A Randomized, Double-Blind, Phase III Study Comparing FTD/TPI Therapy versus Placebo in Patients Who Are Positive for Blood Circulating Tumor DNA after Curative Resection of Colorectal Cancer

ALTAIR study

Initial **a**ttack on **l**atent metastasis using **TA**S-102 for circulating tumor DNA **i**dentified colorectal cancer patients after curative **r**esection

(Protocol No.: EPOC 1905)

Statistical Analysis Plan

Version 1.20

Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East
Representative of the coordinating Investigators

Signature:
Date of approval:

Department of Data Science,
National Cancer Center Hospital East
Person responsible for statistical analysis

Signature:
Date of approval:

EPS Corporation
Person in charge of and responsible for statistical analysis

Signature:
Date of approval:

Revision History

Version No.	Date of preparation	Author	Content of revision
1.00	March 30, 2021	Yuko Yamamoto	First version
1.10	June 17, 2024	Shinnosuke Miyata	• Changes of the representative of coordinating investigators, person responsible for statistical analysis, and person in charge of and responsible for statistical analysis • Overall description adjustment • 4.1. Imputation for Missing Data (addition of detailed description) • 4.2. Handling of Endpoints (addition of the last date of confirmation of survival and the last date of imaging test, addition of detailed description or correction of disease-free survival 1 (DFS1), disease-free survival 2 (DFS2), overall survival, and EORTC QLQ-C30) • 4.4. Handling of Timing (addition of detailed description and correction) • 5.1. Calculation of Summary Statistics (addition of statistics) • 5.3. Software to Be Used for Statistical Analysis (addition of detailed description) • 5.4. Special Notes on Test and Estimation Methods (addition of detailed description and addition of sample SAS code) • Addition of the section, "7. Blinded Review" * Section number + 1 from version 1.00 onward due to the addition • 9.1. Patient Background (addition of items related to allocation factors, baseline, and subgroup analysis, correction of existing items, etc.) • Addition of the section, "9.3. Treatment Summary" • 10.1. Primary Endpoint: Disease-free Survival 1 (addition of detailed description, stratification factors, and sensitivity analysis) • 10.2.1. Rate of Conversion to Negative ctDNA (addition of detailed description and addition of sensitivity analysis) • 10.2.2. Disease-free Survival 2 (addition of detailed description and stratification factors) • 10.2.3. Overall Survival (addition of detailed description, stratification factors, and median observation period) • 10.2.4. Treatment Completion Rate (addition of test name) • 10.2.5. QOL (simplification and correction of description) • Addition of the section, "10.2.6. Time to Conversion to Negative ctDNA" • Addition of the section, "10.3.1. Subgroup Analysis (forest plot)" • 10.3.2. Disease-free Survival 1 (addition of detailed description) • 10.3.3. Rate of Conversion to Negative ctDNA (addition of detailed description) • 10.3.4. Disease-free Survival 2 (addition of detailed description)

			• 10.3.5. Overall Survival (addition of detailed description) • Addition of the section, "11.1. Adverse Events" (detailed description added by dividing it into "11.1.1. Summary of Incidence" and "11.1.2. Incidence of Adverse Events by SOC/PT") • Addition of the section, "11.1.3. Incidence of Adverse Events by Risk" • Addition of the section, "11.1.4 Summary Table of All Deaths by Cause" • Addition of the section, "11.1.5. Subgroup Analysis (incidence of adverse events)" • Addition of the section, "11.1.6. Tabulation of Adverse Events with 10% or Higher Incidence" • Addition of the section, "11.1.7. Tabulation of Adverse Events with 5% or Greater Difference in Incidence among Intrinsic Factors" • Addition of the sections, "11.2.3.1. to 11.2.3.4." (summary statistics of hematology, tabulation by grade, transition charts, etc.) • Addition of the sections, "11.2.4.1. to 11.2.4.4." (summary statistics of biochemistry, tabulation by grade, transition charts, etc.) • Addition of the sections, "11.2.5.1. to 11.2.5.3." (summary statistics of biochemistry, tabulation by grade, etc.) • 12. Appendix (addition of lists and addition of detailed description) • 13. Reference List (addition of detailed description)
1.20	July 1, 2024	Shinnosuke Miyata	• 4.2. Handling of Endpoints (addition of detailed description and correction, “The final handling of events/censors will be discussed and decided in clinical conferences.”, of disease-free survival 1 (DFS1), disease-free survival 2 (DFS2), and overall survival) • 4.4. Handling of Timing (addition of detailed description and correction, "The final handling will be discussed and decided in clinical conferences.", of QOL, vital signs, performance status, and clinical findings) • 10.1. Primary Endpoint: Disease-free Survival 1 (correction of description of stratified analysis and stratification factors, based on the result of blinded review) • 10.2.2. Disease-free Survival 2 (correction of description of stratified analysis and stratification factors, based on the result of blinded review) • 10.2.3. Overall Survival (correction of description of stratified analysis and stratification factors, based on the result of blinded review) • 10.2.6. Time to Conversion to Negative ctDNA (addition of description, “The final handling of events/censors will be discussed and decided in clinical conferences.”)

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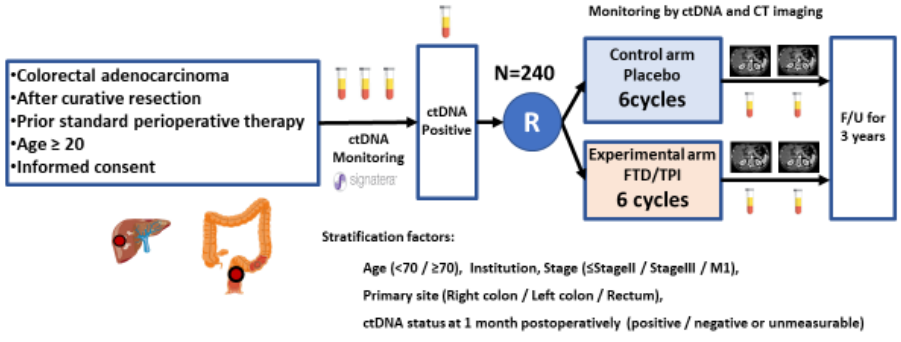
1. Objective

The objective of this protocol, "A Randomized, Double-Blind, Phase III Study Comparing FTD/TPI Therapy versus Placebo in Patients Who Are Positive for Blood Circulating Tumor DNA after Curative Resection of Colorectal Cancer Statistical Analysis Plan" (hereinafter referred to as "analysis plan") is to describe the details of statistical analysis in "a randomized, double-blind, Phase III study comparing FTD/TPI therapy versus placebo in patients who are positive for blood circulating tumor DNA after curative resection of colorectal cancer" (hereinafter referred to as "this study").

2. Outline of the Protocol

<table>
<tr><td>Objective</td><td>The study will be conducted in patients who underwent curative resection of colorectal cancer and then tested positive in monitoring using Signatera™, a system by Natera, Inc. for detecting blood circulating tumor DNA (ctDNA) for the detection of residual tumor, with no apparent relapse on imaging. The objective of the study is to verify the efficacy and safety of preemptive treatment with trifluridine/tipiracil hydrochloride (FTD/TPI) compared with followup, which is the standard of care.

Primary endpoint:
• Disease-free survival 1[*1][*3] (DFS1)
[*1] In this study, a DFS1 event is defined as a relapse, development of a secondary large intestine carcinoma lesion other than a relapse (an intramucosal cancer lesion will not be treated as an event), and death.

