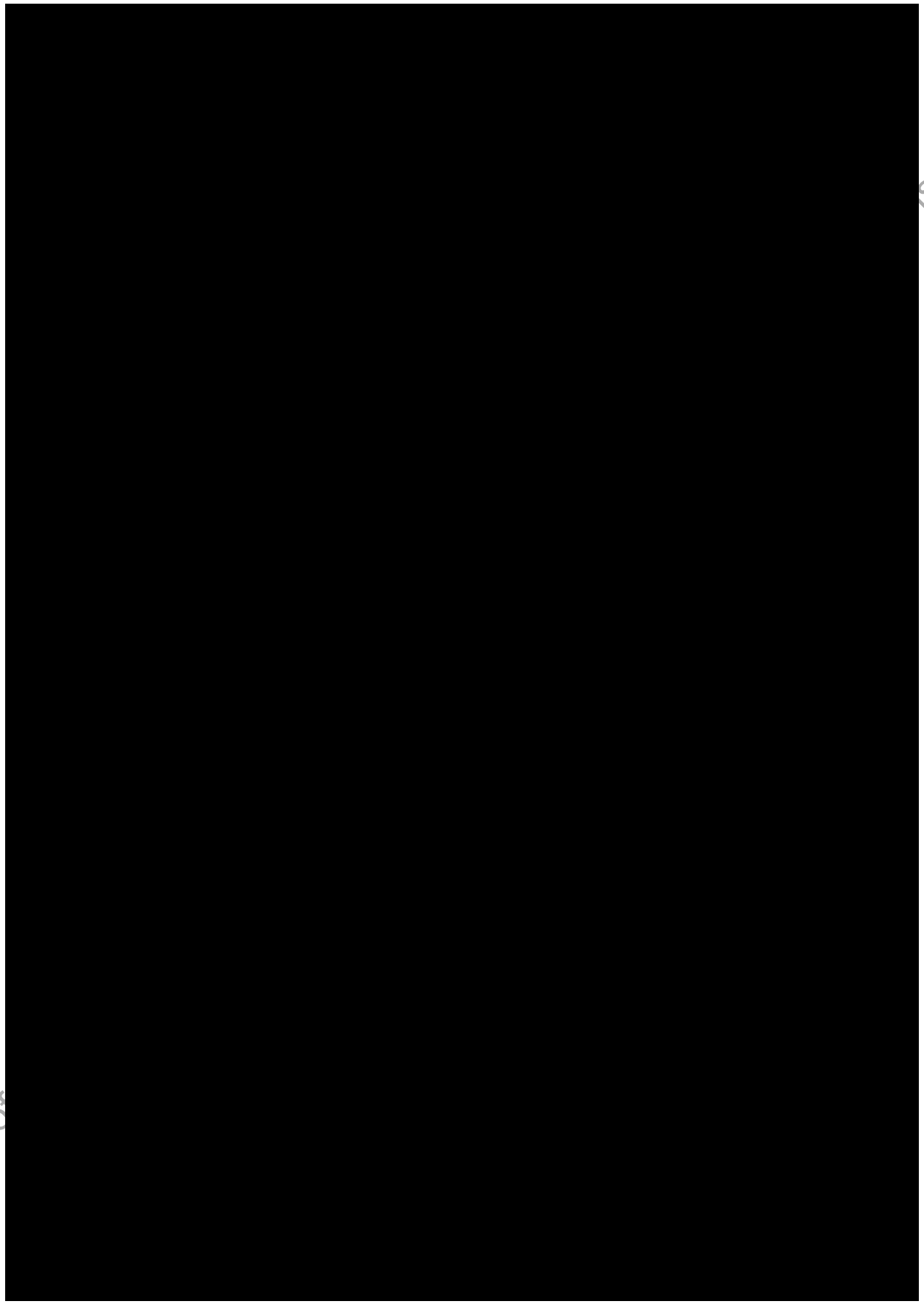

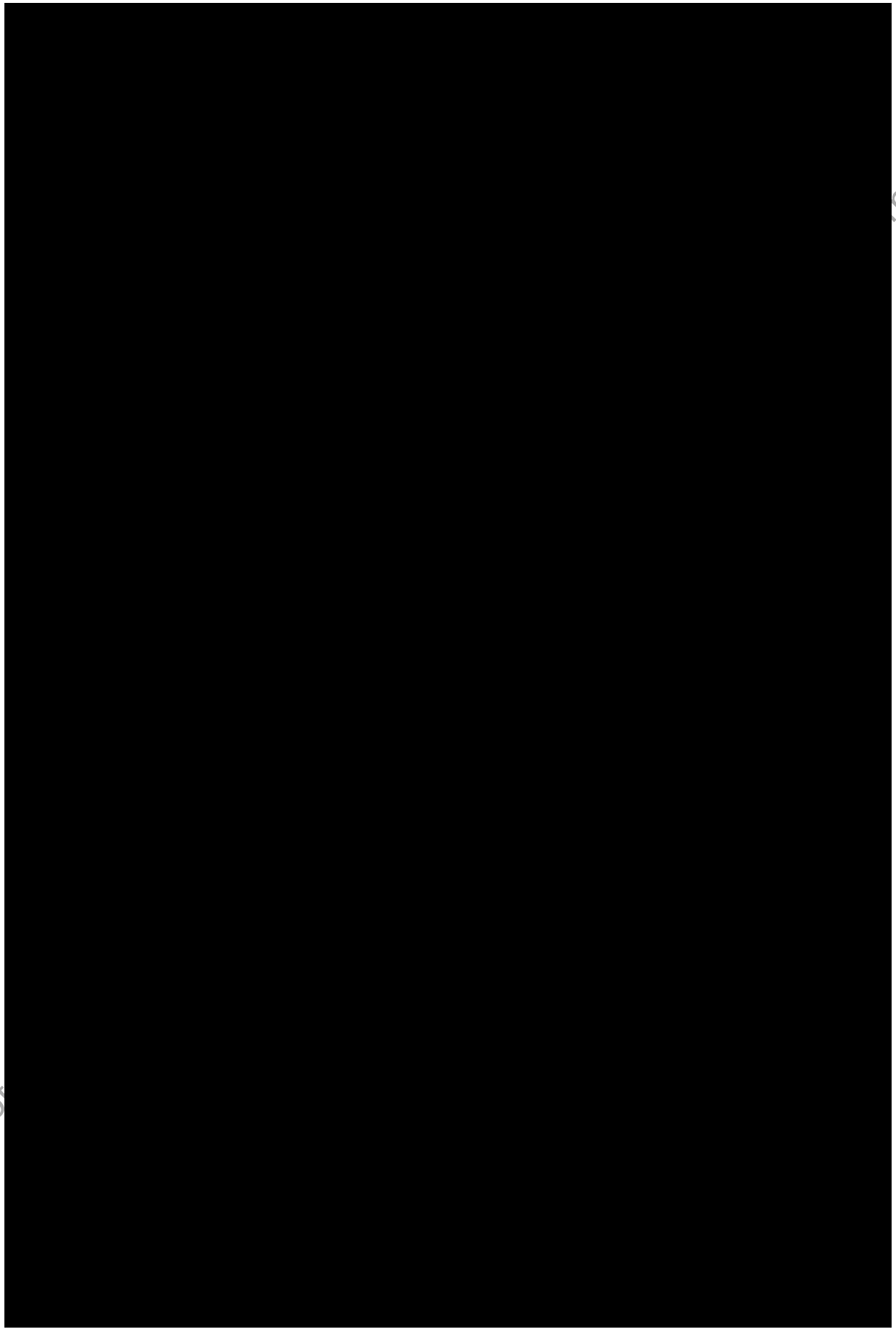

