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

Investigator-Initiated Protocol
Protocol Number : EPOC 1905

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

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Protocol number: EPOC1905
Version number: Version 10.1 Date of preparation: Jul 10, 2024
Approved by
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Revision History:

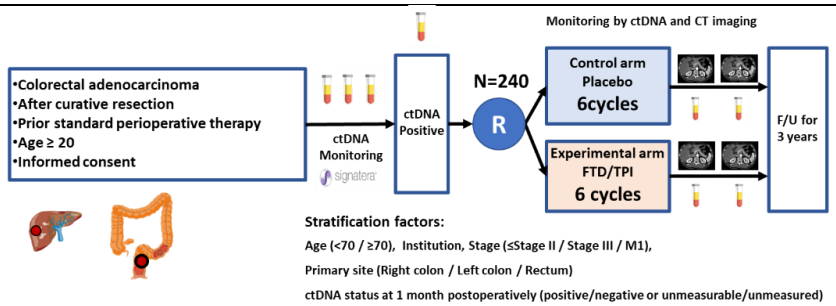
Version Number	Date of Preparation	Details of Revision
Ver.1.0	March 10, 2020	Created
Ver 2.0	May 15, 2020	Revised allocation factors, revised central review of images, and description adjustment
Ver 3.0	Sep 15, 2020	Revised treatment modification criteria, discontinuation Criteria, clarification of description, and description adjustment
Ver.3.1	Feb 1, 2021	Added the clarification to Inclusion Criteria, Exclusion Criteria.
Ver.3.2	Apr 6, 2021	Added the clarification to Inclusion Criteria No.3
Ver.4.1	May 20, 2021	Changes in affiliation of representatives of the coordinating investigators, changes in acceptable ranges for the start date of each course, clarification of procedures, and description adjustment
Ver.4.2	Jun 9, 2021	Correction for Table 8.2 Study Calendar
Ver.5.1	Oct 13, 2021	Added the clarification to Inclusion Criteria, Allocation method, Discontinuation of Study Treatment, Criteria for the Modification of Study Treatment. Correction for Table 8.2 Study Calendar
Ver.6.1	Feb 07, 2022	Change Representative of the coordinating investigators, add the coordinating investigator, change allocation factors
Ver.7.1	Jul 07, 2022	Delete the study coordinating investigator, Added the clarification to Inclusion Criteria No.3, Clarification of test/observation timing, Description adjustment
Ver.8.1	Feb 09, 2023	Clarification of Inclusion Criteria (Not affect to Taiwan site due to Taiwan enrollment period was completed), Extended study enrollment period (only Japan), Change to the latest clinical trial data base
Ver.9.1	Jan 16, 2024	Clarification of Disease-Free Survival 1 and Disease-Free Survival 2
Ver.10.1	Jul 10, 2024	Change in affiliation of coordinating investigator, clarification of factors used in stratified analysis

List of Abbreviations

ALT (GPT)	Alanine aminotransferase (glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (glutamate oxaloacetate transaminase)
BV	Bevacizumab
COI	Conflict of interest
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
DFS	Disease-free survival
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Module C30
EQ-5D-5L	EuroQOL 5 dimensions 5-level
FAS	Full analysis set
FTD/TPI	Trifluridine/tipiracil
GCP	Good clinical practice
G-CSF	Granulocyte colony stimulating factor
Hb	Hemoglobin
HBc	Hepatitis B core
HBV	Hepatitis B virus
HBs	Hepatitis B surface
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
IRB	Institutional Review Board
ITT	Intention to treat
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
OS	Overall survival
PFS	Progression-free survival
PMDA	Pharmaceuticals and Medical Devices Agency
PS	Performance status
RTSM	Randomization and Trial Supply Management System
SP	Safety population
T-Bil	Total bilirubin

UICC	Unio Internationalis Contra Cancrum

Synopsis

Phase	Phase III
Objectives	This trial 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 trial is to verify the efficacy and safety of preemptive treatment with trifluridine/tipiracil hydrochloride (FTD/TPI) compared with follow-up, which is the standard of care. **Primary endpoint**: • Disease-free survival 1[*1][*3] (DFS1) [*1] In this trial, 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 trial, 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 trial period, subjects will be followed up for 5 years in a separate observational study.
Study schema	
Study design	This trial 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 follow-up, which is the standard of care, in patients who underwent

	curative resection of colorectal cancer and then tested positive for ctDNA.
Study population	Patients who meet all of the inclusion criteria and do not meet any of the exclusion criteria will be enrolled as patients who will receive study treatment. **Inclusion criteria:** 1. Patients who have been histopathologically diagnosed with colorectal adenocarcinoma (Stage II or lower/Stage III/M1) 2. Patients who have undergone radical resection[*1] of the primary and metastatic tumors [*1] It is considered to be a radical resection if the tumor is exposed at the edge or on the surface of surgical detachment but is encapsulated. 3. Patients who are subject to postoperative chemotherapy according to the country guideline and/or medical practice, that is Stage III (T any N1*[2]/2 M0) and Stage IV (T any N any M1) (UICC TNM Classification, 8th Edition) for Taiwan must have a history[*4] of standard postoperative chemotherapy*[3]. [*2] N1c (UICC TNM Classification, 8th Edition) is also included in this stage (tumor deposits, or satellite nodules, are seen in the adjacent soft tissues of the colon or rectum without subserosal layer or peritoneal coat, with no regional lymph node metastasis). [*3] Treatments described in the current Japanese and overseas guidelines or study treatments conducted in clinical studies. [*4] In case of patients who do not have a standard postoperative chemotherapy for rational reason, these patients can be enrolled. Note that if sites enroll such patients, record the reason for the decision to medical chart. 4. Patients who tested positive for ctDNA using Signatera™ by an analysis[*5] of the latest blood samples collected within 3 months prior to enrollment [*5] Analyses of blood samples using Signatera™ will be performed in a separate clinical study (see Section 2.10.1.2.). 5. Patients with no obvious relapse confirmed by chest, abdominal, and pelvic CT scans, etc. 6. Patients who are capable of oral ingestion 7. Patients aged 20 years or older at the time of informed consent

	8. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 9. Patients who have no severe disorder in major organs (such as the bone marrow, heart, lungs, liver, and kidneys) and meet the following criteria (Data obtained most recently and within 14 days of the date of enrollment will be used for enrollment. Data obtained 2 weeks before the date of enrollment, on the same day of the week as the enrollment date, may be used for enrollment.) - Neutrophil count ≥ 1,500/mm^3 - Platelet count ≥ 100,000/mm^3 - Hemoglobin ≥ 8.0 g/dL - Serum creatinine ≤ 1.5 mg/dL - Total bilirubin ≤ 1.5 mg/dL - ALT and AST ≤ 100 U/L 10. Patients with no diarrhea or stomatitis of Grade 2 or severer according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 11. Patients who voluntarily gave written consent to participate in the trial after receiving a thorough explanation of the trial before enrolling in the trial **Exclusion criteria** 1. Patients with a history of treatment with FTD/TPI 2. Patients with a history of treatment with 2 or more regimens of postoperative adjuvant chemotherapy[*6] (Preoperative chemotherapy will not be counted as a regimen.) [*6] The timing of initiation of the postoperative adjuvant chemotherapy will not be specified. 3. Patients with a past history of a malignant tumor[*7] other than colorectal adenocarcinoma. [*7] Patients with a relapse-free survival period of 5 years or longer, or patients with basal cell or squamous cell carcinoma of the skin that is considered cured by local treatment, superficial bladder cancer, cervical cancer, carcinoma in situ (intraepithelial cancer) or lesions equivalent to intramucosal cancer, or non-metastatic prostate cancer not requiring systemic treatment may be enrolled. 4. Patients with a local or systemic active infection requiring intervention

	5. Patients who are positive for HBs antigen[*8] or positive for HCV antibody[*9] [*8] HBV-DNA testing is mandatory to be below the limit of detection for patients with a negative HBs antigen test, but with a positive test result for either HBs antibody or HBc antibody [*9] Patients who are positive for HCV antibody but negative for HCV-RNA may be enrolled. 6. Patients who are positive for HIV antibody[*11] (Patients who have not been tested for HIV antibody may be enrolled.) [*11] Patients who are positive HIV antibody but negative for HIV-RNA may be enrolled. 7. Patients with poorly controlled infections or diabetes 8. Patients with a past history of interstitial lung diseases (such as interstitial pneumonia and pulmonary fibrosis) requiring treatment or extensive findings of these diseases on CT 9. Patients with a serious complication[*10] [*10] Gastrointestinal hemorrhage, heart disease, glaucoma, etc. 10. Patients who have been receiving continuous systemic administration (oral or intravenous) of steroids (for 2 weeks or more at a dose of the equivalent of ≥ 10 mg/day of prednisolone) 11. Patients for whom enrollment in the trial is difficult because of clinically problematic psychiatric disorders 12. Pregnant or lactating women 13. Patients with reproductive potential who do not wish to use adequate contraceptive measures during the period of participation in the trial and during the contraception period (see "4.3 Pregnancy and Contraception") 14. Patients who are judged by the attending physician to be ineligible for enrollment in the trial for other reasons
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, α = 0.05 (one-sided 0.025), 1 - β = 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.
Administration 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.
Safety evaluation	CTCAE v5.0 will be used for the evaluation.
Efficacy evaluation	Efficacy will be evaluated 2, 4, 6, 8, 10, 12, 15, 18, 24, 30, and 36 months after the enrollment in this trial. In principle, the presence or absence of relapse will be assessed by chest, abdominal, and pelvic CT (for the definition of a relapse, see "8.3 Imaging Tests"). After the completion of the follow-up period, the investigation will be continued in a separate observational study.
QOL	QOL assessments using EORTC QLQ C-30 and EQ-5D-5L
Screening and follow-up study	The identification of ctDNA-positive patients prior to the enrollment in the trial and the observation after the completion of the follow-up period in the trial will be performed in separate "Genetic alteration and clinical record in radically resected colorectal cancer revealed by liquid biopsy and whole exome analysis (Abbreviated as GALAXY study)" (see Section 2.10.1.2).
Planned study period	Japan, planned enrollment period: From June 2020 to Jun 2023 (3 years) (Taiwan, enrollment period: until March 2022) 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
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Planned study sites	See Appendix

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1 Objectives

This trial 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 trial is to verify the efficacy and safety of preemptive treatment with trifluridine/tipiracil hydrochloride (FTD/TPI) compared with follow-up, which is the standard of care.

2 Background and Rationales for the Protocol

2.1 Epidemiology of Colorectal Cancer

Currently, colorectal cancer remains a life-threatening serious disease. The GLOBOCAN data show that every year in the whole world, 1.36 million people are newly diagnosed with colorectal cancer (746,000 men and 614,000 women; prevalence, 17.2 per 100,000 people), and 693,000 people die of the disease (373,000 men and 320,000 women), resulting in an annual mortality of 8.4 per 100,000 people.[1)] The American Cancer Society estimates that in the U.S., the number of new cases of colorectal cancer in 2017 was 95,520.[2)] In the World Health Organization (WHO) European Region, colorectal cancer is a tumor that ranks first in prevalence, with 471,000 new diagnosis each year and a mean mortality of 28.2 per 100,000 people.[1)] The American Cancer Society has reported that the 5-year survival rate for colon cancer by stage is 90% for the localized type (Stage I, IIA, and IIB), 71% for the regional type (Stage IIC and III), and 14% for the distant type (Stage IV), and that for rectal cancer by stage is 89% for the localized type (Stage I, IIA, and IIB), 70% for the regional type (Stage IIC and III), and 15% for the distant type (Stage IV).[2)]

2.2 Standard of Care by Stage

Radical surgical resection is performed for Stage I to III colorectal cancer. In general, the postoperative standard of care is observation for a progress for Stage I/II without pathological metastases to lymph nodes, and postoperative adjuvant chemotherapy is recommended for Stage III with pathological metastases to lymph nodes. However, postoperative adjuvant chemotherapy is considered in some Stage II patients with high risk factors for relapse. In Stage IV and relapsed cases with distant metastasis, surgical resection of metastatic lesions is considered if radical surgical treatment is possible, and perioperative chemotherapy is used in combination with the surgical resection according to the risk. If radical surgical treatment is difficult, systemic chemotherapy will be performed.

2.3 Postoperative Adjuvant Chemotherapy for Colorectal Cancer

As postoperative adjuvant chemotherapy for colorectal cancer, fluoropyrimidine monotherapy (capecitabine, 5-fluorouracil [5-FU]/leucovorin [LV], UFT+LV, S-1) or oxaliplatin combination therapy (CAPOX, FOLFOX) is performed for 6 months. As a postoperative adjuvant chemotherapy option for Stage III colon cancer, oxaliplatin combination therapy has reproducibly been shown to reduce the relative risk of relapse/death by approximately 20% compared to 5-FU/LV in multiple randomized studies,[3-5)] and is recommended as the most effective treatment option in both Japan and

Western countries. In addition, an integrated analysis of the optimal duration of treatment with oxaliplatin combination therapy for Stage III colon cancer (IDEA collaboration) has shown that the 3-month regimen was not non-inferior to the 6-month regimen in all subjects but was as effective as the 6-month regimen in inhibiting relapses in patients treated with CAPOX, especially in patients at low risk of relapse.[6)] For this reason, 3-month CAPOX therapy can be an option, especially for Stage III colon cancer with a low risk of relapse. In Stage IV colorectal cancer and recurrent colorectal cancer with distant metastases that can be curatively resected, chemotherapy such as oxaliplatin combination therapy is performed in the perioperative period in the same manner as in Stage III colorectal cancer. Postoperative adjuvant chemotherapy has not shown clear efficacy for inhibiting relapses of Stage II colon cancer, and performing postoperative adjuvant chemotherapy indiscriminately for Stage II colon cancer is not recommended. On the other hand, Western guidelines specify a group of patients at high risk of relapse within patients with Stage II colon cancer and recommend postoperative adjuvant chemotherapy for this group. The same treatment regimen as used for Stage III colon cancer has been recommended for this group. With respect to treatment period, an integrated analysis of the optimal duration of treatment with oxaliplatin combination therapy for patients with Stage II colon cancer with high-risk factors for relapse (IDEA collaboration) was conducted and showed that the 3-month regimen was not non-inferior to the 6-month regimen in all subjects.[7)] There is less evidence for postoperative adjuvant chemotherapy for rectal cancer than for the same therapy for colon cancer, and the former is performed in the same manner as the latter. In patients with curative resection of rectal cancer after preoperative chemoradiotherapy, postoperative adjuvant combination chemotherapy with oxaliplatin has been reported to be significantly superior to 5-FU/LV in inhibiting relapses,[8)] and oxaliplatin combination therapy is expected to be effective. With respect to adjuvant chemotherapy after resection of distant metastases, postoperative adjuvant chemotherapy after hepatectomy has been shown to be effective for inhibiting relapses;[9-11)] however, no randomized study that investigated the usefulness of postoperative adjuvant chemotherapy after resection of metastases of colorectal cancer other than liver metastases has been reported . Although the optimal treatment regimen for adjuvant chemotherapy after resection of distant metastases has not yet been established, it has been accepted in clinical practice to use oxaliplatin combination therapy, which is a recommended regimen of postoperative adjuvant chemotherapy for Stage III patients, for patients with resection of distant metastases who are clearly at a higher risk of relapse than Stage III patients. In addition, multiple studies have been conducted to verify whether regimens that have been shown to be

effective for unresectable large intestine carcinoma are effective as postoperative adjuvant chemotherapy, and Phase III studies have shown that none of irinotecan,[12-14] bevacizumab (BV),[15-17] or cetuximab[18,19] provides additional benefit on the standard of care.