Secondary endpoints:
• Rate of conversion to negative ctDNA
• Disease-free survival 2[*2][*3] (DFS2)
• Overall survival[*3] (OS)
• Incidence of adverse events
• Treatment completion rate
• QOL
[*2] In this study, a DFS2 event is defined as a relapse, development of a cancer lesion other than a relapse (secondary cancer), and death.
[*3] After the end of the study period, subjects will be followed up for 5 years in a separate observational study.</td></tr>
<tr><td>Study schema</td><td> 
</td></tr>
</table>

Study design	This study is a randomized, double-blind, multinational Phase III study to evaluate the efficacy and safety of preemptive treatment with FTD/TPI compared with administration of placebo as followup, which is the standard of care, in patients who underwent curative resection of colorectal cancer and then tested positive for ctDNA.
Target number of subjects, statistical analyses	Assuming that the median disease-free survival in the placebo group is 8 months, the hazard ratio in the study treatment group is 0.667, $\alpha = 0.05$ (one-sided 0.025), $1 - \beta = 0.80$, the enrollment period is 2 years, and the follow-up period is 1 year, the number of subjects required (number of events required) is calculated to be approximately 240 subjects (190 events). Depending on the subject accumulation status, increasing the target number of subjects will be considered to increase the power.
Administra-tion method	One course consists of 28 days, and FTD/TPI or placebo will be orally administered twice daily on Days 1 to 5 and Days 8 to 12. The administration will be repeated until completion of 6 courses or until any discontinuation criterion is met.
Planned study period	Planned enrollment period: From June 2020 to June 2023 (3 years) Planned observation period: A total of 1 year from the date of enrollment of the last subject Planned total study period: A total of 1.5 years from the date of enrollment of the last subject

3. Definition of Analysis Populations

Each analysis population is defined in the table below. Subject handling will be determined in accordance with the subject handling criteria prepared based on clinical conferences.

Abbreviation	Analysis Population	Definition
All enrolled subjects (ITT)	Intention to treat	Analysis population based on the intention to treat principle. This population is defined as the population obtained by excluding duplicate and erroneous enrollments from the subjects enrolled in this study.
FAS	Full Analysis Set	Analysis population that is close to the intention to treat principle as completely as possible. This population is defined as the population obtained by excluding subjects who meet any of the following criteria: • No study treatment has been administered at all. • Subjects who have been shown to be ineligible after enrollment and are judged to have a significant impact on the evaluation of the primary endpoint.
SP	Safety Analysis Population	Population consisting of enrolled subjects who have received study treatment at least once.

4. Data Handling

4.1. Imputation for Missing Data

For the conversion of the EORTC QLQ-C30 score, imputation will be performed based on the scoring manual. For other items, imputation of missing values and analysis considering outliers will not be performed.

4.2. Handling of Endpoints

1) Last date of confirmation of survival

The last date of confirmation of survival in the outcome survey will be adopted. However, if any of the dates in the table below is later than the last date of confirmation of survival in the outcome survey, the latest date will be adopted as the last date of confirmation of survival.

Observation/test item	Date
Tumor markers	Date of collection
ctDNA	Date of collection
Imaging test	Date of chest CT
	Date of abdominal CT
	Date of pelvic CT
	Date of MRI
	Other, test date 1
	Other, test date 2
Total colonoscopy	Date of total colonoscopy
Post-treatment	Start date of post-treatment (implementation date)

2) Last date of imaging test

The latest date among the dates of imaging tests listed in the above table for the last date of confirmation of survival (date of chest CT, date of abdominal CT, date of pelvic CT, date of MRI, other, test date 1, and other, test date 2) will be adopted as the last date of imaging test.

3) Disease-free survival 1 (DFS1)

The time from the date of enrollment to any of the following events, whichever occurs first: a relapse, the first development of a secondary large intestine carcinoma lesion other than a relapse (an intramucosal cancer lesion will not be treated as an event) that is confirmed after the date of enrollment, and death from any cause. In principle, events will be assessed by the investigator (investigator assessment).

DFS1 = (Date of confirmation of relapse, date of confirmation of secondary large intestine carcinoma lesion other than a relapse, or date of death, whichever comes first) - (Date of enrollment) + 1

Subjects in whom no event was observed will be censored on the last date of imaging test.

If no imaging test is performed, the subjects will be censored at the date of enrollment (Day 1). For subjects in whom imaging test was skipped, events and censoring will be determined basically using the data after skipping except the cases in which relapse may have occurred at the time of skipping. The final handling of events/censors will be discussed and decided in clinical conferences.

[Definition of an event]

[1] Relapse

Confirmation of a relapse finding that meets any of the following criteria is defined as a "relapse." The date of confirmation of relapse shall be the earliest date of diagnosis either by imaging or pathology. In addition, if a clinical diagnosis of a

relapse is difficult, it is preferable to confirm the relapse by a biopsy. An increased tumor marker level alone will not be treated as a relapse.

A) Diagnostic imaging: The date of imaging with a definitive diagnosis of a relapse on an image is defined as the date of confirmation of relapse.

B) Pathological diagnosis: If a relapse could not be diagnosed clinically and was diagnosed by a biopsy, the date of biopsy is defined as the date of confirmation of relapse.

[2] Secondary large intestine carcinoma lesion other than a relapse that is confirmed after the date of enrollment

The date of the first confirmation of a secondary large intestine carcinoma lesion other than a relapse after the date of enrollment.

An intramucosal cancer lesion will not be treated as an event.

[3] Death from any cause

4) Disease-free survival 2 (DFS2)

The time from the date of enrollment to any of the following events, whichever occurs first: a relapse, development of a cancer lesion other than a relapse (secondary cancer), and death from any cause. In principle, events will be assessed by the investigator (investigator assessment).

DFS2 = (Date of confirmation of relapse, date of confirmation of cancer lesion other than a relapse, or date of death, whichever comes first) - (Date of enrollment) + 1

For subjects in whom no event was observed, the date of censoring will be handled in a comparable way to its handling for DFS1. The final handling of events/censors will be discussed and decided in clinical conferences.

[Definition of an event]

[1] Relapse

The same definition as in DFS1 will be used.

[2] Cancer lesion other than a relapse (secondary cancer)

Date of confirmation of a cancer lesion other than a relapse (secondary cancer).

Gastric cancer localized within the mucosa, large intestine carcinoma and esophageal carcinoma, and cervix carcinoma with curative resection, and basal cell carcinoma or squamous cell carcinoma of the skin are not treated as events.

[3] Death from any cause

5) Overall survival

The time from the date of enrollment to the date of death from any cause.

Overall survival = (Date of death) - (Date of enrollment) + 1

Surviving subjects will be censored on the last date of confirmation of survival.

The final handling of events/censors will be discussed and decided in clinical conferences.

6) Rate of conversion to negative ctDNA

This rate is defined as the proportion of subjects who became negative for ctDNA at the test immediately after completion of study treatment.

Subjects who completed the study treatment will be handled as follows.

[1] If there is ctDNA data after the end date
The latest ctDNA data after the end date of treatment will be adopted.

[2] If there is no ctDNA data after the end date
ctDNA was considered to have not turned negative.

Subjects who discontinued the study treatment will be handled as follows.

[1] If the reason for discontinuation is "relapse of the primary disease" or "death during the study treatment"
ctDNA was considered to have not turned negative.

[2] If the reason for discontinuation is other than the above
The latest ctDNA data after the discontinuation date of treatment will be adopted.