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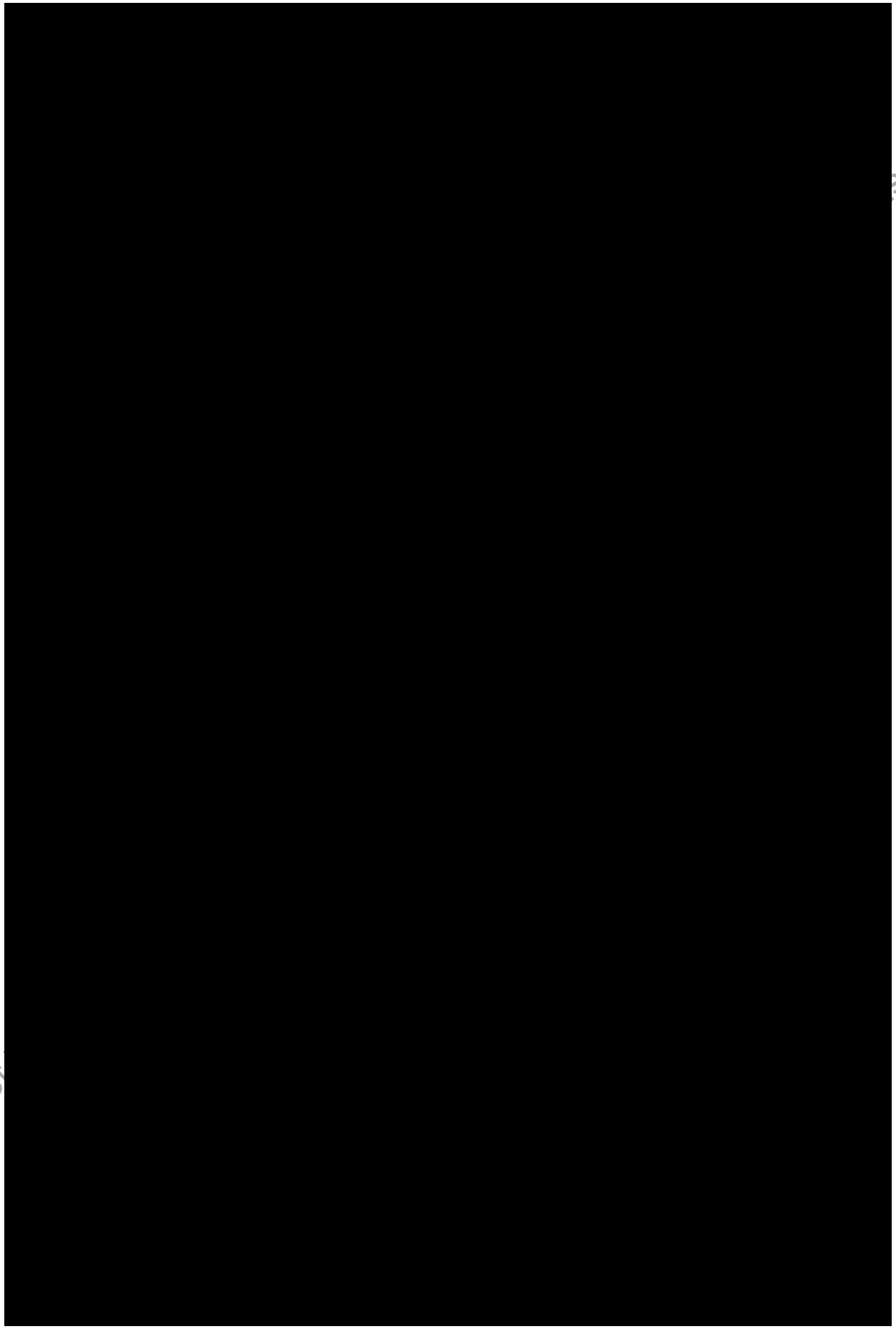