2.4 Follow-up After Colorectal Cancer Surgery

As the standard follow-up for colorectal cancer after curative resection, regular performance of history taking and medical examination, chest to pelvic computed tomography (CT) scan, tumor markers testing, and colonoscopy has been recommended by the guidelines. Although tumor markers have been reported to show abnormal values several months in advance of diagnostic imaging, the clinical benefits thereof for predicting relapses after radical surgical treatment of colorectal cancer have not been established.

2.5 Signatera™, a Minimal Residual Disease Detection System

ctDNA (mutant allele) is known to has an extremely short plasma half-life (shorter than 2 hours) compared with tumor markers (such as CEA and CA19-9).[20] After curative resection, therefore, ctDNA rapidly disappears from the blood if no residual cancer exists. Utilizing these characteristics of ctDNA, a diagnostic system for detecting minimal residual disease (MRD) using a next generation sequencing technology is being developed.[21-24] Signatera™ is a novel ctDNA detection system for MRD detection developed by Natera Inc., U.S.A. First, whole exon analysis of tumor tissue samples is performed, followed by extraction of 16 somatic mutations from the detected tumor-specific single nucleotide variants using an original program, and the primer set that detects these variants is established for each patient and tumor. Signatera™ is a test system that extracts ctDNA from the blood obtained postoperatively, using this primer set, and detects the presence or absence of somatic mutations derived from tumors using a next generation sequencer. In Signatera™, the sensitivity limit for ctDNA allele frequency is 0.005%, the 90% sensitivity limit is 0.010%, and the specificity is at least 99.5%.[25] In a multicenter prospective cohort study in patients with Stage I-III large intestine carcinoma, 130 patients with Stage I-III large intestine carcinoma were enrolled. The ctDNA positive rate at 30 days after the curative resection was 10.6%, and the relapse rate was 7 times or more higher in the ctDNA positive group than in the ctDNA negative group (hazard ratio [HR] = 7.2; 95% CI, 2.7-19.0). In addition, of the 58 patients who were evaluable for ctDNA after completing postoperative adjuvant chemotherapy, 7 patients (12.0%) were positive for ctDNA, and 51 patients (88.0%) were negative for ctDNA, with relapse observed in all ctDNA-positive patients, which was

significantly higher than the relapse rate in ctDNA-negative patients (7/51 patients, 13.7%) (HR = 17.5; 95% CI, 5.4-56.5). Moreover, of the 75 patients who were tested for ctDNA chronologically, 14 out of 15 ctDNA-positive patients (93.3%) had a relapse, and of the 60 patients who were negative for ctDNA, only 2 patients had a relapse. With respect to time to relapse, the median time to confirmation of a relapse by ordinary CT scan was 14.2 months, while the median time to detection of positive ctDNA was 5.5 months.[22)]

2.6 Significance of ctDNA Testing for MRD Detection

The ctDNA gene panel system for detecting MRD in colorectal cancer with curative resection is considered to be useful for identifying patients at an extremely high risk of relapse. The JSCCR Guidelines 2019 for the Treatment of Colorectal Cancer recommends selecting treatment regimens for postoperative adjuvant therapy according to the risk of relapse. If patients at high risk of relapse can be excluded, a population with good prognosis can be extracted and, by considering other clinical prognostic factors, postoperative adjuvant chemotherapy may be omitted in ctDNA-negative patients who have not undergone postoperative adjuvant chemotherapy. On the other hand, the clinical significance of ctDNA-positive patients is not only identification of patients at high risk of relapse or the surveillance of postoperative relapse through monitoring but also early detection of relapse and the improvement of treatment outcomes through intervention with systemic chemotherapy at the time when the relapse is still a minimal residual tumor. The Clinical Guidance for Genetic Testing in Colorectal Cancer Treatment Edition 4 in Japan recommends ctDNA gene panel testing for the detection of MRD in patients with advanced and recurrent resectable large intestine carcinoma as a repeatable test to identify groups at high risk of relapse. In the US, the Centers for Medicare & Medicaid Services (hereinafter referred to as "CMS") decided to pay for Signatera™ as an MRD monitoring test after surgery of large intestine carcinoma (high risk Stage II colon cancer, Stage II rectal cancer, and Stage III colorectal cancer).

2.7 FTD/TPI in Colorectal Cancer

FTD/TPI (TAS-102) is a novel oral nucleoside antineoplastic agent containing, in a 1:0.5 ratio, trifluorothymidine (FTD) and a thymidine phosphorylase (TP) inhibitor that inhibits the degradation of FTD.[26)] FTD/TPI exhibits an antitumor effect by mechanisms that are different from thymidylate synthetase (TS) inhibition by 5-FU, i.e., not only by inhibiting TS but also by being incorporated into DNA through phosphorylation by thymidine kinase (TK) 1. In a nonclinical study, the antitumor effect of FTD/TPI on strains with a low sensitivity to 5-FU anticancer agents was tested using

nude mice with implanted human colon adenocarcinoma cells (DLD-1). In the study, FTD/TPI was shown to have a significant tumor suppression effect compared to 5-FU in a 5-FU resistant DLD-1 implanted mouse model.[27] As a clinical study, a multicenter, multinational, double-blind, randomized, controlled Phase III study for the purpose of verifying the superiority of FTD/TPI to placebo administration (RECOURSE study) was conducted in patients with advanced/recurrent colorectal cancer who were refractory or intolerant after receiving at least 2 regimens of prior treatment, including a fluoropyrimidine antineoplastic agent, irinotecan, oxaliplatin, and an anti-VEGF monoclonal antibody and at least 1 type of anti-EGFR monoclonal antibody in cases where the KRAS gene was a wild type. Comparison with the placebo group in this study showed that the median overall survival (OS), which was the primary endpoint, was significantly longer in the FTD/TPI group (7.1 months) than in the placebo group (5.3 months) (HR = 0.68; 95% CI, 0.58-0.81; $p < 0.0001$). The median progression-free survival (PFS) was also significantly longer in the FTD/TPI group (2.0 months) than in the placebo group (1.7 months) (HR = 0.48; 95% CI, 0.41-0.57; $p < 0.0001$). The response rate was 1.6% in the FTD/TPI group and 0.4% in the placebo group ($p = 0.29$), and the disease control rate was 44% in the FTD/TPI group and 16% in the placebo group ($p < 0.001$).[28] On the basis of these results, FTD/TPI has been established as a standard late-line treatment and is listed in the guidelines in Japan and overseas. In this trial, the relatively frequent adverse events of FTD/TPI were gastrointestinal toxicity (such as nausea, anorexia, diarrhea, and vomiting) and hematotoxicity, and febrile neutropenia accounted for 3.8%. In addition, a multicenter, multinational, double-blind, randomized, Phase III comparative study for the purpose of verifying the superiority of FTD/TPI to placebo administration (TERRA study) was conducted in Asia (China, South Korea, Thailand) in patients with advanced/recurrent colorectal cancer who were refractory or intolerant after receiving at least 2 regimens of prior treatment. This study similarly showed that the median OS, which was the primary endpoint, was significantly longer in the FTD/TPI group (7.8 months) than in the placebo group (7.1 months) (HR = 0.79; 95% CI, 0.62-0.99; $p = 0.035$), and the median PFS was also significantly longer in the FTD/TPI group (2.0 months) than in the placebo group (1.8 months) (HR = 0.43, 95% CI, 0.34-0.54; $p < 0.0001$). The response rate was 1.1% in the FTD/TPI group and 0% in the placebo group ($p = 0.554$), and the disease control rate was 44.1% in the FTD/TPI group and 14.6% in the placebo group ($p < 0.001$).[29]

The efficacy of FTD/TPI as the initial treatment for advanced/recurrent colorectal cancer has also been reported. A randomized Phase II comparative study to verify the efficacy of FTD/TPI plus BV combination therapy compared to capecitabine (Cape) plus

BV in patients with untreated advanced/recurrent colorectal cancer for which intensive chemotherapy is not suited showed that the median PFS, which was the primary endpoint, tended to be longer in the FTD/TPI plus BV group (9.23 months in the FTD/TPI plus BV group and 7.82 months in the Cape plus BV group) (HR=0.71; 95% CI, 0.48-1.06), and the median OS was significantly longer in the FTD/TPI plus BV group (18.0 months) than in the Cape plus BV group (16.2 months) (HR=0.56; 95% CI, 0.32-0.98). [30] The results of this trial suggest that FTD/TPI also exhibits an antitumor effect in patients who have not used any fluoropyrimidine antineoplastic agent.

On the other hand, no report is available on clinical studies to investigate the efficacy of FTD/TPI as postoperative adjuvant chemotherapy; however, the effect of FTD on cancer stem cells has been reported as the result of a preclinical study suggesting that FTD may inhibit relapses. Cancer stem cells are cells with replication competence and multipotency and are considered to be involved in cancer cells' proliferation and differentiation, distant metastasis, and chemoresistance.[31] Using a method called sphere-forming assay to quantify the number of cancer stem cells, 5FU and FTD were evaluated for their inhibitory effect on cancer stem cells. FTD showed a significant inhibition, suggesting that FTD may inhibit tumor relapse.[32]

2.8 Preemptive Treatment of ctDNA-positive Colorectal Cancer

A meta-analysis that investigated the significance of multidisciplinary follow-up for colorectal cancer with curative resection using imaging tests such as CT, colonoscopy, and biomarkers such as tumor markers has been reported. In this investigation, multidisciplinary follow-up has been reported to have led to a significant extension of OS, an increase in the rate of identification of asymptomatic relapses, and an increase in the rate of curative resection upon confirmation of relapse.[33] The incorporation of ctDNA testing for the purpose of detecting MRD in such multidisciplinary follow-up is expected to provide further extension of survival. ctDNA-positive patients are a group at an extremely high risk of relapse, and early treatment interventions in this group can be expected to lead to extended survival. FTD/TPI has been shown to extend prognosis in patients with unresectable large intestine carcinoma who are refractory or intolerant to treatment including fluoropyrimidine and oxaliplatin. Although the efficacy of this drug as a postoperative adjuvant chemotherapy has not been established, we thought that preemptive treatment with FTD/TPI in ctDNA-positive patients in whom the presence of minimal residual disease is strongly suspected is expected to inhibit relapses and extend survival. We planned this trial for this reason.

2.9 Rationale for Setting Treatment Plan

2.9.1 Treatment Regimen for This Trial

FTD/TPI or placebo: In 1 course consisting of 28 days, FTD/TPI 35 mg/m^2/dose or placebo will be orally administered twice daily (after breakfast and dinner) for 5 consecutive days, followed by withdrawal for 2 days. After repeating this cycle twice, the subject is withdrawn from study treatment for 14 days. This treatment will be continued until completion of 6 courses or until the subject meets any discontinuation criterion. Study treatment will be given to the subject either as an inpatient or an outpatient.

2.9.2 Rationale for Setting the Administration and Dosage of FTF/TPI★

In the study treatment used in this trial, we decided to use the administration and dosage that have been shown to be safe and effective in a multicenter, multinational, double-blind, randomized, controlled Phase III study for the purpose of verifying the superiority of FTD/TPI to placebo administration (RECOURSE study).

2.9.3 Efficacy of FTD/TPI

See "2.7 FTD/TPI in Colorectal Cancer."

2.9.4 Safety of FTD/TPI

The representative adverse events observed in patients treated with FTD/TPI in the RECOURSE study and the TERRA study are shown in Table 2-1 below.

Table 2-1 Adverse Events in the FTD/TPI Group

	Phase III Study (RECOURSE Study[28]) N=533 n (%)		Phase III Study (TERRA Study[29]) N=271 n (%)	
	All Grades	Grade3/4	All Grades	Grade3/4
Non-hematologic toxicity				
Nausea	258 (48)	10 (2)	98 (36.2)	2 (0.7)
Vomiting	148 (28)	11 (2)	50 (18.5)	2 (0.7)
Anorexia	208 (39)	19 (4)	67 (24.7)	2 (0.7)
Fatigue	188 (35)	21 (4)	55 (20.3)	4 (1.5)
Diarrhea	170 (32)	16 (3)	40 (14.8)	2 (0.7)
Febrile neutropenia	20 (4)	20 (4)	0 (0)	0 (0)
Hematotoxicity				
Neutropenia	353 (67)	200 (38)	182 (67.2)	90 (33.2)
White blood cell decreased	407 (77)	113 (21)	190 (70.1)	56 (20.7)
Anemia	404 (77)	96 (18)	209 (77.1)	48 (17.7)

Platelets decreased	223 (42)	27 (5)	96 (35.4)	8 (3.0)
ALT increased	126 (24)	10 (2)	48 (17.7)	3 (1.1)
AST increased	155 (30)	23 (4)	63 (23.2)	10 (3.7)
Total bilirubin increased	189 (36)	45 (9)	99 (36.5)	19 (7.0)
Creatinine increased	71 (13)	5 (<1)	13 (4.8)	3 (1.1)

With respect to the long-term safety of FTD/TPI, adverse events have been investigated in patients who received study treatment for a long term (at least 180 days after the first dose) in the above-described RECOURSE study. Long-term administration in these patients was not reported to have caused new adverse events, an increase in the frequency of adverse events, or secondary cancers.

2.10 Study Design

This trial is a randomized, double-blind, multinational Phase III study to evaluate the efficacy and safety of preemptive treatment with FTD/TPI compared with follow-up, which is the standard of care, in patients who underwent curative resection of colorectal cancer and then tested positive for ctDNA. If the results of this trial are promising, we intend to consult with the provider of the investigational drug about the application for approval of FTD/TPI for the indications of colorectal cancer that tested positive for ctDNA after curative resection.

2.10.1 Patients

2.10.1.1 Lines of Treatment

This trial will be conducted in patients with resectable colorectal cancer who underwent curative resection 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.

2.10.1.2 Patients Who Become Positive for ctDNA After Curative Resection

The identification of ctDNA-positive patients for this trial will be performed in separate "Genetic alteration and clinical record in radically resected colorectal cancer revealed by liquid biopsy and whole exome analysis (Abbreviated as GALAXY study*)." This study will be conducted in patients who tested positive for ctDNA in the GALAXY study after undergoing curative resection.

* GALAXY study: A study to perform Signatera™ in patients with colorectal cancer who are scheduled for radical surgery and construct a registry about the relationship between genetic alterations detected in tumor tissues and blood samples and clinical course. The timing of

Signatera™ testing is before surgery, 4 weeks after surgery, every 12 weeks after surgery until 48 weeks after surgery, and then 72 weeks after surgery and 96 weeks after surgery.

2.10.2 Endpoints

The endpoints in this trial are as follows:

Primary endpoint:

- Disease-free survival 1[*1*3] (DFS1)

[*1] In this trial, a DFS1 event is defined as a relapse, development of a secondary colorectal cancer 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 trial, 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 trial period, subjects will be followed up for 5 years in a separate observational study.

2.10.3 Multinational Study

This trial will be conducted as a multinational study enrolling subjects in Japan and Taiwan. The treatments for colorectal cancer such as surgery and chemotherapy in Japan and Taiwan are extremely similar, and this fact is considered to provide good background for a multinational study. This trial is regarded as one prospective multinational study in which the analysis will be performed jointly and will be conducted using a common protocol in Japan and Taiwan.