[3] If there is no ctDNA data after the discontinuation date
ctDNA was considered to have not turned negative.

7) Worst grade of adverse events

CTCAE v5.0 will be used, and the highest grade collected for the same event will be regarded as the worst grade.

8) Treatment completion rate

This rate will be calculated for each subject in accordance with the following equation:

Treatment completion rate (%) = Number of treatment courses completed/6 × 100

9) EORTC QLQ-C30

The following items will be calculated for conversion of EORTC QLQ-C30 score based on the EORTC QLQ-C30 Scoring Manual.[13.1)] Missing items (missing questionnaire questions) will be imputed based on the EORTC QLQ-C30 Scoring Manual. In the conversion of a score calculated based on multiple questions, if at least half of the answers are obtained, the mean value of the obtained answers will be used for imputation to calculate the score. Other missing data will not be imputed and the score will be considered missing.

[1] Global health status / QoL

[2] Functional scales: Physical functioning, Role functioning, Emotional functioning EF, Cognitive functioning CF, Social functioning

[3] Symptom scales / items: Fatigue, Nausea and vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea, Financial difficulties

10) EQ-5D-5L

A conversion formula for the Japanese population[13.2)] will be used for the utility value of EQ-5D.

Missing data will not be imputed and the utility value will be handled as missing.

4.3. Handling of Periods

To express the duration in years, months, and weeks, the number of days will be converted by dividing it with 365.25, 365.25/12, and 7, respectively, as necessary.

4.4. Handling of Timing

For QOL and test values, the adoption range of time point data is determined as follows. Data at the time of discontinuation will be used as data at the relevant time point if the following adoption range is met.

1) QOL

For EORTC QLC-C30 and EQ-5D-5L (Sections 4.2 4.2.9) and 4.2.10)), the data collected within the following acceptable ranges will be adopted. If there are multiple data within the same acceptable window, the data on the date closest to the reference date will be used. If there are data on two dates closest to the reference date, the data before the reference date will be used.

Time point	Reference date	Acceptable window
Baseline	Date of enrollment	- 28 days
8 weeks after enrollment	Date of enrollment + 7*8	± 7 days
16 weeks after enrollment	Date of enrollment + 7*16	± 7 days
24 weeks after enrollment	Date of enrollment + 7*24	± 7 days
32 weeks after enrollment	Date of enrollment + 7*32	± 7 days
40 weeks after enrollment	Date of enrollment + 7*40	± 7 days
48 weeks after enrollment	Date of enrollment + 7*48	± 7 days

The final handling will be discussed and decided in clinical conferences.

2) Vital signs, performance status, and clinical findings

For the following observation/test items, data collected within the acceptable range in the following table will be adopted. If there are multiple data within the same acceptable window, the data on the date closest to the reference date will be used. If there are data on two dates closest to the reference date, the data before the reference date will be used.

(1) Vital signs (systolic/diastolic blood pressure, pulse rate, body temperature)
(2) Performance status (ECOG PS)
(3) Clinical findings
[1] Hematology (red blood cell count, Hb, white blood cell count, neutrophil count, lymphocyte count, platelet count)

[2] Biochemistry (AST [GOT], ALT [GPT], ALP, LDH, albumin, total bilirubin, BUN, creatinine, electrolytes [Na, K, Cl, Ca], blood glucose)

[3] Urinalysis (urine protein [qualitative])

Time point	Reference date	Acceptable window
Baseline	Start date of Course 1	(Date of enrollment - 14 days) to start date of Course 1
Course 1 D15	Start date of Course 1 + 14	± 3 days
Course 2 D1	Start date of Course 2	- 3 days
Course 3 D1	Start date of Course 3	- 3 days
Course 4 D1	Start date of Course 4	- 3 days
Course 5 D1	Start date of Course 5	- 3 days
Course 6 D1	Start date of Course 6	- 3 days
At the time of discontinuation/completion	Date of treatment discontinuation or date of treatment completion (28 days after the start date of Course 6)	- 3 to + 7 days If post-treatment is given, until before the start of post-treatment
30 days after discontinuation/ completion	30 days after the date of tests at the time of discontinuation/completion	- 3 to + 7 days If post-treatment is given, until before the start of post-treatment

The final handling will be discussed and decided in clinical conferences.

5. Description of Statistical Analysis

5.1. Calculation of Summary Statistics

As summary statistics, the number of subjects, mean, standard deviation, 1st quartile, median, 3rd quartile, and range (minimum - maximum) will be calculated.

5.2. Significance Level of Tests and Confidence Coefficients of Interval Estimation

A two-sided significance level of 5% will be used for the tests, and a two-sided confidence coefficient of 95% will be used for interval estimation.

5.3. Software to Be Used for Statistical Analysis

The software to be used for statistical analysis is shown below.

- SAS (SAS Institute Inc.): Version 9.4 (SAS/STAT 15.2) or later

5.4. Special Notes on Test and Estimation Methods

The major procedures used for statistical analysis are specified as follows.

1) Calculation of Summary Statistics

(MEANS procedure)

```
PROC MEANS DATA=[analysis data set];
  VAR [analysis variable];
  BY [group];
    OUTPUT OUT=[output data set]
```

```
    N=N /*number of subjects*/  MEAN=MEAN/*mean*/   STD=STD /*standard deviation*/
    Q1=Q1 /*1st quartile*/  MEDIAN=MEDIAN   /*median*/  Q3=Q3/*3rd quartile*/
    MIN=MIN /*minimum*/  MAX=MAX/*maximum*/ ;
RUN;
```

2) Student t-test calculation (two-group comparison assuming homoscedasticity)
(TTEST procedure)

```
ODS OUTPUT TTESTS=[output data set];
PROC TTEST DATA=[analysis data set];
  VAR [analysis variable];
  CLASS [group];
RUN;
/*[output data set]*/
/*homogeneity of variance:value corresponding to VARIANCES="Equal"*/
```

3) Tabulation of categorical data and frequency
(FREQ procedure)

```
PROC FREQ DATA=[analysis data set];
  TABLE [categorical variable]*[analysis variable]/OUT=[output data set];
RUN;
```

4) Binomial confidence interval (Clopper and Pearson method)
(FREQ procedure, BINOMIAL option)

```
PROC FREQ DATA=[analysis data set];
  TABLES [analysis variable] / BINOMIAL(LEVEL="[reference level]");
  OUTPUT OUT=[output dataset] BINOMIAL;
RUN;
/*lower limit of exact 95% confidence interval:XL_BIN*100    upper limit of exact 95% confidence
interval:XU_BIN*100*/
/*WEIGHT statement and ZEROS option can be used*/
```

5) Fisher's exact test
(FREQ procedure)

```
PROC FREQ DATA=[analysis data set];
  TABLES [group]*[analysis variable] / FISHER;
  OUTPUT OUT=[output data set] FISHER;
RUN;
/*p value : XP2_FISH*/
```

6) Odds ratio and 95% confidence interval by logistic regression
(LOGISTIC procedure)

```
ODS OUTPUT CLODDSWALD=[output data set];
PROC LOGISTIC DATA=[analysis data set];
  CLASS [group](REF='[reference value]'); * to use 1 as reference, '[reverence value]' is to be '1';
```

```
  MODEL [event variable](EVENT='[reference value]')=[group] / RL;
RUN;
/*odds ratio : [output data set] OddsRatioEst*/
/*lower limit of 95% confidence interval of odds ratio : [output data set] LowerCL*/
/*upper limit of 95% confidence interval of odds ratio : [output data set] UpperCL*/
```