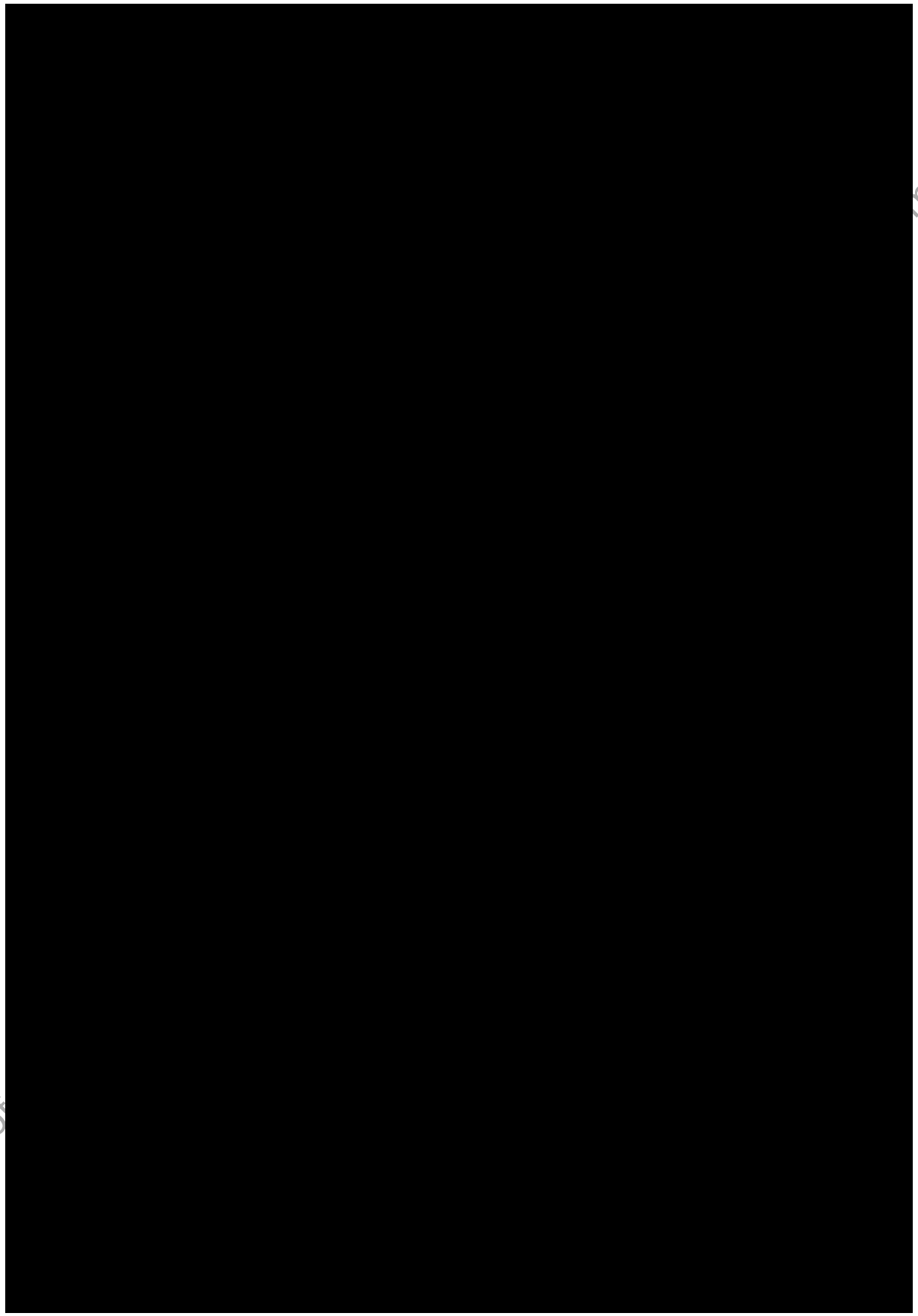

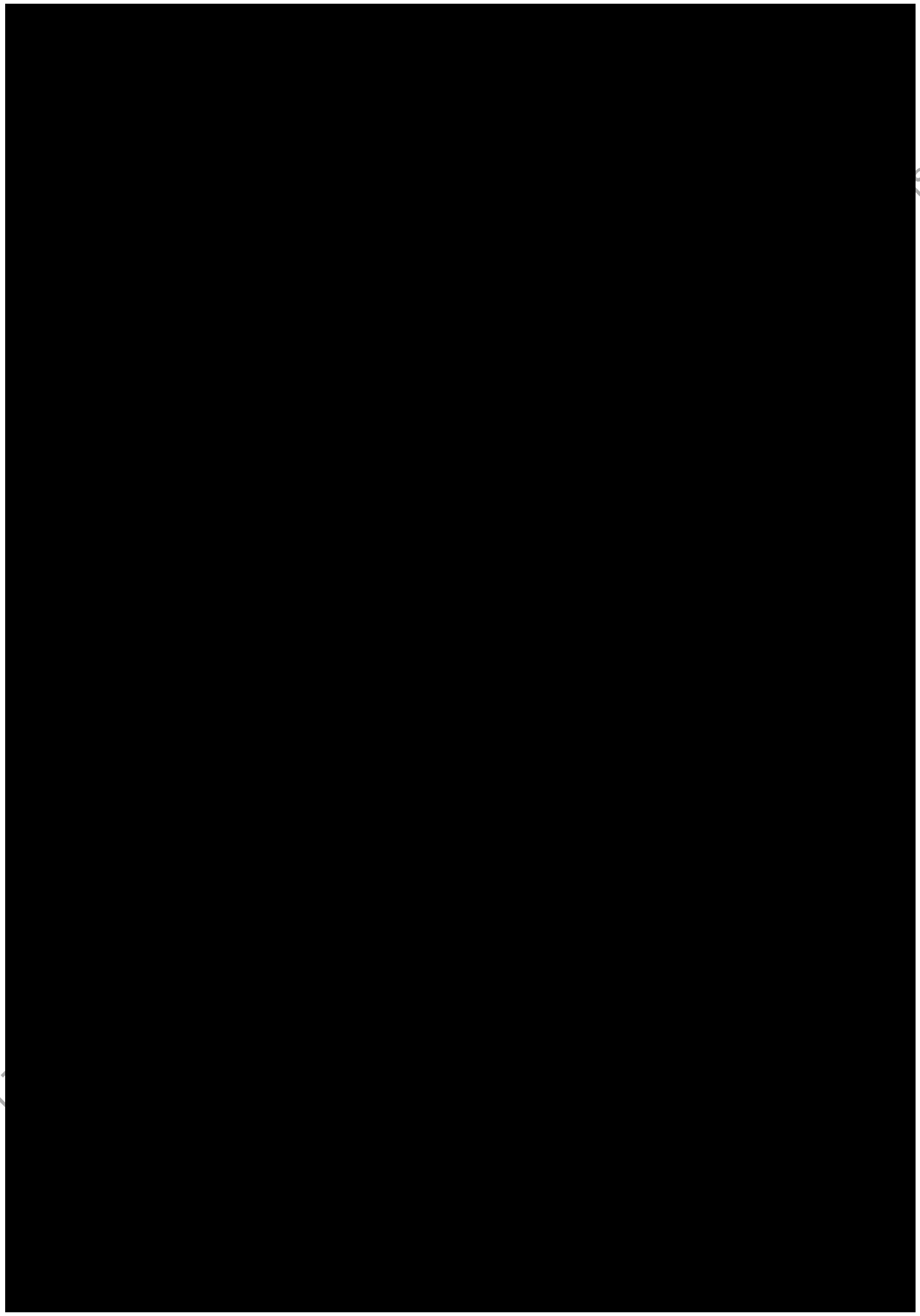

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