2.10.4 Clinical Hypothesis and Rationale for Setting the Number of Subjects

2.10.4.1 Clinical Hypothesis

The clinical hypothesis is as follows: “In patients with colorectal cancer who tested positive for ctDNA after undergoing curative resection, administration of FTD/TPI is superior to follow-up , which is the standard of care, in DFS.” Clinical studies of adjuvant

chemotherapy after curative resection of colon cancer have shown a correlation between OS and DFS, and DFS is used as a surrogate endpoint for OS. Thus, reduction in the risk of relapse leads to a cure and, therefore, to an extended OS. On the other hand, clinical studies of drug therapies for unresectable large intestine carcinoma have shown that the correlation between PFS and OS has been becoming weak because of the emergence of new therapeutic drugs. On the other hand, several studies on initial treatment, including a Phase III study comparing FOLFOXIRI plus bevacizumab therapy versus FOLFIRI plus bevacizumab therapy (TRIBE study) and a Phase III study comparing FOLFIRI plus bevacizumab therapy versus FOLFIRI plus cetuximab therapy (FIRE-3 study), have shown an extension of OS.[34,35] Thus, preemptive treatment performed when the tumor volume is low may extend not only DFS but also OS even in a ctDNA-positive population in which relapses may subsequently occur.

2.10.4.2 Rationale for Setting the Target Number of Subjects

The above-described RECOURSE study has shown that FTD/TPI is significantly superior to placebo in overall survival (5.3 months vs 7.1 months; HR = 0.68) and progression-free survival (2.0 months vs 1.7 months; HR = 0.48). It is assumed that similar efficacy is expected in ctDNA-positive patients. In addition, the median time from the date of the ctDNA-positive blood test to the CT diagnosis of a relapse in the ctDNA-positive group is reported to be 8.7 months. 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, after consideration of the period from the date of the ctDNA-positive test to the date of enrollment in the study, 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.

2.10.4.3 Expected Subject Accumulation, Enrollment Period, and Planned Observation Period

A total of 240 subjects will be enrolled in this trial during the enrollment period of 3 years from June 2020. Depending on the subject accumulation status, increasing the number of subjects to the maximum 300 will be considered.

The planned observation period will be 1 year from the date of enrollment of the last subject. Furthermore, after the end of the trial period, subjects will be followed up for approximately 5 years in a separate observational study.

2.11 Summary of Expected Benefits and Disadvantages Associated with Study Participation

2.11.1 Expected Benefits

Patients with colorectal cancer who tested positive for ctDNA after undergoing curative resection is a population at an extremely high risk of relapse, and interventions with systemic chemotherapy in these patients as an MRD-positive population are expected to improve treatment outcomes. FTD/TPI is expected to extend survival and inhibit relapses in the above patients. Establishment of the efficacy and safety of FTD/TPI in the above-described patients is expected not only to extend the indications of FTD/TPI but also to establish a new disease classification (ctDNA-positive population) and provide new evidence. In addition, even patients who are assigned to the placebo group in this trial are expected to be followed up more closely than in normal follow-up, and this will contribute to early detection.

2.11.2 Expected Risks and Disadvantages

Various adverse events, such as hematotoxicity including neutropenia, which is the main adverse event caused by FTD/TPI, and gastrointestinal toxicity, may possibly occur. In order to minimize the risks and disadvantages of these adverse events, the coordinating investigator will determine whether the actual adverse event is an expected event. In addition, a system will be established in which necessary measures such as reporting to the Data and Safety Monitoring Committee and notification to medical institutions will be taken in cases where a serious adverse event or unexpected adverse event occurs.

3 Criteria and Definitions Used in This Trial

3.1 Stage Classification

In this trial, the "Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, Ninth Edition" and "UICC TNM Classification, 8th Edition" will be followed.

3.1.1 Primary Tumor

The location of large intestine carcinoma will be in accordance with the large intestine segmentation in the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, Ninth Edition.

1) Colon
    a) Cecum (C)
    b) Ascending colon (A)
    c) Transverse colon (T)
    d) Descending colon (D)
    e) Sigmoid colon (S)
2) Rectum
    a) Rectosigmoid (RS)
    b) Upper rectum (Ra)
    c) Lower rectum (Rb)
3) Other
    a) Vermiform appendix (V)
    b) Anal canal (P)
    c) Perianal skin (E)

3.1.2 Macroscopic Classification (Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, Ninth Edition)

1) Basic 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: Unclassified type
2) Type 0: Subtypes of macroscopic type 0
   0-I: Protruded type
      0-Ip: Pedunculated type
      0-Isp: Subpedunculated type

0-Is: Sessile type

0-II: Superficial type

0-IIa: Elevated type

0-IIb: Flat type

0-IIc: Depressed type

3.1.3 Depth of Invasion [T] (Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, Ninth Edition)

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Tumor is confined to the mucosa (M) and does not invade the submucosa (SM)

T1: Tumor is confined to the SM and does not invade the muscularis propria (MP)

T1a: Tumor is confined to the SM, and invasion is within 1000 μm

T1b: Tumor is confined to the SM, and invasion is 1000 μm or more, but it does not extend to the MP

T2: Tumor invasion to, but not beyond, the MP

T3: Tumor invades beyond the MP.

In sites with serosa, the tumor grows into the subserosa (SS).

In sites with no serosa, the tumor grows into the adventitia (A)

T4: Tumor invades or perforates the serosa (SE) or directly invades other organs or structures (SI/AI)

T4a: Tumor invades the serosa or perforates abdominal cavity via the burst through the serosa (SE)

T4b: Tumor directly invades adjacent organs or structures (SI/AI)

3.1.4 Lymph Node Metastasis [N] (Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, Ninth Edition)

NX: Lymph node metastasis cannot be assessed

N0: No evidence of lymph node metastasis*

N1: Metastasis in 1-3 pericolic/perirectal or intermediate lymph nodes

N1a: Metastasis in 1 lymph node

N1b: Metastasis in 2-3 lymph nodes

N2: Metastasis in 4 or more pericolic/perirectal or intermediate lymph nodes

N2a: Metastasis in 4-6 lymph nodes

N2b: Metastasis in 7 or more lymph nodes

N3: Metastasis in the main lymph node (s). In the lower rectal cancer, metastasis in the main and/or lateral lymph node (s) **

* N0 in the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, Ninth Edition includes N1c in the UICC TNM Classification, 8th Edition (tumor deposits, or satellite nodules, are seen in the adjacent soft tissues of the colon or rectum without subserosal layer or peritoneal coat, with no regional lymph node metastasis), which is eligible for this trial.

** N3 in the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, Ninth Edition is treated as one of the regional lymph nodes or non-regional lymph nodes (M1) depending on the location of the metastasis in the UICC TNM Classification, 8th Edition.

3.1.5 Distant Metastasis [M] (Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, Ninth Edition)

M0: No distant metastasis

M1: Distant metastasis

M1a: Distant metastasis confined to one organ. Peritoneal metastasis not present

M1b: Distant metastasis in more than one organ. Peritoneal metastasis not present

M1c: Presence of peritoneal metastasis

M1c1: Metastasis to the peritoneum only

M1c2: Metastasis to the peritoneum and other distant metastasis

3.1.6 Degree of Progression (Stage)

The degree of progression in the UICC TNM Classification, 8th Edition is shown.

The T classification, N classification, and M classification in the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma, Ninth Edition shown in Section 3.1.3 to 3.1.5 are converted into T classification, N classification, and M classification in the UICC TNM Classification, 8th Edition to determine the stage.

<table>
<tr><td rowspan="2"></td><td colspan="4" rowspan="2">M0</td><td colspan="3">M1</td></tr>
<tr><td>M1a</td><td>M1b</td><td>M1c</td></tr>
<tr><td>N0</td><td>N1
(N1a/N1b/N1c)</td><td>N2a</td><td>N2b,N3</td><td colspan="3">Regardless of N</td></tr>
<tr><td>Tis</td><td>0</td><td colspan="6">N/A</td></tr>
<tr><td>T1</td><td rowspan="2">I</td><td rowspan="2">IIIA</td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2">IVA</td><td rowspan="2">IVB</td><td rowspan="2">IVC</td></tr>
<tr><td>T2</td></tr>
</table>

T3	IIA		IIIB				
T4a	IIB		IIIC				
T4b	IIC						

3.2 Classification Criteria for Histological Findings

Histological findings will be classified according to the WHO Classification of Tumors of the Digestive System, 4th Edition.

3.3 Performance status (ECOG Classification)

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

3.4 Criteria for the Assessment of Adverse Events

"Common Terminology Criteria for Adverse Events (CTCAE) v5.0" will be used to determine the terms and grades of adverse events.

3.5 Criteria for Positive ctDNA

The liquid biopsy of blood samples required for the assessment of patients according to the eligibility criteria for this trial will be performed in the GALAXY study, in which Signatera™ will be used (see Section 2.10.1.2).

4 Eligibility Criteria

Patients who meet all of the inclusion criteria and do not meet any of the exclusion criteria will be enrolled as patients who will receive study treatment.

4.1 Inclusion Criteria

1. Patients who have been histopathologically diagnosed with colorectal adenocarcinoma (Stage II or lower/Stage III/M1)
2. Patients who have undergone radical resection*[1] of the primary and metastatic tumors

   *[1] It is considered to be a radical resection if the tumor is exposed at the edge or on the surface of surgical detachment but is encapsulated.
3. Patients who are subject to postoperative chemotherapy according to the country guideline and/or medical practice, that is Stage III (T any N1*[2]/2 M0) and Stage IV (T any N any M1) (UICC TNM Classification, 8th Edition) for Taiwan must have a history*[4] of standard postoperative chemotherapy*[3].

   *[2] N1c (UICC TNM Classification, 8th Edition) is also included in this stage (tumor deposits, or satellite nodules, are seen in the adjacent soft tissues of the colon or rectum without subserosal layer or peritoneal coat, with no regional lymph node metastasis).

   *[3] Treatments described in the current Japanese and overseas guidelines or study treatments conducted in clinical studies.

   *[4] In case of patients who do not have a standard postoperative chemotherapy for rational reason, these patients can be enrolled.
   Note that if sites enroll such patients, record the reason for the decision to medical chart.
4. Patients who tested positive for ctDNA using Signatera™ by an analysis*[5] of the latest blood samples collected within 3 months prior to enrollment

   *[5] Analyses of blood samples using Signatera™ will be performed in a separate clinical study (see Section 2.10.1.2.).
5. Patients with no obvious relapse confirmed by chest, abdominal, and pelvic CT scans, etc.
6. Patients who are capable of oral ingestion
7. Patients aged 20 years or older at the time of informed consent
8. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1

9. Patients who have no severe disorder in major organs (such as the bone marrow, heart, lungs, liver, and kidneys) and meet the following criteria (Data obtained most recently and within 14 days of the date of enrollment will be used for enrollment. Data obtained 2 weeks before the date of enrollment, on the same day of the week as the enrollment date, may be used for enrollment.)
   - Neutrophil count ≥ 1,500/mm^3
   - Platelet count ≥ 100,000/mm^3
   - Hemoglobin ≥ 8.0 g/dL
   - Serum creatinine ≤ 1.5 mg/dL
   - Total bilirubin ≤ 1.5 mg/dL
   - ALT and AST ≤ 100 U/L
10. Patients with no diarrhea or stomatitis of Grade 2 or severer according to CTCAE v5.0
11. Patients who voluntarily gave written consent to participate in the trial after receiving a thorough explanation of the trial before enrolling in the trial

4.2 Exclusion Criteria

1. Patients with a history of treatment with FTD/TPI
2. Patients with a history of treatment with 2 or more regimens of postoperative adjuvant chemotherapy[*6] (Preoperative chemotherapy will not be counted as a regimen.)

   [*6] The timing of initiation of the postoperative adjuvant chemotherapy will not be specified.
3. Patients with a past history of a malignant tumor[*7] other than colorectal adenocarcinoma.

   [*7] Patients with a relapse-free survival period of 5 years or longer, or patients with basal cell or squamous cell carcinoma of the skin that is considered cured by local treatment, superficial bladder cancer, cervical cancer, carcinoma in situ (intraepithelial cancer) or lesions equivalent to intramucosal cancer, or non-metastatic prostate cancer not requiring systemic treatment may be enrolled.
4. Patients with a local or systemic active infection requiring intervention
5. Patients who are positive for HBs antigen[*8] or positive for HCV antibody[*9]

   [*8] HBV-DNA testing is mandatory to be below the limit of detection for patients with a negative HBs antigen test, but with a positive test result for either HBs antibody or HBc antibody

   [*9] Patients who are positive for HCV antibody but negative for HCV-RNA may be enrolled.

6. Patients who are positive for HIV antibody[*11] (Patients who have not been tested for HIV antibody may be enrolled.)
   [*x11] Patients who are positive HIV antibody but negative for HIV-RNA may be enrolled.
7. Patients with poorly controlled infections or diabetes
8. Patients with a past history of interstitial lung diseases (such as interstitial pneumonia and pulmonary fibrosis) requiring treatment or extensive findings of these diseases on CT
9. Patients with a serious complication[*10]
   [*10] Gastrointestinal hemorrhage, heart disease, glaucoma, etc.
10. Patients who have been continuously receiving systemic administration (oral or intravenous) of steroids (for 2 weeks or more at a dose of the equivalent of ≥ 10 mg/day of prednisolone)
11. Patients for whom enrollment in the trial is difficult because of clinically problematic psychiatric disorders
12. Pregnant or lactating women
13. Patients with reproductive potential who do not wish to use adequate contraceptive measures during the period of participation in the trial and during the contraception period (see "4.3 Pregnancy and Contraception")
14. Patients who are judged by the attending physician to be ineligible for enrollment in the trial for other reasons

4.3 Pregnancy and Contraception

Women of childbearing potential (including those without menstruation for medical reasons such as chemical menopause) include all women who have experienced menarche, have not undergone sterilization (hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or the like), and are not postmenopausal. "Postmenopausal" is defined as being amenorrheic continuously for 1 year or longer in the absence of a special reason. Women using oral contraceptives or mechanical contraceptive measures such as intrauterine devices or barrier methods are considered to have childbearing potential. If a female subject is judged to have no childbearing potential, the fact will be documented in the subject's source documents.

For both men and women of childbearing potential, the contraception period will be between the time point of informed consent and at least 6 months after the last dose of the investigational drug.

With respect to contraception, subjects will need to agree to use an effective contraceptive method, avoid sexual intercourse, or take a reliable contraceptive measure

(double-barrier method that includes any 2 measures selected from diaphragm, condom, contraceptive sponge, spermicide, bilateral tubal ligation, and vasectomy). Effective methods of contraception include:

- Combination hormonal contraceptives (containing estrogen and progestogen) that inhibit ovulation:
  - Oral contraceptive
  - Intravaginal contraceptive
  - Percutaneous contraceptive
- Hormonal contraceptives containing progestogen only that inhibit ovulation:
  - Oral contraceptive
  - Injectable contraceptive
  - Implantable contraceptive
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomy or vasectomy of the subject's partner
- Complete sexual abstinence (avoiding heterosexual intercourse from the time point of informed consent until at least 6 months after the last dose of the investigational drug). Periodic abstinence (calendar method, sympto-thermal method, and ovulation methods) is not acceptable as a method of contraception.

Men must not perform sperm cryopreservation or donate sperm from the time point of informed consent, through the trial period, and until at least 6 months after the last dose of the investigational drug. If sperm preservation is needed, performing it before enrollment in this trial shall be considered.

Women must not donate eggs or harvest eggs for their own use from the time point of informed consent, through the period of study treatment, and until at least 6 months after the last dose of the investigational drug.