7) Longitudinal data analysis
(MIXED procedure)

```
ODS OUTPUT LSMeans=[output data set 1] Diffs=[output data set 2];
PROC MIXED DATA=[analysis data set] method = reml;
  CLASS [group](REF='[reference value]') [case]  [time point]; * to use 1 as reference, '[reference
  value]' is to be '1' ;
  MODEL [change from baseline]=[group] [time point] [group]*[time point] [baseline value]/S CL
  DDFM=KR;
    LSMEANS [group]*[time point]/ alpha=0.05 pdiff CL;
    REPEATED [time point]/SUB=[case] TYPE=UN ;
RUN;
/* If no convergence, change program code in the order of TYPE =AR(1), CS, and VC and analyze. */
```

8) Stratified log-rank test Kaplan-Meier estimate (confidence interval: Greenwood's formula)
(LIFETEST procedure)

```
ODS OUTPUT PRODUCTLIMITESTIMATES=[output data set 1]
                HOMTESTS=[output data set 2] ;
  PROC LIFETEST DATA=[analysis data set] CONFTYPE=LOGLOG
    TIMELIST=[start time point of analysis] TO [final time point of analysis] BY [width of time
    point];
    TIME [time variable]*[event/censoring variable]([censoring level]);
    /* example: if event=1, censoring=0 [event variable/censoring variable](0) */
    STRATA [stratification variable] / group= [group] ; /*in stratified log-rank test, stratification
    factors are set*/
    SURVIVAL OUT=[output data set 3] STDERR;
RUN;
/* [output data set 1] */
/* estimated survival rate:SURVIVAL */
/* standard error:STDERR */
/* [output data set 2] */
/* two-sided p value is PROBCHISQ corresponding to TEST="log-rank" */
/* [output data set 3]: if obtaining survival probability for each event/censoring */
/* estimated survival rate:SURVIVAL */
/* standard error:SDF_STDERR, lower limit of 95% confidence interval:SDF_LCL, upper limit of 95%
confidence interval SDF_UCL*/
```

9) Median follow-up period Kaplan-Meier estimate (Reverse Kaplan-Meier method)
(LIFETEST procedure)

```
ODS OUTPUT QUARTILES=[output data set] ;
PROC LIFETEST DATA=[analysis data set] CONFTYPE=LOGLOG
  TIME [time variable]*[event/censoring variable]([censoring level]);
  /* example:  if event=0, censoring=1 [event variable/censoring variable] (0)
               *Because of Reverse KM method, event will be censoring, and censoring will be event */
  STRATA  [group] ;
RUN;
/* [output data set] */
/* value corresponding to PERCENT=50 is obtained.
median: ESTIMATE, 95%CI:LOWERLIMIT UPPERLIMIT*/
```

10) Cox proportional hazard model
(PHREG procedure)

```
ODS OUTPUT PARAMETERESTIMATES=[output data set];
PROC PHREG DATA=[analysis data set];
  CLASS [group][explanatory variable](REF='[reference value]')/PARAM=GLM; *to use 1 as reference,
  '[reference value]' is to be '1';
  MODEL  [time variable]*[event/censoring variable]([censoring level])= [group] [explanatory variable
         1] [explanatory variable 2]
         / RL TIES=exact ; /*processing of tie data is to be exact*/
         /* example: if event=1, censoring=0 [event variable](0) */
  STRATA [stratification variable] ; /*add this statement for stratified analysis*/
RUN;
/* [output data set] */
/* hazard ratio : HazardRatio */
/* lower limit of 95% confidence interval of hazard ratio : HRLowerCL, upper limit of 95% confidence
interval of hazard ratio : HRUpperCL */
```

11) Cox hazard model interaction P value for subgroup analysis
(PHREG procedure)

```
OCDS OUTPUT MODELANOVA=[output data set];
PROC PHREG DATA=[analysis data set];
  CLASS [group] [subgroup item](REF='[reference value]')/PARAM=GLM;
  /* to use 1 as reference, '[reference value]' is to be '1' */
  MODEL  [time variable]*[event/censoring variable]([censoring level])= [group] [subgroup item]
         [group]*[subgroup item] / RL TIES=exact ; /*processing of tie data is to be exact*/
         /* example: if event=1, censoring=0 [event variable](0) */
RUN;
/* [output data set] */
/* PROBCHISQ value corresponding to EFFECT="[group]*[subgroup item]" is obtained. */
```

12) Logistic regression model interaction P value for subgroup analysis
(LOGISTIC procedure)

```
ODS OUTPUT MODELANOVA=[output data set];
PROC LOGISTIC DATA=[analysis data set];
```

```
  CLASS [group] [subgroup item](REF='[reference value]'); /* to use 1 as reference, '[reference value]' is to
  be '1'*/
  MODEL [event variable](EVENT='[reference value]')=[group] [subgroup item] [group]*[subgroup item] / RL;
RUN;
/* [output data set] */
/* PROBCHISQ value corresponding to EFFECT="[group]*[subgroup item]" is obtained. */
```

13) Cumulative incidence and Gray's test considering competing risks (LIFETEST procedure)

```
ODS OUTPUT CIF=[output data set 1]  GrayTest=[output data set 2] ;
PROC LIFETEST DATA=[analysis data set] CONFTYPE=LOGLOG
  TIMELIST=[start time point of analysis] TO [final time point of analysis] BY [width of time point] ;
  TIME   [time variable]*[event/censoring/competitive risk variable]([censoring level) / eventcode = 1 ;
         /* example:    if censoring=0, event=1, competing risk 2,3,4
                        [event variable/censoring/competitive risk variable](0) / eventcode =1 */
  STRATA [stratification variable];
RUN;
/* [output data set 1] */
/* estimated cumulative incidence: CIF */
/* standard error: STDERR, lower limit of 95% confidence interval: CIF_LCL, upper limit of 95%
confidence interval CIF_UCL*/
/* [output data set 2] */
/* p-value of Gray's test is PROBCHISQ */
```

14) Hazard ratio of Fine and Gray's model (PHREG procedure)

```
ODS OUTPUT PARAMETERESTIMATES=[output data set];
PROC PHREG DATA=[analysis data set];
  CLASS [group][explanatory variable](REF='[reference value]')/PARAM=GLM; *to use 1 as reference,
  '[reference value]' is to be '1';
  MODEL [time variable]*[event/censoring/competing risk variable]([censoring level])= [group]
        / RL TIES=exact / eventcode = 1 ; /*processing of tie data is to be exact*/
        /* example:    if censoring=0, event=1, competing risk 2,3,4
                       [event variable/censoring/competitive risk variable](0) / eventcode =1 */
RUN;
/* [output data set] */
/* hazard ratio : HazardRatio */
/* lower limit of 95% confidence interval of hazard ratio : HRLowerCL, upper limit of 95% confidence
interval of hazard ratio : HRUpperCL */
```

6. Interim Analysis

In principle, no interim analysis for efficacy will be performed. However, periodical central monitoring will be performed on the status of occurrence of adverse events related to safety, treatment compliance, and study implementation status, and the result will be reported to the Data and Safety Monitoring Committee of this study.

7. Blinded Review

In the planned stratified analysis for the primary and secondary endpoints, the stratified analysis will be unstable if there are very few events in certain strata. Therefore, adequacy of the stratification factors will be examined in the blind review. With the double-blindness maintained, distribution of the number of subjects and the number of events for each factor, the hazard ratio between subgroups, etc. will be confirmed, and correction of the stratification factors and the categorization used for the stratified analysis will be considered.