5 Enrollment and Allocation

5.1 Enrollment Procedures

After ascertaining that the subject meets all inclusion criteria and none of the exclusion criteria and obtaining written informed consent from the subject as an eligible patient, the subject will be enrolled through a Web enrollment system. If eligibility is confirmed, the enrollment center will notify the medical institution of the registration number and the drug number obtained by allocation through the Web enrollment system.

■ Contact information and hours for subject enrollment

The URL of the Web enrollment system will be separately notified by "RTMS System Operation Manual."

(Enrollment is possible 24 hours a day, 365 days a year. However, in cases where the system becomes inaccessible due to maintenance, etc., such fact will be notified in advance on the information screen of the Web enrollment system.)

■ Information about enrollment

The contact information for the help desk, etc. will be separately notified by "RTMS System Operation Manual."

(Mon-Fri, 9:00 a.m. to 6:00 p.m., excluding Saturdays, Sundays, holidays, and December 29 to January 4)

■ Information about subject inclusion criteria

Coordinating investigators or the trial coordinating office
E-mail: prj-altair_core@eps.co.jp

5.2 Reminders for Enrollment

1) Enrollment after starting study treatment will not be permitted without an exception.
2) Enrollment with incomplete confirmation of eligibility will not be permitted until all eligibility criteria have been met.
3) Enrollment numbers will be issued after eligibility has been confirmed. Enrollment is completed by issuing an enrollment number.
4) Enrolled subjects will not be withdrawn from enrollment (deleted from the database) except in cases of withdrawal of consent, including refusal to use the data for the research. In the case of a duplicate enrollment, the initial enrollment information (enrollment number) will be adopted under any circumstances.
5) When an error or duplicate in enrollment is found, promptly notify a person in charge.

6) If the subject is seeing another hospital or department at the time of enrollment, the attending physician shall be informed of the fact that the subject will participate in this trial.

5.3 Allocation Method

In enrollment, subjects will be randomized, in a 1:1 ratio, to the active drug (FTD/TPI) group or the placebo group by the Registration Center. In randomization, a minimization method using the following 4 factors as the allocation factors will be used in order to prevent bias. The detailed procedure of the allocation method will not be disclosed to participating investigators.

[Allocation factors]

(i) Age (less than 70 years/70 years or more)

(ii) Site

(iii) Disease stage (Stage II or lower/Stage III/M1)

(iv) Primary location of lesion* (right colon/left colon/rectum)

(v) ctDNA status at 1 month postoperatively

(positive / negative or unmeasurable/Unmeasured)

* right colon: cecum to transverse colon, left colon: descending colon to Rs,

rectum: Ra/Rb

[Rationale for setting allocation factors]

(i) Age (less than 70 years/70 years or more): This factor is used as an allocation factor because the prognosis may differ with age.

(ii) Site: This factor is used as an allocation factor because it has been reported that there was inter-site gap in the results of colon cancer surgery.

(iii) Disease stage (Stage II or lower/Stage III/M1): This factor is used as an allocation factor because this trial includes colon and rectal cancer at different stages with different prognosis, and patients with resection of distant metastases (M1) have poor prognoses. In addition, it is specified that the proportion of M1 patients should be approximately 50% of the total.

(iv) Primary location of lesion (right colon/left colon/rectum): The survival after recurrence is reported to be poorer in patients with lesions in the right colon than in patients with lesions in the left colon. In addition, many of the previous reports of postoperative adjuvant chemotherapy are about colon cancer. Thus, right colon (cecum to transverse colon), left colon (descending colon to Rs), and rectum (Ra/Rb) are used as the stratification factors.

(v) ctDNA status at 1 month postoperatively (positive / negative or unmeasurable/Unmeasured): The prognosis may differ depending on the difference in the time tested positive for ctDNA

5.4 Control of Allocation Information

This trial will be conducted in a double-blind manner. As the results of allocation will not appear on the enrollment confirmation email or the screens of the Web enrollment system, the allocation group data cannot be viewed by medical institutions, coordinating investigators, the trial coordinating office, monitors, etc.

The results of allocation (allocation group data) will be stored electronically within the enrollment center, and only the enrollment center of this trial will have access to the allocation group table.

6 Treatment Plan and Treatment Modification Criteria

Treatment and treatment modifications will be made following the descriptions in this section, unless subject safety is threatened. In cases where following this protocol is considered to be medically hazardous, treatment modifications will be made according to the medical judgment of the principal investigator or sub-investigator (hereinafter, referred to as "investigator").

6.1 Study Treatment

The study treatment in this trial is treatment with FTD/TPI (TAS-102) or placebo.

Study treatment will be initiated within 8 days after enrollment (including the date of enrollment). If administration of the investigational drug cannot be started within 8 days after enrollment, such fact shall be communicated to a coordinating investigator to consider the handling of the subject. Study treatment will be given to the subject either as an inpatient or an outpatient.

The following terms will be used in this protocol:

- Discontinuation: Not resuming the administration of the investigational drug
- Delay: Delaying the administration of the investigational drug from the scheduled administration date
- Skip: Not taking the investigational drug on the date of administration of the investigational drug within a course after the course has started
- Withdrawal period: Period during which the investigational drug is not administered

6.1.1 Dose

1) The initial dose of FTD/TPI will be 35 mg/m^2/dose BID (70 mg/m^2/day). For determining the actual dose, body surface area will be calculated for each patient, and the dose specified in "Table 6.1 Dose of FTD/TPI" will be administered twice daily after breakfast and after dinner. Body surface area will be calculated by the Web enrollment system. The medical institution will enter actual dose calculated by the institution into the web enrollment system and prescribe the investigational drug corresponding to the obtained drug number.

2) Recalculation of dose due to body weight changes after the start of administration will be performed only when the subject lost body weight after the start of administration by 10% or more compared to the time of enrollment, by correcting the dose of FTD/TPI course by course. The drug number of investigational drugs prescribed in each course

will be obtained by entering actual dose calculated in the institution into the web enrollment system.

The following formula will be used to calculate body surface area. If the dose is reduced once, the dose will not be increased.

Dubois formula: Body surface area (m^2) = weight $(kg)^{0.425}$ x height $(cm)^{0.725}$ x 71.84 ÷ 10000

3) In the event of an overdose as defined below, the principal investigator will report the event to a coordinating investigator within 24 hours of learning of the event, and the coordinating investigator will report the event to the provider of the investigational drug within 1 business day.

[Definition of overdose] An overdose is defined as having occurred when a patient takes the drug beyond the "recommended daily dose (mg/day)" or the "administration schedule."

Table 6.1 Dose of FTD/TPI

Body Surface Area (m^2)	Daily Dose (mg/day)	Single Dose (mg); Number of Tablets Prescribed			
		Morning		Evening	
Less than 1.07	70	35mg	15-mg tablet × 1, 20-mg tablet × 1	35mg	15-mg tablet × 1, 20-mg tablet × 1
Not less than 1.07 and less than 1.23	80	40mg	20-mg tablet × 2	40mg	20-mg tablet × 2
Not less than 1.23 and less than 1.38	90	45mg	15-mg tablet × 3	45mg	15-mg tablet × 3
Not less than 1.38 and less than 1.53	100	50mg	15-mg tablet × 2, 20-mg tablet × 1	50mg	15-mg tablet × 2, 20-mg tablet × 1
Not less than 1.53 and less than 1.69	110	55mg	15-mg tablet × 1, 20-mg tablet × 2	55mg	15-mg tablet × 1, 20-mg tablet × 2
Not less than 1.69 and less than 1.84	120	60mg	20-mg tablet × 3	60mg	20-mg tablet × 3
Not less than 1.84 and less than 1.99	130	65mg	15-mg tablet × 3, 20-mg tablet × 1	65mg	15-mg tablet × 3, 20-mg tablet × 1
Not less than 1.99 and less than 2.15	140	70mg	15-mg tablet × 2, 20-mg tablet × 2	70mg	15-mg tablet × 2, 20-mg tablet × 2
Not less than 2.15	150	75mg	15-mg tablet × 1, 20-mg tablet × 3	75mg	15-mg tablet × 1, 20-mg tablet × 3

6.1.2 Dosage Regimen

1) In 1 course consisting of 28 days, FTD/TPI or placebo will be orally administered twice daily after breakfast and after dinner for 5 consecutive days (Days 1 to 5 and Days 8 to 12), followed by withdrawal for 2 days. After repeating this cycle twice, the subject is withdrawn from study treatment for 14 days (see the figure).

2) The start of administration on Day 1 may either be after breakfast or after dinner. The start of administration on Day 8 will be after breakfast if the start of administration on Day 1 was after breakfast and will be after dinner if the start of administration on Day 1 was after dinner. The time of start of administration on Day 1 may be changed in each course.

3) Administration will be continued until 6 courses are completed or until any of the criteria described in "6.2.1. Discontinuation Criteria" is met.

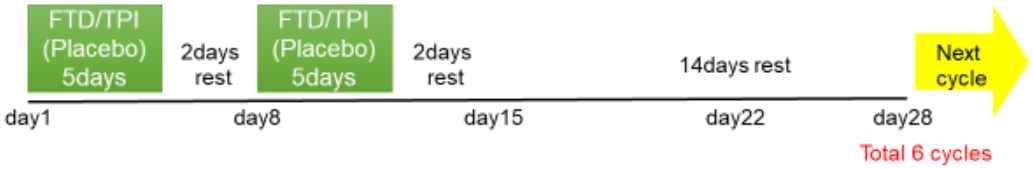


Figure. Dosage Regimen for FTD/TPI

6.2 Discontinuation of Study Treatment

6.2.1 Discontinuation Criteria

Study treatment will be discontinued if any of the following criteria is met:

1) Relapse of the primary disease
2) Study treatment cannot be continued due to an adverse event
   (i) The planed start date of the next course is set as the first day, and the start of the next course is delayed more than the same day of the week 4 weeks later in accordance with "6.3. Criteria for the Modification of Study Treatment"
   (ii) After a dose reduction to 30 mg/day in accordance with "6.3. Criteria for the Modification of Study Treatment," a further dose reduction is judged to be necessary
3) The patient requested to discontinue study treatment
4) Death during study treatment
5) The subject is shown to be out of the scope of this trial
6) The investigator judges that the trial needs to be discontinued
7) Discontinuation due to reasons other than those described above 1) to 6)

6.2.2 Data Collection and Subject Follow-Up After Discontinuation of Study Treatment

If the subject meets any of the discontinuation criteria, study treatment will be discontinued, and then the time point of discontinuation and the reasons therefor will be recorded in the case report forms (CRFs), and the tests specified for the follow-up period will be performed. If the study treatment is discontinued due to relapse of the primary disease, only the outcome survey should be conducted after the discontinuation/completion tests and after 30 days test specified in Table 8.2 Study Calendar are conducted. However, these tests may not be performed if the investigator judges that such various types of tests cannot or need not be performed because of ethical considerations or in view of the safety and benefits of the subject. If various types of tests have not been performed, the investigator will state the reason for the judgment in the original document.

6.3 Criteria for the Modification of Study Treatment

The investigator will assess which toxicity is attributed to FTD/TPI and adjust the dose of FTD/TPI according to the following recommendations. Dose modifications will always be based on the most severe preceding toxicity (CTCAE v5.0). Increasing the dose after a dose reduction will not be allowed.

1) At the start of Course 2 and the subsequent courses

(i) The course will be started after confirming that the subject meets all of the initiation and resumption criteria shown in Table 6.2. on the day of start of the course (acceptable range: ±3 days).

(ii) If the subject does not meet all of the initiation and resumption criteria shown in Table 6.2., the start of the course will be delayed until the subject meets all of the criteria.

(iii) The planed start date of the next course is set as the first day, and after delaying the start, if the subject does not meet all of the initiation and resumption criteria shown in Table 6.2. by the same day of the week 4 weeks later, study treatment will be discontinued.

2) During administration in each course

(i) If the subject meets any of the skip criteria shown in Table 6.2. during the administration period in each course, administration will be skipped until the subject meets all of the initiation and resumption criteria shown in the Table 6.2.

(ii) Even in cases where the subject resumes administration in the same course, the subject will not take the planned but unadministered doses and will take the investigational drug according to the prescribed administration schedule (Days 1

to 5 and Days 8 to 12 of each course). In addition, any unused drug for missed doses shall not be taken later.

(iii) In cases where the subject does not meet all of the initiation and resumption criteria shown in Table 6.2. by Day 12 after the skip, the next course will be started after confirming that the subject meets all of the initiation and resumption criteria shown in Table 6.2 after 14 days after the date of the last dose.

(iv) The planed start date of the next course is set as the first day, and if the start of the next course is delayed more than the same day of the week 4 weeks later, study treatment will be discontinued.

3) All time points (regardless of during administration, skipping, etc.)

(i) If the subject meets any of the dose reduction criteria shown in Table 6.2., the dose will be reduced by 10 mg/day as the daily dose course by course (the dose will be reduced in the next course and will not be reduced during the current course).

(ii) If a further dose reduction from 30 mg/day is required, study treatment will be discontinued.

(iii) After a dose reduction, the dose will not be increased.

Table 6.2. Initiation and Resumption Criteria, Skip Criteria, and Dose Reduction Criteria

	Initiation and Resumption Criteria	Skip Criteria (Within a Course)	Reduction Criteria[*1]
Neutrophil count	≧1,500/mm^3	＜1,000/mm^3	＜500/mm^3
Hemoglobin	≧8.0 g/dL	＜7.0 g/dL	
Platelet count	≧75,000/mm^3	＜50,000/mm^3	＜50,000/mm^3
Total bilirubin	≦1.5mg/dL	＞2.0mg/dL	
AST(GOT)	≦100U/L	＞100U/L	
ALT(GPT)	≦100U/L	＞100U/L	
Creatinine	≦1.5mg/dL	＞1.5mg/dL	
Adverse events other than the above	All adverse events[*2] ≤ Grade 1	All adverse events[*2] ≥ Grade 3	
Other (judged by the investigator)	The subject meets the above criteria and the investigator judges that study treatment can be initiated .	The investigator judges that continuation of administration is difficult due to an adverse event that is not listed above.[*3]	The investigator judges that a dose reduction is necessary to ensure the safety of the patient.[*3]
Remarks	If the investigator judges that it is difficult to initiate or resume a course from the viewpoint of ensuring patient		

	Initiation and Resumption Criteria	Skip Criteria (Within a Course)	Reduction Criteria*1
	safety, the course may be delayed or skipped even when the subject meets the above criteria.*3		

*1 If the subject meets the dose reduction criteria, administration within the current course will be skipped, and the dose will be reduced in the next course.

*2 Alopecia, skin hyperpigmentation, and dysgeusia are excluded. In addition, any adverse event that is obviously judged not to be caused by the investigational drug may be excluded at the discretion of the investigator. In this case, the reasons for the judgment shall be recorded in the medical records, etc.

*3 The bases for the judgment shall be recorded in the medical records etc.