8. Target Patients

8.1. Subject Composition

The number of enrolled subjects will be presented by group according to the following classification. Breakdown of reasons for discontinuation will be presented for discontinued subjects.

[Classification]

Enrolled subjects, untreated subjects, treated subjects, discontinued subjects, completed subjects

8.2. Analysis Population

For enrolled subjects, the number of subjects included in each analysis population, the number of subjects excluded from each analysis population, and breakdown of reasons for exclusion will be presented by group.

9. Demographic and Other Baseline Characteristics

9.1. Patient Background

For the following items in each of [all enrolled subjects], [FAS], and [SP], frequency distributions will be presented for categorical items and summary statistics will be calculated for continuous items by group.

Country	"Japan" "Taiwan"
Sex	"Male" "Female"
Age at the time of informed consent	Summary statistics
Age categories at the time of informed consent	"Less than 70 years" "70 years or more"
	"Less than 65 years" "65 years or more"
	"Less than 75 years" "75 years or more"
Disease stage (allocation information at registration)	"Stage II or lower " "Stage III" "M1"
Disease stage (value of allocation information including corrections after registration)	"Stage II or lower" "Stage III" "M1"
Primary location of lesion (allocation information at registration)	"Right colon" "Left colon" "Rectum"
Primary location of lesion (value of allocation information including corrections after registration)	"Right colon" "Left colon" "Rectum"
Primary location of lesion (2 categories)	"Right colon" "Left colon (including rectum)"

ctDNA status at 1 month after curative resection (allocation information at registration) (2 categories)	"Positive" "Negative/unmeasurable/unmeasured"
ctDNA status at 1 month after curative resection (value of allocation information including corrections after registration) (2 categories)	"Positive" "Negative/unmeasurable/unmeasured"
Height	Summary statistics
Weight	Summary statistics
Medical history/complications	"Yes" "No"
Pregnancy test	"Positive" "Negative"
Electrocardiogram	"No clinically significant abnormalities are observed" "Clinically significant abnormality(ies) is/are observed"
HBs antigen	"Positive" "Negative"
HBs antibody	"Positive" "Negative"
HBc antibody	"Positive" "Negative"
HBV-DNA	"Not detected"
HBV-DNA (excluding not detected cases)	Summary statistics
HCV antibody	"Positive" "Negative"
HCV-RNA	"Not detected"
HCV-RNA (excluding not detected cases)	Summary statistics
HIV antibody	"Positive" "Negative"
CEA	Summary statistics
CA19-9	Summary statistics
ECOG PS	"0" "1"
Liver function (NCI classification)	"Group A (normal)" "Group B (mild)" "Group C (moderate)" "Group D (severe)"
Renal function (Ccr [mL/min]) category	"Less than 30" "30 or more and less than 60" "60 or more and less than 90" "90 or more"
GALAXY study information	
Chemotherapy before curative resection	"Yes" "No"
Adjuvant chemotherapy	"Yes" "No"
Radiotherapy before curative resection	"Yes" "No"
Another Surgery Before Registration of GALAXY Study	"Yes" "No"
Detail of Lesion (surgery information) Surgical procedure	"Polypectomy" "Local excision" "Ileocecal resection" "Partial colectomy" "Right hemicolectomy" "Left hemicolectomy" "Sigmoidectomy" "High anterior resection" "Low anterior resection" "Ultra low anterior resection" "Intersphincteric resection" "Hartmann's procedure" "Rectal amputation" "Total pelvic exenteration" "Other"

Approach	"Laparotomy" "Laparoscopy" "Other"
Combined resection organs (multiple choice)	"Esophagus" "Stomach" "Duodenum" "Small intestine" "Colon" "Rectum" "Liver" "Gallbladder/bile duct" "Pancreas" "Lung" "Breast" "Uterine cervix" "Uterine body" "Ovary" "Fallopian tube" "Vagina" "Peritoneum" "Bone" "Skin" "Kidney/bladder/urinary tract" "Brain" "Appendix" "Spleen" "Anal canal" "Other"
Results of ctDNA at 1 month after curative resection (EDC data)	"MRD-negative" "MRD-positive" "Not performed"
Initial information	
Pathological tissue findings of primary lesions	
Primary location of lesion (EDC data)	"Right colon" "Left colon" "Rectum" "Other"
Histological type Tumor	"Benign epithelial tumor" "Malignant epithelial tumor" "Non-epithelial tumor" "Lymphoma" "Unclassified tumor" "Metastatic tumor" "Tumor-like lesion" "Hereditary tumor and gastrointestinal polyposis" "Unknown"
If malignant epithelial tumor is selected	"Adenocarcinoma" "Adenosquamous carcinoma (asc)" "Squamous cell carcinoma (scc)" "Carcinoid tumor" "Endocrine cell carcinoma" "Miscellaneous histological types of malignant epithelial tumors" "Unknown"
Details of adenocarcinoma	"Papillary adenocarcinoma (pap)" "Tubular adenocarcinoma (tub)" "Poorly differentiated adenocarcinoma (por)" "Mucinous adenocarcinoma (muc)" "Signet-ring cell carcinoma (sig)" "Medullary carcinoma (med)" "Unknown"
Details of tubular adenocarcinoma	"Well differentiated type (tub1)" "Moderately differentiated type (tub2)" "Unknown"
Details of poorly differentiated adenocarcinoma	"Solid type (por1)" "Non-solid type (por2)" "Unknown"
Macroscopic classification	"Type 0: Superficial type" "Type 1: Polypoid type" "Type 2: Ulcerated type with clear margin " "Type 3: Ulcerated type with infiltration" "Type 4: Diffusely infiltrating type" "Type 5: Unclassifiable type "
Depth of tumor invasion "T" (Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, 9th edition)	"TX" "T0" "Tis" "T1a" "T1b" "T2" "T3" "T4a" "T4b"
Number of lymph node metastasis	Summary statistics

Lymph node metastasis "N" (Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, 9th edition)	"NX" "N0" "N1a" "N1b" "N2a" "N2b" "N3"
Distant metastasis "M" (Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, 9th edition)	"M0" "M1a" "M1b" "M1c1" "M1c2"
Surgical findings	
Extent of lymph node dissection "D"	"DX" "D0" "D1" "D2" "D3"
Number of dissected lymph nodes	Summary statistics
Number of dissected lymph nodes categories	"Less than 12" "12 or more"
Tumor diameter (maximum diameter)	Summary statistics
Liver metastasis	"HX" "H0" "H1" "H2" "H3"
Peritoneal metastasis	"PX" "P0" "P1" "P2" "P3"
Other distant	"Yes" "No"
TNM classification "T" (UICC TNM classification, 8th edition)	"TX" "T0" "Tis" "T1" "T2" "T3" "T4a" "T4b"
TNM classification "N" (UICC TNM classification, 8th edition)	"NX" "N0" "N1a" "N1b" "N1c" "N2a" "N2b"
TNM classification "M " (UICC TNM classification, 8th edition)	"M0" "M1a" "M1b" "M1c"
Disease stage (Stage) (UICC TNM classification, 8th edition)	"0" "I" "IIA" "IIB" "IIC" "IIIA" "IIIB" "IIIC" "IVA" "IVB" "IVC"
Lymphatic invasion	"LyX" "Ly0" "Ly1a" "Ly1b" "Ly1c" "Ly1x"
Venous invasion	"VX" "V0" "V1a" "V1b" "V1c" "V1x" "V2"
Perineural invasion	"PnX" "Pn0" "Pn1a" "Pn1b" "Pn1x"
Extramural cancer deposit without lymph node structure	"Yes" "No" "Unknown"

9.2. Treatment Compliance

For the number of implemented courses, concomitant drugs, and presence or absence of concomitant therapies in each of [all enrolled subjects], [FAS], and [SP], frequency distribution will be presented by group.