Table 6.3. Dose of FTD/TPI After Dose Reduction

Daily Dose (mg/day)	Single Dose (mg); Number of Tablets Prescribed			
	Morning		Evening	
30	15mg	15-mg tablet × 1	15mg	15-mg tablet × 1
40	20mg	20-mg tablet × 1	20mg	20-mg tablet × 1
50	20mg	20-mg tablet × 1	30mg	15-mg tablet × 2
60	30mg	15-mg tablet × 2	30mg	15-mg tablet × 2
70	35mg	15-mg tablet × 1, 20-mg tablet × 1	35mg	15-mg tablet × 1, 20-mg tablet × 1
80	40mg	20-mg tablet × 2	40mg	20-mg tablet × 2
90	45mg	15-mg tablet × 3	45mg	15-mg tablet × 3
100	50mg	15-mg tablet × 2, 20-mg tablet × 1	50mg	15-mg tablet × 2, 20-mg tablet × 1
110	55mg	15-mg tablet × 1, 20-mg tablet × 2	55mg	15-mg tablet × 1, 20-mg tablet × 2
120	60mg	20-mg tablet × 3	60mg	20-mg tablet × 3
130	65mg	15-mg tablet × 3, 20-mg tablet × 1	65mg	15-mg tablet × 3, 20-mg tablet × 1
140	70mg	15-mg tablet × 2, 20-mg tablet × 2	70mg	15-mg tablet × 2, 20-mg tablet × 2

6.4 Specific Instructions for Subjects

The investigator or a trial collaborator will instruct the subject to comply with the method of administration of FTD/TPI and placebo and the following items. Medication compliance of FTD/TPI and placebo at an outpatient visit will be thoroughly interviewed and investigated (e.g., by collecting the investigational drug that has not been taken), and the results will be recorded in the medical records and the CRFs.

[Instructions]

1) Subjects will be instructed to take the FTD/TPI or placebo roughly within 1 hour after breakfast and dinner.
2) Any subject who vomited after taking FTD/TPI or placebo will be instructed not to take any additional doses to compensate for the vomited drug.
3) The investigator or a trial collaborator will instruct subjects to comply with the method of administration of FTD/TPI or placebo and to return the unused drug for any missed doses, etc.

4) Any subject who consults another hospital or department for another disease, etc. will be instructed to report to the hospital or department that the subject is participating in the trial, and any subject who needs to take a drug because of this consultation will be instructed to contact the investigator.
5) Male subjects and female subjects of childbearing potential will be instructed to take reliable measures to avoid pregnancy from the date of consent until 6 months after the last dose.
6) Subjects will be instructed to keep the investigational drug in a safe place out of reach of children under appropriate storage conditions and not to take the next dose of tablets out of the package in advance.

6.5 Permitted Concomitant Therapy/Prohibited Concomitant Therapy

Concomitant therapy will include all medications taken by the subject from the start of study treatment until 30 days after the last administration of study treatment or until the day before the start of the post-treatment, whichever is earlier. All concomitant therapies shall be reported to the investigator and recorded in the medical records and the CRFs.

Any treatment or surgical procedure that is not specified in the protocol and is performed during the trial period will be treated as concomitant therapy and must be recorded. Information to be recorded about concomitant medications and therapies will include the date of the use of the medication, treatment, or procedure and the reasons for using it.

Any drugs used for various tests and diagnoses may not be reported in the CRFs, unless necessary to determine the causal relationship of adverse events and the like.

6.5.1 Permitted Concomitant Therapy

In principle, concomitant medications/therapies deemed necessary for the subject are permitted. If the investigator is unsure whether a particular medication or procedure can be prescribed or used to a subject of this trial, the investigator shall contact a coordinating investigator.

In the event of nausea, vomiting, or diarrhea, an effective symptomatic therapy shall be started. Loperamide is recommended as an initial treatment for diarrhea.

G-CSF may be used for febrile neutropenia in accordance with the guideline of the medical institution or other guidelines (e.g., American Society of Clinical Oncology [ASCO] guidelines), but G-CSF shall not be used for the primary prevention of neutropenia. G-CSF shall be discontinued by 48 hours prior to the next cycle of study treatment.

6.5.2 Prohibited Concomitant Therapy

During the study treatment period, subjects will not be permitted to receive any cancer treatment (including surgery, chemotherapy, molecular target drugs, therapeutic antibodies, hormone therapy, immunotherapy, and radiation therapy) and any other investigational drugs. Except standard of care for the management of specific adverse events, concomitant use of long-term systemic steroid therapy (equivalent to treatment with 10 mg/day or more of prednisolone for 2 weeks or more) or other immunosuppressants will not be permitted. Inhaled corticosteroids or intraarticular corticosteroids will not be included in the prohibited therapy in this trial.

Concomitant use of nutritional supplements, medications not prescribed by the investigator, and alternative/complementary therapy is not prohibited but not recommended.

6.6 Post-treatment

In principle, after completion or discontinuation of the study treatment, no postoperative adjuvant therapy other than the study treatment will be performed for the primary disease until a relapse occurs or until follow-up of this trial is completed (1 year from the enrollment of the last patient). This limitation will not apply after a relapse occurs, or follow-up of the trial is completed.

7 Information on Investigational Drug

7.1 Drug Information

FTD/TPI is a novel nucleoside antineoplastic agent containing, in a molar ratio of 1:0.5, α,α,α-trifluorothymidine (FTD) and 5-chloro-6-(2-iminopyrrolidin-1-yl) methyl-2,4(1H,3H)-pyrimidinedione hydrochloride (TPI). The physicochemical findings on the active ingredient and an outline of the investigational drug are presented in the table.

Table 7.1 Physicochemical Findings on Active Ingredient

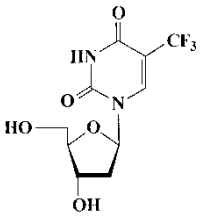
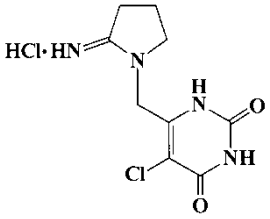
	FTD	TPI
Generic name	Trifluridine	Tipiracil hydrochloride
Chemical name	α,α,α-trifluorothymidine	5-chloro-6-(2-iminopyrrolidin-1-yl)methyl-2,4(1*H*,3*H*)-pyrimidinedione hydrochloride
Structural formula		
Molecular formula	$C_{10}H_{11}F_3N_2O_5$	$C_9H_{11}ClN_4O_2 \cdot HCl$
Molecular weight	296.20	279.12

Table 7.2 Outline of Investigational Drug (FTD/TPI)

Investigational drug code name	TAS-102
Dosage form	Tablets TAS-102 tablets (15 mg): round TAS-102 tablets (20 mg): round
Description	TAS-102 tablets (15 mg): white tablets TAS-102 tablets (20 mg): light-red tablets
Ingredients/quantity	TAS-102 tablets (15 mg): One tablet contains 15 mg of FTD and 7.065 mg of TPI. TAS-102 tablets (20 mg): One tablet contains 20 mg of FTD and 9.42 mg of TPI.

	TAS-102 tablets (15mg) and TAS-102 tablets (20mg) contain as additives lactose hydrate, partly pregelatinized starch, stearic acid, hypromellose, macrogol 6000, titanium oxide, iron sesquioxide (20 mg tablets only) and magnesium stearate.
Expiration date	See the Accountability Procedure for the Investigational Drug.
Packaging form	<TAS-102 tablets (15 mg)> 1 PTP sheet: TAS-102 15 mg × 10 tablets <TAS-102 tablets (20 mg)> 1 PTP sheet: TAS-102 20 mg × 10 tablets
Labeling	Labeling will include the investigational drug code name "TAS-102 or placebo," content, manufacturing number, quantity, and storage and will display the fact that the investigational drug is for clinical trials. In addition to the above information, information required to comply with local regulatory requirements will be printed on the label.
Storage of the drug product	Store at room temperature (1-30°C).

Table 7.3 Outline of the Investigational Drug (Placebo)

Dosage form	Tablets TAS-102 tablets (15 mg) placebo: round TAS-102 tablets (20 mg) placebo: round
Description	TAS-102 tablets (15 mg) placebo: white tablets TAS-102 tablets (20 mg) placebo: light-red tablets
Ingredients/quantity	Tablets that do not contain the active ingredient of the investigational drug (TAS-102) and are indistinguishable in appearance from the investigational drug (TAS-102)
Expiration date	See the Accountability Procedure for the Investigational Drug.
Packaging form	<TAS-102 tablets (15 mg) placebo> 1 PTP sheet: 10 tablets <TAS-102 tablets (20 mg) placebo> 1 PTP sheet: 10 tablets
Labeling	Labeling will include the investigational drug code name "TAS-102 or placebo," content, manufacturing number, quantity, and storage and will display the fact that the investigational drug is for clinical trials. In addition to the above information, information required to comply with local regulatory requirements will be printed on the label.
Storage of the drug product	Store at room temperature (1-30°C).

7.2 Investigational Drug Accountability

The investigational drug TAS-102 tablets (15 mg), TAS-102 tablets (20 mg), and placebo tablets will be provided by the provider of the investigational drug, Taiho Pharmaceutical Co., Ltd. The investigational drug provider will also provide records of manufacturing of the investigational drug and records of the quality testing. The investigational drug will be sent from Taiho Pharmaceutical Co., Ltd. to the warehouse company through a packaging company, and will be distributed from warehouse company to each medical institution participating in the trial via a conveyancer, etc.

7.3 Disclosure of Allocation Results

Disclosure of the allocation results for the entire trial is performed at the main analysis. Disclosure of the allocation results prior to main analysis will only be performed if it is necessary to ensure patient safety. Unless necessary, the allocation results shall not be disclosed.

In cases where the investigator or an authorized designee needs to know the allocation results in an emergency, the investigator or designee report the necessary information (including subject enrollment number, and reasons for disclosure), and request disclosure of allocation to a coordinating investigator. Coordinating investigator perform emergency blind-breaking by entering necessary information in the Web enrollment system, and report the allocation results to the investigator or designee.

Unblinded subjects need to discontinue the administration of the investigational drug.

7.4 Expected Adverse Events

Of the adverse events of FTD/TPI, those whose occurrence itself or trend of occurrence such as the number, frequency, and condition of occurrence cannot be predicted from the current investigator's brochure for the investigational drug will be treated as "unknown," and those occurrence or trend of occurrence can be predicted will be treated as "known."

8 Endpoints, Laboratory Tests and Assessment Schedule

8.1 Observations and Tests

The assessment items of this trial are as follows. All information required by the protocol will be recorded.

Table 8.1 Observations and Tests

Treatment status	Dose of FTD/TPI (placebo), date of administration, presence or absence of dose modification and the reasons therefor, presence or absence of delay of administration and the reasons therefor
Subject demographics	Sex, age (at the time of informed consent)、Date of informed consent, medical history (including major diseases requiring outpatient treatment or inpatient hospitalization and medical history of malignancy), complications, prior treatment history (chemoradiotherapy or chemotherapy prior to curative resection, information on initial surgery in case of relapse) Patient ID for GALAXY study (at the time of determination of eligibility) ctDNA status at 1 month postoperatively, etc.
Details of lesions	Histopathological findings on the primary tumor: primary location (right colon/left colon/rectum), tissue-type, gross classification, depth of invasion, number of lymph node metastases Surgical findings: Extent of lymph node dissection, number of dissected lymph nodes, tumor diameter (maximum diameter), presence or absence of liver metastasis, presence or absence of peritoneal metastasis, presence or absence of other distant metastasis, stage classification, presence or absence of lymphatic invasion, presence or absence of venous invasion, presence or absence of neuroinvasion, presence or absence of extramural cancer deposits without lymph node structure Surgical information: Date of surgery, surgical procedure, approach (laparotomy, laparoscopy), presence or absence of combined resection of an organ and postoperative complications
Physical measurements	Height, weight
Vital signs	Systolic/diastolic blood pressure, pulse rate, body temperature * At all time points, measurements will be performed in the same posture by subject.
Performance status	ECOG PS
Adverse events	Presence or absence of adverse events and the severity thereof according to CTCAE v5.0, causal relationship with investigational drug, date of occurrence, date of reaction outcome, reaction outcome, presence or absence of treatment for investigational drug
Concomitant medications/therapies	Name of drug (or concomitant therapy), route of administration, period of concomitant use, reasons for concomitant use
Electrocardiogram	Resting 12-lead electrocardiogram
Hematological tests	Red blood cell count, Hb, white blood cell count, neutrophil count, lymphocyte count, platelet count

Biochemistry tests	AST (GOT), ALT (GPT), ALP, LDH, albumin, total bilirubin, BUN, creatinine, electrolytes (Na, K, Cl, Ca), blood glucose
Urinalysis	Urine protein (qualitative)
Pregnancy test	Serologic test if pregnancy is suspected by urinalysis * To be performed in women who are premenopausal or who had the last menstruation less than 1 year ago.
Infectious disease test*1	HBs antigen, HBs antibody, and HBc antibody (HBV-DNA if needed*2), HCV antibody (HCV-RNA if needed*3), HIV antibody*4 *1 Any test results performed within 12 months prior to enrollment may be used as substitutions. *2 HBV-DNA testing is mandatory to be below the limit of detection for patients with a negative HBs antigen test, but with a positive test result for either HBs antibody or HBc antibody *3 HCV-RNA testing is mandatory for patients with a positive test result for HCV antibody *4 HIV antibody testing is not mandatory.
Tumor markers	CEA/CA19-9
Imaging tests	Thoracic-abdominal-pelvic CT*1 or MRI*1 and, if needed, brain CT, brain MRI, and bone scintigraphy *1 This test may be performed without using a contrast agent in patients with allergies/hypersensitivity to contrast agents used for CT and MRI. However, the results will be assessed chronologically using the same modality.
Total colonoscopy	If the entire large intestine cannot be observed before or after surgery, perform it within one year after enrollment. Thereafter, every year if neoplastic lesion is observed, but every three to five years if there is no neoplastic lesion. If a total colonoscopy performed before or after surgery does not reveal any neoplastic lesion other than the target lesion, the test should be performed every three to five years after enrollment. *1 For total colonoscopy, the results of the test performed at other hospitals may be used as substitutions.
ctDNA test	A ctDNA analysis will be performed using Signatera™.
QOL	QOL assessments using EORTC QLQ C-30 and EQ-5D-5L
Outcome survey	Presence or absence of relapse; in the event of a relapse, the date of relapse (the date of imaging or biopsy), presence or absence of treatment, details thereof, and start date thereof Date of death or the date of final survival confirmation; in the event of death, cause of death

8.2 Study Calendar

Consent must be obtained prior to starting any trial-related assessments and procedures. The tests listed in "Table 8.1 Observations and Tests" will be performed at the time points shown in "Table 8.2 Study Calendar" and when they are considered to be clinically required. If necessary, clinically significant laboratory assessments will be repeated until the test values return to baseline values or clinically stabilize or until another treatment is started.

As long as the proper sequence of procedures, such as confirmation of initiation criteria and dose, and implementation of observations and tests, is maintained, a delay in starting study treatment of up to ±3 days will be allowed at the Course 2 and the subsequent courses. A delay in schedule due to a long period of public holidays, such as year-end to new-year holidays, will not be treated as a deviation. See also "Table 8.2 Study Calendar" for the time window for study treatment and various tests.

Table 8.2 Study Calendar

Administration Course	Before Enrollment*		During Study Treatment Period*				At Discontinuation /Completion[10]		Follow-up Period		At Recurrence
			Course 1		Course 2 - 6						
Test/observation date	Within 28 days[17]	Within 14 days[17]	D1	D15	D1**	D15[7]	At discontinuation /completion[9]	After 30 days	Up to 1 year	Up to 3 years	Up to 3 years
Time window (days)			-3	±3	±3	±3	-3～+7	-3 ～ +7			±1 month
Treatment											
Administration of investigational drug			●[5,6]		●[6]						
Concomitant medications/therapies			→	→	→	→	→	→			
Examination findings[1]											
Patient demographics	● (until the day before enrollment)										
Details of lesions	● (until the day before enrollment)										
Height		●									
Weight		●			●		●	●			
Vital signs		●[4]	●[4]	●	●[8]	○	●	●			
PS		●[4]	●[4]	●	●[8]	○	●	●			
Subjective and objective symptoms		●[4]	●[4]	●	●[8]	○	●	●			
Clinical findings[1]											
Hematological tests		●[4]	●[4]	●	●[8]	○	●	●			
Biochemistry tests		●[4]	●[4]	●	●[8]	○	●	●			
Urinalysis		●[4]	●[4]	●	●[8]	○	●	●			
Pregnancy test[2]		●									
Electrocardiogram	●										
HBV/HCV/HIV	●[3]										
CEA/CA19-9	●		Every 8 weeks (± 1 week) until 1 year from enrollment[12]							●[13]	
Signatera™	●[11]		Every 8 weeks (± 1 week) until 1 year from enrollment[12]							●[14]	●[18]
QOL	●		Every 8 weeks (± 1 week) from enrollment[12]								
Imaging assessments											
Thoracic-abdominal-pelvic CT or MRI	●		Every 8 weeks (± 1 week) until 1 year from enrollment[12]							●[13]	
Total colonoscopy			●[15]								
Follow-up											
Outcome survey									Every year[16]		

● Required ○Performed as necessary

*The test result performed within the acceptable range before obtaining informed consent may be used as substitutions for the pre-enrollment tests or the test result (pre-dose) on Day 1 (QOL surveys will be conducted after obtaining informed consent).

**If a test/observation for this day is postponed, it will be performed as one on Day 29.

1) See "Table 8.1 Observations and Tests" for the details of examination findings and clinical findings.
2) Performed in women who are premenopausal or who had the last menstruation less than 1 year ago.
3) Any test results performed within 12 months prior to enrollment may be used as substitutions.
4) In principle, the test (pre-dose) on Day 1 is performed after enrollment. However, the pre-enrollment tests performed within 3 days before administration may be used as the tests (pre-dose) on Day 1. The test will be performed before administration. If there are test results both within 3 days before administration and (pre-dose) on Day 1, the start of administration is judge by the test result (pre-dose) on Day 1.
5) Administration of the investigational drug will be started within 8 days after enrollment including the date of enrollment. See Section 6.1 for dose and administration schedule.
6) The investigational drug will be taken after all of the tests specified for each day of visit have been performed.
7) The tests and observation on Day 15 after the start of Course 2 is not mandatory. These tests and observation will be performed if the investigator judges that such various types of tests and observation need to be performed.
8) The pre-course tests performed within 3 days before administration may be substituted for the tests on Day 1 (pre-dose).
9) The time window will be from 3 days before the date of discontinuation/completion (28 days after the start of 6th course) to 7 days after the date of discontinuation/completion (28 days after the start of 6th course). However, if it is impossible to perform the tests and observations within the time window because of the subject's condition, they will be performed as soon as possible. These tests and observations will not be required if they overlap with other specified tests and observations.
10) The time window of the tests on Day 30 after discontinuation/completion tests

will be from 3 days before Day 30 after discontinuation/completion test to 7 days after Day 30 after discontinuation/completion test. In cases where the post-treatment is performed, discontinuation/completion tests or tests on Day 30 after discontinuation/completion tests will be performed before the administration of post-treatment (If the post-treatment is started within 7 days after the end of discontinuation, only the discontinuation tests is performed). The discontinuation tests or observation during follow-up period will not be required if study treatment is discontinued before administration of investigational drug.

11) Subjects will have tested positive for ctDNA in the GALAXY study by an analysis of the latest blood samples collected within 3 months prior to enrollment.

12) With the enrollment date as the first day, these tests will be performed as described even when treatment is delayed.
Time window of test/observation is 1 week before and after including the same day of the week as reference date.

13) With the enrollment date as the first day, these tests will be performed 15, 18, 24, 30, and 36 months (one month is defined as the same day of the following month) after enrollment.
Time window of test/observation is 2 weeks before and after including the same day of the week as reference date.
After the completion of the follow-up period, the investigation will be continued in a separate observational study.

14) With the enrollment date as the first day, these tests will be performed 15, 18, and 24 months (one month is defined as the same day of the following month) after enrollment.
Time window of test/observation is 2 weeks before and after including the same day of the week as reference date.

15) If the entire large intestine cannot be observed preoperatively or postoperatively, this test will be performed within 1 year after enrollment. Thereafter, with the observation date as the first day, this test will be performed every year if tumorous lesions are observed. If the entire large intestine can be observed preoperatively or postoperatively, and tumorous lesions are observed, with the observation date as the first day, this test will be performed every year if a total colonoscopy performed before or after surgery does not reveal any neoplastic lesion other than the target lesion, the test

should be performed every three to five years after enrollment.

Time window of test/observation is 4 weeks before and after including the same day of the week as reference date.

16) This survey will be performed from the end of treatment until death or the last follow-up of the trial (every year after enrollment). Time window of test/observation is 4 weeks before and after including the same day of the week as reference date.

Even when direct follow-up is not possible because of patient transfer, etc., the outcome will be ascertained as far as possible by, for example, making inquiries at the hospital to which the subject is transferred, and the results of inquiries will be recorded in the medical records.

17) The date includes the same day of the week as the registration day.

18) If the test result which blood sampling date is within 1 month before and after (1 month defined as the same day of the following month) of recurrence date, additional blood test is not required.

8.3 Imaging Tests

In principle, the presence or absence of relapse will be ascertained by imaging tests and tumor markers every 8 weeks (± 1 week) from the date of enrollment until 1 year after enrollment in this trial and 15, 18, 24, 30, and 36 months (with a time window of 2 weeks before and after these time points) after enrollment from Year 1 to 3. For CT assessments, contrast-enhanced CT of the chest, abdominal, and pelvic regions will be performed in principle. Imaging requirements are as follows: slice thickness: 5mm or less, anatomic coverage: from lung apex to inferior border of ischium.

The definitive diagnosis of relapse will be made as follows:

1) Liver metastasis: CT or MRI
2) Lung metastasis: CT
3) Lymph node metastasis: CT or MRI
4) Peritoneal metastasis: CT or MRI
5) Bone metastasis: CT or MRI, bone scintigraphy
6) Local relapse: CT, MRI, total colonoscopy
7) Other metastasis: Ultrasonography or CT, MRI

If there is any cancer lesion other than a relapse, the location and date of confirmation (the date of imaging tests) will be reported in the CRFs.*

*: Intramucosal cancer will not be treated as a relapse.

[Definition of a relapse]

Confirmation of a relapse finding that meets any of the following criteria is defined as a "relapse." The date 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.

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

In addition, the date and method of confirmation of a relapse will be reported in the CRFs.

8.4 QOL Survey

The survey will be performed within 28 days prior to enrollment, and every 8 weeks (± 1 week) from the date of enrollment until 1 year after enrollment in this trial. As QOL questionnaires, EORTC QLQ-C30 and EQ-5D-5L will be used. The assessments for the

survey items will be performed after visiting the hospital and before receiving the investigator's examination (including dosing).

[EQ-5D-5L Score]

Mobility	
I have no problems walking.	□
I have slight problems walking.	□
I have moderate problems walking.	□
I have severe problems walking.	□
I am unable to walk.	□
Self-care	
I have no problems washing or dressing myself.	□
I have slight problems washing or dressing myself.	□
I have moderate problems washing or dressing myself.	□
I have severe problems washing or dressing myself.	□
I am unable to wash or dress myself.	□
Usual activities (e.g., work, study, housework, family or leisure activities)	
I have no problems doing my usual activities.	□
I have slight problems doing my usual activities.	□
I have moderate problems doing my usual activities.	□
I have severe problems doing my usual activities.	□
I am unable to do my usual activities.	□
Pain/discomfort	
I have no pain or discomfort.	□
I have slight pain or discomfort.	□
I have moderate pain or discomfort.	□
I have severe pain or discomfort.	□
I have extreme pain or discomfort.	□
Anxiety/depression	
I am not anxious or depressed.	□
I am slightly anxious or depressed.	□
I am moderately anxious or depressed.	□
I am severely anxious or depressed.	□
I am extremely anxious or depressed.	□

[EORTC QLQ C-30 Score]

About physical symptoms	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or suitcase?	1	2	3	4
Do you have any trouble taking a long walk?	1	2	3	4
Do you have any trouble taking a short walk outside of the house?	1	2	3	4
Do you need to stay in bed or a chair during the day?	1	2	3	4
Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
Were you limited in doing either your work or other daily activities?	1	2	3	4
Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
Were you short of breath?	1	2	3	4
Have you had pain?	1	2	3	4
Did you need to rest?	1	2	3	4
Have you had trouble sleeping?	1	2	3	4
Have you felt weak?	1	2	3	4
Have you lacked appetite?	1	2	3	4
Have you felt nauseated?	1	2	3	4
Have you vomited?	1	2	3	4
Have you been constipated?	1	2	3	4
Have you had diarrhea?	1	2	3	4
Were you tired?	1	2	3	4
Did pain interfere with your daily activities?	1	2	3	4

Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
Did you feel tense?	1	2	3	4
Did you worry?	1	2	3	4
Did you feel irritable?	1	2	3	4
Did you feel depressed?	1	2	3	4
Have you had difficulty remembering things?	1	2	3	4
Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

How would you rate your overall health during the past week?						
1	2	3	4	5	6	7
(Very poor)						(Excellent)

How would you rate your overall quality of life during the past week?						
1	2	3	4	5	6	7
(Very poor)						(Excellent)

8.5 Outcome Survey

Survival status (in the event of death, cause of death) and the presence or absence of relapse will be surveyed every year (with a time window of 4 weeks before and after these time points) after enrollment in the enrolled subjects. Even when direct follow-up is not possible because of patient transfer, participation in another trial, etc., the outcome will be ascertained as far as possible by, for example, making inquiries at the hospital to which the subject is transferred, and the results of inquiries will be recorded in the medical records. For all subjects, the follow-up period will continue until death, loss to follow-up, withdrawal of consent, or completion of the trial, whichever occurs first.

9 Data Collection

9.1 Handling and Storage of CRF Data

EPS corporation will be in charge of data management, including management and storage of CRF data. A data management plan will be prepared, and restrictions on entries and access to the database will be set up in the plan to appropriately manage and store records.

9.2 Identification of Source Documents

The source documents for this trial shall be as follows:

- Medical records
- Informed consent forms
- QOL questionnaires
- Drug accountability forms
- Laboratory data
- Diagnostic imaging films, etc.

10 Reporting of Adverse Events

10.1 Assessment of Adverse Events

10.1.1 Definition of an Adverse Event

An adverse event can be any unfavorable and unintended sign (including an abnormal laboratory variation), symptom, or disease in a subject administered the investigational drug, whether or not considered related to the investigational drug.

A subjective or objective symptom of Grade 1 or higher that has been observed since before the start of administration (at baseline evaluation) will be treated as an adverse event only when the grade of the adverse event worsens from the grade before the start of administration.

10.1.2 How To Describe Adverse Events

Each adverse event will be graded with the closest definition of Grades 1-5.

If the diagnosis includes a sign (including an abnormal laboratory finding) or symptom, a diagnosis based on CTCAE v5.0, rather than individual signs or symptoms, will be recorded in the CRFs, whenever possible.

A laboratory abnormality alone will be recorded as an adverse event only if it is judged by the investigator to meet any of the following criteria:

(i) The abnormality has induced clinical signs or symptoms.
(ii) The abnormality is judged to be clinically significant.
(iii) The abnormality requires treatment.
(iv) The abnormality requires an additional test (excluding cases where a retest alone is required).
(v) The abnormality requires discontinuation, a delay, etc. of the investigational drug.

10.1.3 Information to Be Included in the Description of Adverse Events

The following information will be recorded in the CRFs for each adverse event that has occurred:

(i) Term of adverse event
(ii) Severity (CTCAE Grade 1-5 and “serious/non-serious”)
(iii) Causal relationship to the investigational drug
(iv) Date of onset, date of outcome, and outcome
(v) Presence or absence of an action taken for the investigational drug

10.1.4 Causality Assessment

The causal relationship with the investigational drug will be assessed into 2 classes as follows: If a reasonable causal relationship with the investigational drug cannot be ruled out, the assessment will be "related"; and if a reasonable causal relationship with the investigational product can be ruled out, the assessment will be "not related."

10.1.5 Actions to Be Taken at the Onset of an Adverse Event

In the event of an adverse event, the investigator will immediately take appropriate measures.

Follow-up will be performed until the symptom (or test value) is shown to have resolved or improved, even after the end of the period for the assessment of adverse events (see "10.1.6 Period for the Assessment of Adverse Events"). However, follow-up of adverse events may be terminated if any of the following apply.

* Follow-up of adverse events will be terminated in the following cases:

- The adverse event is not serious, and it is judged that a causal relationship can be ruled out. In addition, the adverse event occurred not less than 30 days after the date of the last dose.
- The investigator judges that the symptom is stable and causes no medically significant problem.
- A post-treatment has been performed, and the causal relationship with the investigational drug cannot be assessed.
- Follow-up is difficult because of patient transfer, etc.
- The subject refuses follow-up.
- The subject dies.

10.1.6 Period for the Assessment of Adverse Events

In this trial, the period for the assessment of adverse events will be from "the start date of the administration of the investigational drug" to "30 days after the last dose of the investigational drug or the day before the start of post-treatment, whichever occurs first," and adverse events occurring during this period will be collected.

An adverse event that is judged to be causally related to the investigational drug will be collected even if the event occurred 31 days or more after the last dose of the investigational drug.

An adverse event that is detected after confirmation of a relapse of the primary disease and is due to a progression of the primary disease that newly developed will not be collected.

10.2 Reporting of Serious Adverse Events

10.2.1 Definition of a Serious Adverse Event

An adverse event that is specified in "10.1 Assessment of Adverse Events" and that meets any of the following criteria is defined as a "serious adverse event":

(i) An adverse event that results in death

(ii) An adverse event that is life-threatening

(iii) An adverse event that results in persistent or significant disability/incapacity

(iv) An adverse event that causes a congenital anomaly/birth defect

(v) An adverse event that requires inpatient hospitalization or prolongation of existing hospitalization, excluding

- Hospitalization or death due to progression of the primary disease (PD)
- Hospitalization or prolongation of existing hospitalization for the purpose of reducing the burden of subjects who have to visit the hospital from remote areas
- Pre-planned hospitalization or prolongation of existing pre-planned hospitalization
- Hospitalization or prolongation of existing hospitalization not related to an adverse event
- Hospitalization or prolongation of existing hospitalization for less than 24 hours for observation purpose only

(vi) An adverse event that is medically important, i.e., is defined as any event that may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

10.2.2 Procedure for Reporting from the Investigator to the Head of the Medical Institution and a Coordinating Investigator

(i) Initial report

If a serious adverse event (see "10.2.1 Definition of a Serious Adverse Event") occurs, the investigator will immediately take appropriate measures. The subinvestigator will promptly report the event to the principal investigator.

The principal investigator will report the event to the head of the medical institution within 24 hours of learning of the occurrence of the serious adverse event and also report it to a coordinating investigator and the trial coordinating office.

The format and procedure for reporting serious adverse events will be based on "Procedure for Handling Safety Information."

(ii) Follow-up reports

The principal investigator will follow up on serious adverse events (see "10.1.45 Causality Assessment

The causal relationship with the investigational drug will be assessed into 2 classes as follows: If a reasonable causal relationship with the investigational drug cannot be ruled out, the assessment will be "related"; and if a reasonable causal relationship with the investigational product can be ruled out, the assessment will be "not related."