9.3. Treatment Summary

For the following items related to the treatment in each of [all enrolled subjects], [FAS], and [SP], frequency distributions will be presented for categorical items and summary statistics will be calculated for continuous items by group.

Skipped dose	"Yes" "No"
Dose reduced	"Yes" "No"
Dose reduced by 10 mg/day or more	"Yes" "No"
First dose reduction course	Median (minimum - maximum)
Dose reduced by 20 mg/day or more	"Yes" "No"
First dose reduction course	Median (minimum - maximum)
Dose redued by 30 mg/day or more	"Yes" "No"
First dose reduction course	Median (minimum - maximum)
Delay of administration	"Yes" "No"
Missed dose	"Yes" "No"
Total Treatment Days [day] * Last course administration end date - First administration start date + 1	Summary statistics
Cumulative Dosage [mg/m^2] * Cumulative dosage [mg] / Body surface area at enrollment [m^2]	Summary statistics
Actual Dose Intensity (DI) [mg/m^2/week] < Pattern 1: Based on administration period > * Cumulative Dosage [mg/m^2]/((Last course administration start date - First administration start date + 28 [day])/7 [day])	Summary statistics
RDI [%] < Pattern 1: Based on administration period > * Pattern 1 actual DI [mg/m^2/week]/Planned DI [mg/m^2/week] Planned DI [mg/m^2/week] = First administration dosage 35 [mg/m^2] * 2 [time] * 10 [day]/4 [week]	Summary statistics
Actual dose Intensity (DI) [mg/m^2/week] < Pattern 2: Based on 6 courses > * Cumulative Dosage [mg/m^2] /((6 [cource] * 28 [day])/7 [day])	Summary statistics
RDI [%] < Pattern 2: Based on 6 courses > * Pattern 2 actual DI [mg/m^2/week]/Planned DI [mg/m^2/week] Planned DI [mg/m^2/week] = First administration dosage 35 [mg/m^2] * 2 [time] * 10 [day]/4 [week]	Summary statistics

10. Efficacy Evaluation

10.1. Primary Endpoint: Disease-free Survival 1

This endpoint will be assessed in the FAS.

DFS curves will be estimated using the Kaplan-Meier method for disease-free survival 1. Moreover, every 3 months, DFS and its 95% confidence interval will be calculated. The median DFS and its 95% confidence interval will be calculated for each study group. A stratified log-rank test will be performed to compare the DFS curves of the two groups. The null hypothesis will be rejected if the p value of the stratified log-rank test is less than 0.05, the significance level, and it will be concluded that there is a statistically significant difference between the 2 groups. The stratification factors, which were arranged to be finalized in the blinded review described in Section 7, are the allocation factors in the table below. The hazard ratio of the allocation groups and its 95% confidence interval will be calculated using the Cox proportional hazard model stratified by the allocation factors shown in the following table. For the allocation factors, a stratified analysis using allocation information will be performed as primary analysis. As some of the information was corrected after enrollment, a stratified sensitivity analysis using the allocation information at the time of enrollment will also be performed. In addition, regarding the stratified analysis for allocation factors using the allocation information performed as primary analysis, the "analysis excluding the subjects assessed as relapse by central review of images at baseline" and the " analysis excluding the subjects with changed ctDNA results due to standard bioinformatics pipeline revisions " will be performed as sensitivity analyses.

The primary analysis will also be performed in the [all enrolled subjects] and [SP] populations as sensitivity analyses.

Stratum (allocation factor)	Categories
Age categories at the time of informed consent	"Less than 70 years" "70 years or more"
Disease stage	"Stage II or lower" "Stage III" "M1"
Primary location of lesion (2 categories)*	"Right colon" "Left colon (including rectum)"
ctDNA status at 1 month after curative resection (2 categories)	"Positive" "Negative/unmeasurable/unmeasured"

* Among the categories of an allocation factor, primary location of lesion (right colon, left colon, rectum), left colon and rectum were combined into one category.

* Based on the result of blinded review, the stratification factors were decided as below. The 2 factors of disease stage (3 categories: "Stage II or lower", "Stage III", and "M1") and ctDNA status at 1 month after curative resection (2 categories: "Positive" and "Negative/unmeasurable/unmeasured"), as shown in the table above, are used as stratification factors. However, if there exists a stratum that has a group of 0 events in these 2 factors, the 1 factor of "disease stage" will be used as stratification factor.

* The "ctDNA status 1 month after curative resection" was assessed using the following data from the GALAXY trial:

- For Cohort E cases, those with blood drawn 4 weeks ± 1 week after surgery were classified as having "measured" ctDNA (either positive or negative). Cases that fell significantly outside this range were classified as "not measured" (a deviation of approximately 2 days was allowed).
- For cases other than Cohort E, the data measured by GALAXY at "4 weeks after surgery" was used. Even if the data deviated significantly from the 4 weeks ± 1 week window, it was still utilized.

Moreover, the total number of events, breakdown of events (relapse, death, cause of death, etc.), total number of censored subjects, and the frequency and proportion of breakdown of censoring (no imaging test, no event, etc.) will be calculated in the FAS for each group. As a sensitivity analysis, the " analysis excluding the subjects with changed ctDNA results due to standard bioinformatics pipeline revisions " will also be performed.

10.2. Secondary endpoints

10.2.1. Rate of Conversion to Negative ctDNA

This endpoint will be assessed in the FAS.

The proportion of subjects with conversion to negative ctDNA at the latest test after the completion of study treatment and its 95% confidence interval will be estimated for each group. Fisher's exact test will be performed for intergroup comparison, and the odds ratio and 95% confidence interval will be estimated using a logistic regression model. As a sensitivity analysis, the " analysis excluding the subjects with changed ctDNA results due to standard bioinformatics pipeline revisions " will also be performed.

10.2.2. Disease-free Survival 2

This endpoint will be assessed in the FAS.

DFS curves will be estimated using the Kaplan-Meier method for disease-free survival 2. Moreover, every 3 months, DFS and its 95% confidence interval will be calculated. The median DFS and its 95% confidence interval will be calculated for each study group. A stratified log-rank test will be performed to compare the DFS curves of the two groups. Based on the result of blinded review, the stratification factors were decided as below.

The 2 factors of disease stage (3 categories: "Stage II or lower", "Stage III", and "M1") and ctDNA status at 1 month after curative resection (2 categories: "Positive" and "Negative/unmeasurable/unmeasured") are used as stratification factors. However, if there exists a stratum that has a group of 0 events in these 2 factors, the 1 factor of "disease stage" will be used as stratification factor. The hazard ratio of the allocation groups and its 95% confidence interval will be calculated using the Cox proportional hazard model stratified by the same stratification factors as those in the stratified log-rank test.

The above analysis will also be performed in the [all enrolled subjects] and [SP] populations as sensitivity analyses.

Moreover, the total number of events, breakdown of events (relapse, death, cause of death, etc.), total number of censored subjects, and the frequency and proportion of breakdown of censoring (no imaging test, no event, etc.) will be calculated in the FAS for each group.

10.2.3. Overall survival

This endpoint will be assessed in the FAS.

OS curves will be estimated using the Kaplan-Meier method for overall survival, and OS every 3 months and its 95% confidence interval will be calculated. The median OS and its 95% confidence interval will be calculated for each study group. A log-rank test will be performed to compare the OS curves of the two groups. As the reason not to perform a stratified log-rank test, based on the result of blinded review, it was finally decided that an analysis without stratification be performed. The hazard ratio of the allocation groups and its 95% confidence interval will be calculated using the Cox proportional hazard model.

In addition, for overall survival, median observation period by Reverse Kaplan Meier method (median of the distribution when censoring fatal cases and regarding censored cases as events) and its 95% confidence interval will be calculated for each group.

After the end of the study period, follow-up will be conducted separately in an observational study (GALAXY), and the analysis of overall survival will be performed in the observational study (GALAXY).

The above analysis will also be performed in the [all enrolled subjects] and [SP] populations as sensitivity analyses.

The total number of deaths, the breakdown of deaths (causes of death, etc.), the total number of censored subjects, and the frequency and proportion of breakdown of censoring (survival, lost to follow-up, etc.) will be calculated in the FAS for each group.

10.2.4. Treatment Completion Rate

This endpoint will be assessed in the FAS.

Summary statistics of the treatment completion rate will be calculated for each group, and intergroup comparison by Student t-test will be performed.

10.2.5. QOL

This endpoint will be assessed in the FAS.

Summary statistics and standard error of the following items will be calculated by group and time point.

Longitudinal data will be compared between groups using a linear mixed model.

[Items]

EORTC QLQ-C30:

[1] Global health status / QoL
[2] Functional scales: Physical functioning, Role functioning, Emotional functioning EF, Cognitive functioning CF, Social functioning
[3] Symptom scales / items: Fatigue, Nausea and vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea, Financial difficulties

EQ-5D-5L: Score, VAS

10.2.6. Time to Conversion to Negative ctDNA

This endpoint will be assessed in the FAS.

For each group, the curve of cumulative incidence taking into account competing risks will be estimated for the time to conversion to negative ctDNA, and the cumulative incidence of negative conversion and its 95% confidence interval will be calculated every 3 months. The P value of the Gray's test will be shown. The hazard ratio of the allocation groups and its 95% confidence interval will be calculated using the Fine and Gray model.

The time point when negative conversion is observed for the first time after enrollment is regarded as an event, and an analysis will be performed taking into account a relapse, the first development of a secondary large intestine carcinoma lesion other than a relapse (an intramucosal cancer lesion will not be treated as an event) that is confirmed after the date of enrollment, and death as competing risks. The period and censoring are defined as follows:

Time to conversion to negative ctDNA = ("Date of initial conversion to negative ctDNA, date of relapse, date of development of a secondary large intestine carcinoma lesions other than a relapse, or date of death," whichever comes first) - (Date of enrollment) + 1

For subjects in whom neither events nor competing risk events are observed, the date of censoring will be regarded as the last date of confirmation of survival.

The final handling of events/censors will be discussed and decided in clinical conferences.

As a sensitivity analysis, the " analysis excluding the subjects with changed ctDNA results due to standard bioinformatics pipeline revisions " will also be performed.

10.3. Subgroup Analysis

10.3.1. Subgroup Analysis (forest plot)

This endpoint will be assessed in the FAS.

For disease-free survival 1, disease-free survival 2, and overall survival, a forest plot will be prepared to show the hazard ratio of the Cox proportional hazard model using the placebo group as reference and its 95% confidence interval for each category of the following subgroup items. The interaction P value for the hazard ratio between subgroups will also be calculated. For disease-free survival 1, a forest plot will also be prepared by specifying only site (Site 1 to 39) as a subgroup item.

For the rate of conversion to negative ctDNA, the odds ratio of subjects with negative conversion of ctDNA in a logistic regression model and its 95% confidence interval will be calculated. A forest plot showing the odds ratio of the logistic regression model and its 95% confidence interval will be prepared. In addition, the interaction P value for the odds ratio between subgroups will be calculated.

Age categories at the time of informed consent	"Less than 70 years" "70 years or more"
Disease stage	"Stage II or lower" "Stage III" "M1"
Primary location of lesion (2 categories)	"Right colon" "Left colon (including rectum)"
Country	"Japan" "Taiwan"
Sex	"Male" "Female"
Disease stage (allocation information at registration)	"Stage II or lower" "Stage III" "M1"
Disease stage (value of allocation information including corrections after registration)	"Stage II or lower" "Stage III" "M1"
Primary location of lesion (allocation information at registration)	"Right colon" "Left colon" "Rectum"
Primary location of lesion (value of allocation information including corrections after registration)	"Right colon" "Left colon" "Rectum"
Primary location of lesion (2 categories)	"Right colon" "Left colon (including rectum)"
ctDNA status at 1 month after curative resection (allocation information at registration) (2 categories)	"Positive" "Negative/unmeasurable/unmeasured"
ctDNA status at 1 month after curative resection (value of allocation information including corrections after registration) (2 categories)	"Positive" "Negative/unmeasurable/unmeasured"
Results of ctDNA at 1 month after curative resection (EDC data)	"MRD-negative" "MRD-positive" "Not performed"
Chemotherapy before curative resection	"No" "Yes"
Adjuvant chemotherapy	"No" "Yes"
Radiotherapy before curative resection	"No" "Yes"
Another Surgery Before Registration of GALAXY Study	"No" "Yes"

10.3.2. Disease-free Survival 1

This endpoint will be assessed in the FAS.

For each category of the following allocation factors among subgroup items, using the values of allocation information including correction after enrollment, the DFS curve will be estimated by the Kaplan-Meier method every 3 months, DFS and its 95% confidence interval will be calculated. The median DFS and its 95% confidence interval will be calculated for each group. The P value of the log-rank test without stratification will be presented, and the hazard ratio of the allocation groups and its 95% confidence interval will be calculated using a Cox proportional hazard model.

Age	"Less than 70 years" "70 years or more"
Disease stage	"Stage II or lower" "Stage III" "M1"
Primary location of lesion (2 categories)	"Right colon" "Left colon (including rectum)"

Results of ctDNA at 1 month after curative resection (2 categories)	"Positive" "Negative/unmeasurable/unmeasured"

10.3.3. Rate of Conversion to Negative ctDNA

This endpoint will be assessed in the FAS.

The proportion of subjects with conversion to negative ctDNA and its 95% confidence interval will be estimated for each item in 10.3.2 and for each group. Fisher's exact test will be performed for intergroup comparison, and the odds ratio and 95% confidence interval will be estimated using a logistic regression model.

10.3.4. Disease-free Survival 2

This endpoint will be assessed in the FAS.

For each item in 10.3.2 and for each group, DFS curves will be estimated using the Kaplan-Meier method every 3 months, DFS and its 95% confidence interval will be calculated. The median DFS and its 95% confidence interval will be calculated for each group. The P value of the log-rank test without stratification will be presented, and the hazard ratio of the allocation groups and its 95% confidence interval will be calculated using a Cox proportional hazard model.

10.3.5. Overall survival

This endpoint will be assessed in the FAS.

For each item in 10.3.2 and for each group, OS curves will be estimated using the Kaplan-Meier method every 3 months, OS and its 95% confidence interval will be calculated. The median OS and its 95% confidence interval will be calculated for each group. The P value of the log-rank test without stratification will be presented, and the hazard ratio of the allocation groups and its 95% confidence interval will be calculated using a Cox proportional hazard model.