Actions to Be Taken at the Onset of an Adverse Event. Additional information shall be promptly reported to the head of the medical institution and a coordinating investigator in accordance with "Procedure for Handling Safety Information."

Contact information for coordinating investigators and the trial coordinating office:
E-mail : prj-altair_core@eps.co.jp
TEL : 03-6759-9904 FAX : 03-5842-6432

The investigator will respond to any requests for further information from coordinating investigators, the head of the medical institution, the Institutional Review Board, and the provider of the investigational drug.

10.2.3 Coordinating Investigators' Reporting Obligations and Procedures

With respect to the serious adverse events reported in the initial report and follow-up reports, a coordinating investigator will determine the seriousness, causal relationship, expectedness, and the need for reporting to regulatory authorities (Pharmaceuticals and Medical Devices Agency [PMDA]) (on the basis of "Article 80-2, Paragraph 6 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" and "Article 273 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices").

The details of the reporting procedure will be in accordance with "Procedure for Handling Safety Information."

1) Reporting to each principal investigator

A coordinating investigator will promptly report to each principal investigator the reported serious adverse event along with the results of the above-mentioned determination. Each principal investigator will report the event to the head of the medical institution, as soon as possible if necessary, in accordance with the rules of each medical institution.

2) Reporting to the PMDA

If a coordinating investigator determines that it is necessary to report an event to the PMDA, the coordinating investigator takes actions on the basis of Article 273 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices and related notifications.

3) Reporting to the Data and Safety Monitoring Committee

If a coordinating investigator determines that a serious adverse event needs to be reviewed by the Data and Safety Monitoring Committee, the coordinating investigator will report the event to the committee in writing and seek the committee's opinion about the principal investigator's and the coordinating investigator's views on the adverse event and the appropriateness of the response to the adverse event.

4) Reporting to the provider of the investigational drug

A coordinating investigator will promptly report the serious adverse event reported by the investigator to Taiho Pharmaceutical Co., Ltd., which is the provider of the investigational drug. In addition, if a coordinating investigator is requested to provide information other than "Serious Adverse Event Report," the investigator will respond as needed.

10.2.4 Responsibilities of the Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee will review the reports on adverse events and make recommendations in writing to the coordinating investigator regarding what actions to take, such as whether the trial should be continued and whether the protocol needs to be revised. The procedure will be based on the "Procedure of the Data and Safety Monitoring Committee," which is established separately.

10.3 Collection of Safety Information

When a coordinating investigator obtains information on the safety of the investigational drug from the provider of the investigational drug, the coordinating investigator will take actions on the basis of Article 273 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices and related notifications. The coordinating investigator will report the safety information to each principal investigator, and each investigator will report the information to the head of the medical institution as soon as possible in accordance with the rules of each medical institution.

The details of the reporting procedure will be in accordance with "Procedure for Handling Safety Information."

In addition, the coordinating investigator will determine whether the protocol and the informed consent form and written information need to be revised and whether the information needs to be explained to subjects and will take actions if necessary.

10.4 Overdose

Any overdose will be recorded in the CRFs regardless of whether or not the overdose is associated with an adverse event. If applicable, any serious and non-serious adverse events associated with the overdose will be recorded in the adverse event section of the CRFs.

If the overdose is associated with a serious adverse event, the principal investigator will report the event to the head of the medical institution and a coordinating investigator within 24 hours. The details of the reporting procedure will be in accordance with "Procedure for Handling Safety Information."

10.5 Medication Errors

A medication error in this trial is defined as any unintended error in the prescription, dispensation, and administration of the investigational drug that occurred while the investigational drug is being managed by a healthcare professional or subject.

Any of the following medication errors, whether or not related to an adverse event or a serious adverse event, will be reported by the investigator to the provider of the investigational drug via the trial coordinating office using the reporting form specified by the provider of the investigational drug promptly after the investigator first learned of the occurrence of the error.

- An error in the administration of the investigational drug that resulted in an adverse event
- An error in the administration of the investigational drug that resulted in an overdose
- Inappropriate route of administration of the investigational drug
- Other incorrect administration of the investigational drug

* A missed dose, an incorrect dose of the investigational drug, or a medication error that resulted in a dose that exceeds the prescribed dose (but does not meet the definition of an overdose) may not be reported using the reporting form and will be identified by the record of the use of the investigational drug in the CRFs.

10.6 Information on Pregnancy and Lactation

Any information reported by a subject about pregnancy of a female subject or the partner of a male subject and lactation of a female subject during the period of participation in the trial or the contraception period for individual subjects will be

reported using the prescribed form in accordance with the procedure described in Section 10.2. In the case of a female subject, the study treatment will be discontinued. Reporting of the information by the investigator to the head of the medical institution will not be essential. The investigator will follow up on the delivery and report it in writing.

11 Definition of Endpoints

11.1 Definition of Primary Endpoint

11.1.1 Disease-Free Survival 1 (DFS1)

A DFS1 event in this trial 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, and DFS1 generally refers to relapse-free survival (RFS).

For survives with no evidence of recurrence, DFS1 data will be censored at the last imaging date of confirmed no recurrence. Subjects for which no imaging have been performed, DFS1 data will be censored at the date of enrollment.

In principle, events will be assessed by the investigator.

1) Definition of 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.

2) Definition of an event

(i) Relapse

Confirmation of a relapse finding that meets any of the following criteria is defined as a "relapse." The date 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 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 relapse.

(ii) 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.

(iii) Death from any cause

11.2 Definition of Secondary Endpoints

11.2.1 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. Rate of conversion to negative ctDNA has been investigated as a substitute indicator for DFS that can be assessed in a short period of time, although the clinical significance of the rate is not clear. It has been determined that in the future, investigators of the European Society for Medical Oncology (ESMO), Japan, and the U.S. will conduct a meta-analysis on data of individual subjects collected from clinical studies on ctDNA for the purpose of detecting MRD. Thus, it is possible that this endpoint may be recommended as an indicator of efficacy in the target patients of this trial by the time the results of this trial are available. In addition, this trial is a study designed to extend the indications of FTD/TPI to this target population of this trial depending on the results obtained, and the appropriateness of this endpoint will also be discussed with the PMDA, etc. in the future. This endpoint is treated as the key secondary endpoint at present and may be reclassified to a primary endpoint (co-primary endpoint) when the rationale is established for inclusion in the primary analysis.

11.2.2 Disease-free survival 2 (DFS2)

1) Definition of 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. For survives with no evidence of recurrence, DFS2 data will be censored at the last imaging date of confirmed no recurrence. Subjects for which no imaging have been performed, DFS2 data will be censored at the date of enrollment.

In principle, events will be assessed by the investigator.

2) Definition of an event

(i) Relapse

The same definition as in DFS1 will be used.

(ii) Cancer lesion other than a relapse (secondary cancer)

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

(iii) Death from any cause

11.2.3 Overall Survival (OS)

1) Definition of OS

The time from the date of enrollment to the date of death from any cause. In surviving subjects, the last date of confirmation of survival (the confirmation may be performed by telephone, and the fact of confirmation shall be recorded in the medical records.) will be treated as the end of this period. In subjects lost to follow-up, the last date of confirmation of survival before loss to follow-up will be treated as the end of this period.

11.2.4 Incidence of Adverse Events

For each of the adverse events due to the following study treatment, the frequency of cases with the worst grade in all courses according to CTCAE v5.0 will be calculated using all treated patients as the denominator.

11.2.5 Treatment Completion Rate

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

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

11.2.6 QOL

QOL will be assessed using EORTC QLQ C-30 and EQ-5D-5L.

12 Statistical Matters

An outline of the statistical analysis plan is described below. The details will be described in the separately prepared statistical analysis plan.

12.1 Subject Handling

Subject handling will be determined in accordance with the subject handling criteria. The subject handling criteria will be prepared based on clinical conferences.

12.2 Definition of Analysis Populations

Each analysis population is defined in "Table 12-1 Analysis Populations."

Table 12-1 Analysis Populations

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 trial.
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.

12.3 Efficacy Analysis

12.3.1 Primary Endpoint

This endpoint will be assessed in the FAS. DFS curves will be estimated using the Kaplan-Meier method for DFS1, and the annual DFS ratio and the confidence interval will be calculated. A stratified log-rank test will be performed for the null hypothesis that the DFS curves of the two groups are equal.

The stratification factors, the allocation factors and categories shown in the table below, used for the stratified analyses were selected based on the results of the blinded review. Details of the analysis method are specified in the Statistical Analysis Plan.

The strata (allocation factors)	Categories
Disease stage classification (3 categories)	Stage II or lower Stage III M1
ctDNA status one month after curative resection (2 categories)	positive negative / unmeasurable / unmeasured

12.3.2 Secondary Endpoints

The analysis of the secondary efficacy endpoints is defined as follows:

(i) See "11.2.1 Rate of Conversion to Negative ctDNA" for the rate of conversion to negative ctDNA.

(ii) The same analyses as performed for the primary endpoint will also be performed on DFS2 Regarding overall survival, an unstratified analysis will be performed without setting stratification factors *.

(iii) For each adverse event, the frequency of cases with the worst grade in all courses according to CTCAE v5.0 will be calculated.

(iv) Treatment completion rate will be calculated on the basis of the definition described in "11.2.5. Treatment Completion Rate."

(v) With respect to QOL, the mean of each group and each time point and the standard error will be described chronologically for the analysis variables. In addition, intergroup comparisons will be made using approaches based on analysis of variance, model analysis, etc.

* The two stratification factors for DFS2 were disease stage (3 categories: Stage II or less, Stage III, M1) and ctDNA one month after curative resection (2 categories: Positive, Negative/Unmeasurable/Not measured). The analysis was performed using only single factor of disease stage for the stratified analyses for the overall survival. These stratification factors were determined based on the results of a blinded review. Additionally, details of the analysis method are specified in the Statistical Analysis Plan.

12.4 Data Handling

How to handle data (e.g., requirements for inclusion in or exclusion from an analysis population) will be determined by the coordinating investigators after discussion.

12.4.1 Handling of Missing Values and Outliers

Imputation of missing values and analysis of outliers will not be performed in principle. However, if the existence of missing values and outliers that may significantly affect the results of analyses was found before data finalization, measures therefor will be described in the statistical analysis plan.

12.4.2 Handling of Additional Analyses

Analyses performed after the statistical analysis plan has been finalized will be treated as additional analyses. The results of additional analyses will either be reported in such a manner that it is clear that the analyses have not been planned in advance or be reported in the report of the results of additional analyses, which is separately prepared.

12.5 Target Number of Subjects

Enrollment will be continued until it is confirmed that 240 subjects have been enrolled as the FAS of "subjects tested positive for ctDNA."

12.5.1 Rationale

See "2.10.4 Clinical Hypothesis and Rationale for Setting the Number of Subjects."

12.6 Interim Analyses

No interim analysis on efficacy will be performed in principle because if an interim analysis was to be conducted 1 year after the start of the trial, only 20% of the planned events (190 events) would have occurred, and it is expected to be difficult to perform an interim analysis using statistical methods such as consumption function and predicted probability while subjects are being enrolled. 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 trial.

13 Ethical Matters

13.1 Policies, Laws and Regulations, and Norms to Be Complied With in the Trial

This trial will be conducted in compliance with the protocol, the Declaration of Helsinki, ICH-GCP guidelines, Article 80-2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, "Ordinance on the Standards for the Conduct of Clinical Trials on Drugs" (the Ministry of Health and Welfare Ordinance No. 28, dated March 27, 1997), the ordinances for the revisions thereof, and related notifications.

13.2 Informed Consent

13.2.1 Information for Subjects

The investigator will deliver the written information approved by the Institutional Review Board to the subject himself/herself and explain the following orally and thoroughly to the subject.

(i) The fact that the trial involves research
(ii) The purpose of the trial
(iii) Name and contact information of the principal investigator or sub investigator
(iv) Study methodology (including experimental aspects of the study and the inclusion criteria for subjects)
(v) Anticipated clinical benefits and risks or inconveniences
(vi) Presence or absence of alternative treatment methods and their expected important benefits and risks
(vii) Expected duration of the subject's participation in the trial
(viii) The fact that the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled
(ix) The fact that monitors, auditors, the Institutional Review Board, etc., and regulatory authorities have access to the source documents related to medical care, without violating the confidentiality of the subject. The fact that by affixing name and seal or signature to a written informed consent form, the subject is authorizing such access
(x) The fact that if the results of the trial are published, the subject's confidentiality will be protected

(xi) The consultation office of the medical institution to make inquiries to or contact for further information regarding the trial and the rights of trial subjects and in the event of trial-related health damage

(xii) The compensation and treatment available to the subject in the event of trial-related health damage

(xiii) The planned number of subjects involved in the trial

(xiv) The fact that the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial

(xv) Conditions or reasons under which the subject's participation in the trial may be terminated

(xvi) The expenses, if any, to the subject

(xvii) The payment, if any, to the subject

(xviii) The subject's responsibilities

(xix) Types of the Institutional Review Board that investigates and reviews the appropriateness, etc. of the clinical trial, matters to be investigated and reviewed by each Institutional Review Board, and other matters related to the Institutional Review Board involved in the clinical trial

(xx) The fact that the subject may read the procedures, etc. for the Institutional Review Board under the preceding paragraph and that if the subject wishes to read the procedures, etc. of the Institutional Review Board, the subject is encouraged to make a request. In addition, if the procedures, etc. of the Institutional Review Board are on the website, the address of the website; if they are not, the fact that they are available for general public perusal

(xxi) The possibility of secondary use of data

13.2.2 Consent

The investigator will explain this trial to the patient, give the patient enough time to think about the trial, confirm that the patient understands the trial well, and then request the subject to participate. If the patient consented to participate, the investigator who gave the explanation, the trial collaborator who gave a supplementary explanation, and the subject who was given the explanation and consented will each enter the date of explanation and the date of consent into the written informed consent from approved by the Institutional Review Board and sign it. The investigator will store the signed informed consent form in the medical records and hand a copy of the signed informed consent form to the subject.

If information becomes available that may affect the subject's willingness to continue participation in the trial, the investigator will promptly communicate the information to the subject participating in the trial, will ascertain the subject's willingness to continue participation in the trial, and record the result in writing. In addition, if the principal investigator judges that the informed consent form and written information need to be revised, on the basis of the information or for other reasons, the principal investigator will promptly revise these documents and obtain approval of the revision from the Institutional Review Board. After approval of the Institutional Review Board, an explanation will be given again using the revised informed consent form and written information, and re-consent will be obtained in writing.

13.3 Protection of Personal Information and Subject Identification

With an understanding that information concerning privacy such as personal information should be protected intensively and handled cautiously under the spirit of respect for individual personalities, every effort will be made to protect privacy by taking thoroughgoing control measures, and the Act on the Protection of Personal Information (Act No. 57 of May 30, 2003) and the revisions thereof will be followed.

13.3.1 Purpose of Use of Personal Information and Items Used

1) Information that can identify an individual
   Subject identification number, enrollment number
2) Management of anonymization and correspondence table
   Any personal information that is provided outside the medical institution will be anonymized in advance. As the minimum information required to identify a subject, subject identification number and enrollment number will be used as the "information that can identify an individual." The correspondence table showing the correspondence between information such as patient name and enrollment number (subject identification number) will be controlled appropriately under the responsibility of the principal investigator at each medical institution in accordance with the policy of the medical institution. In other words, information that can identify an individual by itself without a correspondence table, such as the name of a subject, will not be disclosed to the outside from the medical institution.
3) Method for Collecting Personal Information
   The subject's personal information will be collected by entry of the information into the CRFs by the investigator or a trial collaborator and by reporting it to the Data Center.