11. Safety Evaluation

11.1. Adverse Events

11.1.1. Summary of Incidence

The analysis will be performed in the SP.

The number of subjects with the following events and the incidence will be calculated for each group.

1) Adverse events
2) Adverse events of Grade 3 or more
3) Serious adverse events
4) Adverse events leading to study discontinuation
5) Adverse events leading to death
6) Adverse events related to investigational drug
7) Adverse events of Grade 3 or more related to investigational drug
8) Serious adverse events related to investigational drug
9) Adverse events related to investigational drug leading to study discontinuation

10) Adverse events related to investigational drug leading death

11.1.2. Incidence of Adverse Events by SOC/PT

The analysis will be performed in the SP.

For each adverse event in the following 1) to 12) and for each group, the worst grade for each adverse event will be identified by SOC and PT, and the number of subjects with events and the incidence by group will be calculated for each grade, all grades, and Grade 3 or more. The order of output will be "SOC internationally agreed order, PT code (ascending order)" of MedDRA.

1) Adverse events
2) Serious adverse events
3) Adverse events leading to study discontinuation
4) Adverse events leading to death
5) Adverse events leading to skipping
6) Adverse events leading to dose reduction
7) Adverse events related to investigational drug
8) Serious adverse events related to investigational drug
9) Adverse events related to the investigational drug that led to study discontinuation
10) Adverse events related to the investigational drug that led to death
11) Adverse events related to the investigational drug that led to dose skipping
12) Adverse events related to the investigational drug that led to dose reduction

11.1.3. Incidence of Adverse Events by Risk

The analysis will be performed in the SP.

The analysis comparable to that in 11.1.2 will be performed for the following adverse events only. The PT code for each event will be identified before data lock.

- Adverse events related to bone marrow suppression
- Adverse events related to infection
- Adverse events related to ileus
- Adverse events related to interstitial lung disease
- Adverse events related to cardiac disorders

11.1.4. Summary Table of Cause of Death

The analysis will be performed in the SP.

A summary table of all deaths by cause (including deaths due to the primary disease) will be prepared.

11.1.5. Subgroup Analysis (incidence of adverse events)

The analysis will be performed in the SP.

The analysis comparable to 11.1.1 and 11.1.2 will be performed for each category of the following subgroup items.

Age categories at the time of informed consent	"Less than 65 years" "65 years or more"

	"Less than 75 years" "75 years or more"
Country	"Japan" "Taiwan"
Sex	"Male" "Female"
ECOG PS	"0" "1"
Liver function (NCI classification)	"Group A (normal)" "Group B (mild)" "Group C (moderate)" "Group D (severe)"
Renal function (Ccr [mL/min]) category	"Less than 30" "30 or more and less than 60" "60 or more and less than 90" "90 or more"
Chemotherapy Before Curative Resection	"Yes" "No"
Adjuvant Chemotherapy	"Yes" "No"

11.1.6. Tabulation of Adverse Events with 10% or Higher Incidence

The analysis will be performed in the SP.

A table will be prepared by extracting the events with a 10% or higher incidence for all grades in either group in the analysis of "1) Adverse events" and "7) Adverse events related to investigational product" in 11.1.2.

11.1.7. Tabulation of Adverse Events with 5% or more Difference in Incidence among Intrinsic Factors

The analysis will be performed in the SP.

A table will be prepared by extracting the events with a 5% or greater difference in incidence for all grades in either group within each subgroup category in the analysis in "1) Adverse events" in 11.1.2, for each of all subgroups in 11.1.5.

11.2. Test Values

The analysis will be performed in the SP.

11.2.1. Vital Signs

For the items, systolic/diastolic blood pressure, pulse rate, and body temperature, frequency distribution will be presented for categorical items, and summary statistics will be calculated for continuous items, by group and time point.

11.2.2. Performance Status

For ECOG PS, frequency distribution will be presented for categorical items, and summary statistics will be calculated for continuous items, by group and time point.

11.2.3. Hematology

The following analyses will be performed for red blood cell count, Hb, white blood cell count, neutrophil count, lymphocyte count, and platelet count.

11.2.3.1. Summary Statistics

Frequency distribution will be presented for categorical items, and summary statistics will be calculated for continuous items, by group and time point.

11.2.3.2. Tabulation by Grade

For the test items that can be graded based on CTCAE v5.0, the number and proportion of subjects by group will be calculated for each grade, all grades, and Grade 3 or more for the worst grade.

11.2.3.3. Summary Statistics of "Worst Value" of Grade 3 or more, "Time to Worst Value," and "Time to Recovery"

The summary statistics of the "worst value," "time to worst value," and "time to recovery" for the worst Grade 3 or more will be calculated for each group. The definition of the periods will be as follows.

Time to worst value = (Date of worst value) - (Date of first dose) + 1

Time to recovery = (Date of first recovery to Grade 2 or lower) - (Date of worst value) + 1

11.2.3.4. Transition Charts

A transition chart will be prepared for each subject, with test values on the vertical axis and (test date from date of first dose + 1) on the horizontal axis.

11.2.4. Biochemistry

For the items, AST (GOT), ALT (GPT), ALP, LDH, albumin, total bilirubin, BUN, creatinine, electrolytes (Na, K, Cl, Ca), and blood glucose, the following analysis will be performed.

11.2.4.1. Summary Statistics

The analysis comparable to 11.2.3.1 will be performed.

11.2.4.2. Tabulation by Grade

The analysis comparable to 11.2.3.2 will be performed.

11.2.4.3. Summary Statistics of "Worst Value" of Grade 3 or more, "Time to Worst Value," and "Time to Recovery"

The analysis comparable to 11.2.3.3 will be performed.

11.2.4.4. Transition Charts

The analysis comparable to 11.2.3.4 will be performed.

11.2.5. Urinalysis

The following analysis will be performed for urine protein (qualitative).

11.2.5.1. Summary Statistics

The analysis comparable to 11.2.3.1 will be performed.

11.2.5.2. Tabulation by Grade

The analysis comparable to 11.2.3.2 will be performed.

11.2.5.3. Summary Statistics of "Time to Worst Value" of Grade 3 or more and "Time to Recovery"

The analysis comparable to 11.2.3.3 will be performed except for the summary statistics of "worst value."

12. Appendix

1) Listing of inclusion or exclusion of subjects (analysis populations, deviation, etc.)
2) Listing of discontinued subjects
3) Listing of medical history/complications
4) Listing of patient background (subject background, information on GALAXY study, initial information, surgical findings, etc.)
5) Listing of previous treatment
6) Listing of concomitant Medications/therapies
7) Listing of adverse events
8) Listing of death subjects
9) Listing of subjects who died within 30 days after completion of administration
10) Listing of adverse events leading to death
11) Listing of serious adverse events
12) Listing of individual efficacy response data (efficacy endpoints, test values, imaging assessments of relapse, etc., ctDNA, etc.)
13) Listing of follow-up treatment
14) Listing of exposure to study medication

13. Reference List

1) The EORTC Quality of Life Group. EORTC QLQ-C30 Scoring Manual [Internet]. Third edition. Brussels Quality of Life Unit EORTC Data Center; 2001 [cited 2024 MAR 12]. Available from: https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf
2) Ikeda S, Shiroiwa T, Igarashi A, et al. Developing a Japanese version of the EQ-5D-5L value set. Journal of the National Institute of Public Health. 2015;64(1):47-55.