13.3.2 Secondary Use of Data

Data obtained in this trial may be used for secondary uses (such as translational researches, dossiers supporting overseas registration application for drugs or in vitro diagnostic products, and meta-analyses) in a form containing no link to personal identifiers, only if such use has been approved by the coordinating investigators and the provider of the investigational drug.

13.3.3 Safety Control Administration System

When using personal information, various safety control measures will be taken in accordance with the rules of each medical institution in order to minimize the risk of information leaks. The Data Center will be managed appropriately in accordance with the guidelines for personal information handled by the National Cancer Center Japan.

13.3.4 Handling of Requests to Disclose Subject Information, etc.

If a subject requests disclosure of privacy-related information belonging to this trial, the investigator of the medical institution in charge of the subject will handle the matter in principle.

13.4 Approval of the Institutional Review Board (IRB)

13.4.1 Approval at the Start of Trial

Before conducting this trial, the principal investigator must submit the documents specified in the GCP ordinance, such as the protocol and the informed consent form and written information, to the head of the medical institution and must obtain approval by the IRB. After approval of the IRB, the principal investigator will promptly send a copy of the IRB approval document and the informed consent form and written information used specifically by the medical institution to the trial coordinating office and retain the original IRB approval document.

Individual medical institutions will not be allowed to make changes to the protocol. A common protocol will be used in all medical institutions. If the IRB requests modification of the protocol text, the principal investigator will consult with coordinating investigators and consider how to handle the matter.

13.4.2 IRB Approval of Appropriateness of Continuation of Trial

The appropriateness of continuing the trial must be reviewed annually by the IRB. If the IRB approves the continuation of the trial, the original IRB approval document will be retained.

13.4.3 Changes to the Protocol

Any revision of the protocol, the informed consent form and written information, etc. will be made in accordance with the written procedures for the creation of each document.

13.4.4 Categories of Changes to the Protocol

In this trial, changes to the protocol will be handled as follows:

1) Revision

Revision refers to changes to the protocol. It requires approval of the IRB.

2) Notification letter

A notification letter will be issued if it is judged that before a protocol revision, the details of the revision need to be promptly communicated to the study personnel. The coordinating investigators will determine whether the revision requires review by the IRB of each medical institution and inform the institutions of the result.

3) Q&A

The interpretation of wordings of the protocol will be communicated to the study personnel by issuing Q&A.

13.4.5 Approval of the IRB at the Time of Protocol Revision

If the protocol is revised during the trial, the revised documents must be approved by the IRB.

13.5 Management of Conflicts of Interest (COI)

The COI of the persons involved in this trial, such as investigators and coordinating investigators, will be managed appropriately according to the regulations of the medical institution. In addition, conflicts of interest in the company are being managed by the work rules and compliance programs of the company.

The provider of the investigational drug (Taiho Pharmaceutical Co., Ltd.) will have no involvement in the matters related to the fundamentals of the trial, such as the operation of the trial and the interpretation of the results. Any additional studies (such as biomarker study and observational study) will be conducted after a collaborative study agreement has been concluded.

13.6 Compensation

In the event of health damage to subjects attributable to this trial, the medical institution will compensate for the damage in accordance with “Procedure for Compensation for Health Damage,” even if the medical institution is not legally liable.

In this trial, such compensation will consist of provision of medical care and payment of health care costs, medical allowance, and compensation. The principles of compensation will not interfere with the subject's right to claim for damages.

14 Monitoring and Auditing

14.1 Monitoring

Monitoring will be performed in accordance with “Monitoring Procedure.”

On-site monitoring will verify that the trial is being conducted appropriately and that the reliability of data is maintained adequately, by means such as direct access to the source documents. After an on-site monitoring visit, a monitoring report will be prepared and submitted to the coordinating investigators, the persons conducting the clinical trial independently, and the head of the medical institution.

Central monitoring will be performed periodically on the status of occurrence of adverse events related to safety, treatment compliance, and study implementation status, and the results will be reported to the Data and Safety Monitoring Committee.

14.2 Protocol Deviations/Violations

The investigator will record any deviation from the protocol regardless of the reasons. Any deviation from the protocol that was caused to eliminate immediate hazards to the subjects and for other medically necessary reasons will be reported by the principal investigator in writing to the head of the medical institution in accordance with the procedure of the medical institution. In addition, the principal investigator will submit a copy of the document reported to the head of the medical institution to a coordinating investigator.

Deviations will be classified into one of the following categories after consideration by coordinating investigators:

1) Major deviation

A deviation from the stipulations of the protocol that is clinically inappropriate and that meets multiple items of the following criteria will be classified as a “major deviation.”

(i) A deviation that affects the evaluation of the endpoints of the trial
(ii) An intentional or systematic deviation
(iii) A dangerous or considerable deviation

2) Deviation

Deviations excluding those listed in (i) above

14.3 Auditing

Auditors will perform audits in accordance with “Auditing Procedure” and “Auditing Plan” and verify that the trial is being conducted appropriately and that the reliability of data is maintained adequately, by means such as direct access to the source documents.

14.4 Direct Access

The medical institution will assist in monitoring, audits, and investigations by the IRB and regulatory authorities and provide direct access to all trial-related records such as source documents as necessary. A request from the provider of the investigational drug for direct access will be handled in the same manner.

15 Special Notes

15.1 Central Review of Images

In this trial, central review of images before enrollment will be performed at an independent institution. The principal investigator will submit subject images for central review. “Procedure of the Diagnostic Imaging Committee” will be prepared and implemented to specify the details of central review and the central review laboratory.

15.2 Record Retention

15.2.1 Persons Conducting the Clinical Trial Independently

Records will be retained until the day 5 years after the date of marketing approval (if it has been learned that the records are not attached to the application for approval, the day 3 years after the date of notification of such fact or the day 3 years after the discontinuation or completion of the trial, whichever comes later). The details will be in accordance with “Procedure for Record Retention.”

15.2.2 Medical Institutions

The head of the medical institution and the founder of the IRB will retain the essential documents and records to be retained in accordance with the GCP ordinance until one of the following dates, whichever comes later. If longer retention period is required, the head of the medical institution and the founder of the IRB will discuss the retention period and the retention method with coordinating investigators. The head of the medical institution will appoint a record retention manager for the retention of records.

(i) The date of marketing approval of the test drug (if it has been notified that the development was terminated or that the results of the trial are not attached to the application for approval, the day 3 years after the date of decision of termination of development or the date of notification of the fact that the results are not attached to the application)

(ii) The day 3 years after the date of termination or completion of the trial

15.3 Completion of Trial

When the trial is completed, the principal investigator will notify the head of the medical institution of the fact in writing and report a summary of the trial results in writing to the head of the medical institution.

15.4 Termination at Medical Institutions

If the persons conducting the clinical trial independently consider that a medical institution hinders the proper conduct of the trial because of major or continued

noncompliance with the GCP ordinance or the protocol, the persons conducting the clinical trial independently may terminate the trial at the medical institution. In this case, the persons conducting the clinical trial independently will report to the head of the medical institution in writing that the trial at the medical institution will be canceled. In addition, the persons conducting the clinical trial independently will report to the regulatory authorities in writing that the trial has been terminated. The investigator will promptly inform the subjects of the fact and provide appropriate medical care and take other necessary measures.

15.5 Suspension of the Trial and Premature Termination of the Entire Trial

15.5.1 Suspension of the Trial

If the principal investigator or a coordinating investigator judges that subject safety is considered to be significantly compromised because the occurrence of adverse events exceeded the acceptable range during the progress of the trial or because of serious adverse drug reactions or new information about the investigational drug and that thus the trial must be suspended, the principal investigator will promptly notify the head of the medical institution of the fact and the detailed reasons for the suspension in writing. In addition, the coordinating investigator will notify the regulatory authorities in writing that the clinical trial has been suspended.

15.5.2 Termination of the Entire Trial

If the principal investigator or a coordinating investigator judges that subject safety is considered to be significantly compromised because of serious adverse drug reactions or new information about the investigational drug and that thus the trial must be prematurely terminated, the principal investigator will promptly notify the head of the medical institution of the fact and the reasons for the termination in writing. In addition, the principal investigator will notify the regulatory authorities in writing that the clinical trial has been prematurely terminated. The investigator will promptly inform the subjects of the fact and provide appropriate medical care and take other necessary measures.

16 Study Organization

This trial is a multicenter, investigator-initiated clinical trial, with coordinating investigators.

16.1 Organization for Conducting the Trial

See Appendix 1.

16.2 Source of Funds for the Clinical Trial

This trial will be conducted with the investigational drug (including placebo) pro vided to joint research institute Alpha A Co., Ltd. at no charge by Taiho Pharmac eutical Co., Ltd. and funds provided by the company on the basis of a contract. H ealth care cost for a subject other than the cost of the investigational drug will be borne by the subject, and compensation for subject burden will not be paid.

17 Ownership of Study Results and Publication of Study Results

Information about this trial will be disclosed on jRCT (Japan Registry of Clinical Trials) (https://jrct.niph.go.jp/) and, ClinicalTrials.gov (database of clinical trials) provided by the U.S National Library of Medicine.

The study results will belong to the National Cancer Center Japan. Publication of the study results in an academic meeting or as a paper will be determined by the coordinating investigators after discussion with the principal investigators, etc. at the time of publication.

18 References

1. http://www-dep.iarc.fr/.

2. http://www.cancer.org/research/cancer-facts-statistics.html.

3. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009;27:3109-16.

4. Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. J Clin Oncol 2011;29:3768-74.

5. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol 2011;29:1465-71.

6. Grothey A, Sobrero AF, Shields AF, et al. Duration of Adjuvant Chemotherapy for Stage III Colon Cancer. N Engl J Med 2018;378:1177-88.

7. Iveson T, Sobrero AF, Yoshino T, et al. Prospective pooled analysis of four randomized trials investigating duration of adjuvant (adj) oxaliplatin-based therapy (3 vs 6 months {m}) for patients (pts) with high-risk stage II colorectal cancer (CC). J Clin Oncol 2019;37:3501-.

8. Hong YS, Nam BH, Kim KP, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. The Lancet Oncology 2014;15:1245-53.

9. Portier G, Elias D, Bouche O, et al. Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. J Clin Oncol 2006;24:4976-82.

10. Mitry E, Fields AL, Bleiberg H, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. J Clin Oncol 2008;26:4906-11.

11. Hasegawa K, Saiura A, Takayama T, et al. Adjuvant Oral Uracil-Tegafur with Leucovorin for Colorectal Cancer Liver Metastases: A Randomized Controlled Trial. PLoS One 2016;11:e0162400.

12. Saltz LB, Niedzwiecki D, Hollis D, et al. Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803. J Clin Oncol 2007;25:3456-61.

13. Van Cutsem E, Labianca R, Bodoky G, et al. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. J Clin Oncol 2009;27:3117-25.

14. Ychou M, Raoul JL, Douillard JY, et al. A phase III randomised trial of LV5FU2 + irinotecan versus LV5FU2 alone in adjuvant high-risk colon cancer (FNCLCC Accord02/FFCD9802). Ann

Oncol 2009;20:674-80.

15. Allegra CJ, Yothers G, O'Connell MJ, et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. J Clin Oncol 2011;29:11-6.

16. de Gramont A, Van Cutsem E, Schmoll HJ, et al. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. The Lancet Oncology 2012;13:1225-33.

17. Kerr RS, Love S, Segelov E, et al. Adjuvant capecitabine plus bevacizumab versus capecitabine alone in patients with colorectal cancer (QUASAR 2): an open-label, randomised phase 3 trial. The Lancet Oncology 2016;17:1543-57.

18. Alberts SR, Sargent DJ, Nair S, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. Jama 2012;307:1383-93.

19. Taieb J, Tabernero J, Mini E. Adjuvant FOLFOX4 with or without cetuximab (CTX) in patients (pts) with resected stage III colon cancer (CC): DFS and OS results and subgroup analyses of the PETACC8 Intergroup Phase III trial. Annals of Oncol 2012;23.

20. Diehl F, Schmidt K, Choti MA, et al. Circulating mutant DNA to assess tumor dynamics. Nat Med 2008;14:985-90.

21. Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. Nature 2017;545:446-51.

22. Reinert T, Henriksen TV, Christensen E, et al. Analysis of Plasma Cell-Free DNA by Ultradeep Sequencing in Patients With Stages I to III Colorectal Cancer. JAMA oncology 2019;5:1124-31.

23. Christensen E, Birkenkamp-Demtroder K, Sethi H, et al. Early Detection of Metastatic Relapse and Monitoring of Therapeutic Efficacy by Ultra-Deep Sequencing of Plasma Cell-Free DNA in Patients With Urothelial Bladder Carcinoma. J Clin Oncol 2019;37:1547-57.

24. Coombes RC, Page K, Salari R, et al. Personalized Detection of Circulating Tumor DNA Antedates Breast Cancer Metastatic Recurrence. Clin Cancer Res 2019;25:4255-63.

25. Sethi H, Salari R, Navarro S, et al. Abstract 4542: Analytical validation of the Signatera RUO assay, a highly sensitive patient-specific multiplex PCR NGS-based noninvasive cancer recurrence detection and therapy monitoring assay. Cancer Res 2018;78:4542.

26. Tanaka N, Sakamoto K, Okabe H, et al. Repeated oral dosing of TAS-102 confers high trifluridine incorporation into DNA and sustained antitumor activity in mouse models. Oncol Rep 2014;32:2319-26.

27. Emura T, Suzuki N, Yamaguchi M, Ohshimo H, Fukushima M. A novel combination antimetabolite, TAS-102, exhibits antitumor activity in FU-resistant human cancer cells through a mechanism involving FTD incorporation in DNA. Int J Oncol 2004;25:571-8.

28. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic

colorectal cancer. N Engl J Med 2015;372:1909-19.

29. Xu J, Kim TW, Shen L, et al. Results of a Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Trifluridine/Tipiracil (TAS-102) Monotherapy in Asian Patients With Previously Treated Metastatic Colorectal Cancer: The TERRA Study. J Clin Oncol 2018;36:350-8.

30. Lesniewski-Kmak K, Moiseenko V, Saunders M, et al. Phase II study evaluating trifluridine/tipiracil + bevacizumab and capecitabine + bevacizumab in first-line unresectable metastatic colorectal cancer (mCRC) patients who are non-eligible for intensive therapy (TASCO1): Results of the primary analysis. Annals of Oncology 2018;29.

31. Zeuner A, Todaro M, Stassi G, De Maria R. Colorectal Cancer Stem Cells: From the Crypt to the Clinic. Cell stem cell 2014;15:692-705.

32. Tsunekuni K, Konno M, Haraguchi N, et al. CD44/CD133-Positive Colorectal Cancer Stem Cells are Sensitive to Trifluridine Exposure. Sci Rep 2019;9:14861.

33. Pita-Fernandez S, Alhayek-Ai M, Gonzalez-Martin C, Lopez-Calvino B, Seoane-Pillado T, Pertega-Diaz S. Intensive follow-up strategies improve outcomes in nonmetastatic colorectal cancer patients after curative surgery: a systematic review and meta-analysis. Ann Oncol 2015;26:644-56.

34. Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. The Lancet Oncology 2015;16:1306-15.

35. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. The Lancet Oncology 2014;15:1065-75.

Appendix 1: EORTC QLQ-C30

Appendix 2: EQ-5D-5L