1. PROTOCOL AND AMENDMENTS

The final global protocol for study TO-TAS-102-203 (Original version, dated 14 June 2016) is provided in this appendix. This original protocol was not amended at any time during or after the study.

A Phase 2 Study with Safety Lead-in, Evaluating TAS-102 Plus Nivolumab in Patients with Microsatellite-Stable Refractory Metastatic Colorectal Cancer

TAS-102

Protocol Number: TO-TAS-102-203

IND Number: CCI

Final: 14 June 2016

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This clinical study will be conducted in accordance with International Council for Harmonisation Good Clinical Practice (GCP) Guidelines.

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1. SYNOPSIS

Name of Sponsor/Company:	Taiho Oncology, Inc.
Name of Investigational Product:	TAS-102 and nivolumab
Name of Active Ingredients:	TAS-102: trifluridine (FTD) and tipiracil hydrochloride (TPI); Nivolumab: nivolumab
Title of Study: **A Phase 2 Study with Safety Lead-in, Evaluating TAS-102 Plus Nivolumab in Patients with Microsatellite-Stable Refractory Metastatic Colorectal Cancer**	
Protocol Number:	TO-TAS-102-203
Phase of Development:	2
Indication:	Refractory metastatic colorectal cancer
Background/Rationale:	• TAS-102 is an oral combination of 1M trifluridine (FTD) and 0.5M tipiracil hydrochloride (TPI). • The primary mechanism of action of FTD, an antineoplastic thymidine-based nucleoside analog, is incorporated into DNA via phosphorylation, resulting in a different cytotoxic mechanism from 5-fluorouracil and 2'-deoxy-5-fluorouridine (uracil-based thymidylate synthase inhibitors). • TAS-102 has been shown to significantly improve overall survival (OS) in patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not candidates for fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) biological therapy, and an anti-epidermal growth factor receptor (EGFR) therapy.[9] • Treatment with pembrolizumab (an anti-programmed cell death-1 [PD-1] antibody similar to nivolumab), shows activity in patients with mCRC. However, in patients with microsatellite instability (MSI) tumors, anti-PD-1 activity was much higher than in patients with microsatellite-stable (MSS) tumors. The median progression-free survival (PFS) and OS were not reached in the MSI-high mCRC patient. In contrast, the median PFS and OS were 2.2 months and 5.0 months, respectively, in the cohort with MSS mCRC patients (hazards ratio for PFS was 0.10 [$P < .001$], and hazards ratio for OS was 0.22 [$P = .05$]). Moreover, the overall response rate (ORR) for mCRC patients with MSI-high and MSS was 40% and 0%, respectively.[10] • In a preclinical study, the tumor growth inhibitory activity of TAS-102 in combination with an anti-mouse PD-1 antibody was significantly higher than that of each monotherapy against mouse colorectal cancer cell (CMT-93/MSS cell line). The results of this preclinical study showed that synergistic effects occurred when using TAS-102 with anti-mouse PD-1 antibody in mouse colorectal cancer cells. • The proposed mechanism for the observed additive or synergistic effect is an increase in tumor immunogenicity after treatment with TAS-102, leading to a better tumor response to anti-PD-1 antibody therapy. Increased tumor immunogenicity may be triggered by TAS-102 DNA incorporation. This Phase 2 study will examine this hypothesis.

Study Objectives:	To evaluate the following objectives in patients with mCRC receiving TAS-102 in combination with nivolumab: **Primary Objective** • To estimate the immune-related overall response rate (irORR) of TAS-102 and nivolumab combination therapy in mCRC patients **Secondary Objectives** • To confirm the recommended Phase 2 dose for the combination therapy of TAS-102 and nivolumab • To assess the safety of TAS-102 and nivolumab given as combination therapy • To estimate the ORR using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 • To estimate the PFS based on immune-related response criteria (irRC) and RECIST • To estimate the disease control rate (DCR) using irRC and RECIST • To estimate the OS CCI [redacted]
Study Design:	This is a multicenter, single arm, safety lead-in, Phase 2 study, using Simon's 2-stage design evaluating the safety and efficacy of TAS-102 plus nivolumab in patients with MSS refractory mCRC. Patients will undergo screening to assure eligibility. Screening will include confirmation of MSS status based on an analysis of either archived or fresh biopsy tissue. Microsatellite instability testing is standardized and performed in Clinical Laboratory Improvement Amendments -certified laboratories without need for assay development. CCI [redacted] The test will be performed using a certified immunohistochemistry or polymerase chain reaction-based tests for eligibility. The starting dose of TAS-102 will be 35 mg/m^2/dose orally twice daily (BID) and 3 mg/kg/dose intravenously every 2 weeks for nivolumab. Patients who are eligible will be enrolled sequentially in the following stages: Stage 1 – The first 6 patients will be enrolled and after Cycle 1 treatment, they will be evaluated for the safety and tolerability of the combination therapy. TAS-102 and nivolumab are not expected to have significant overlapping toxicities. A safety team comprised of the medical monitor and treating investigators will review safety data from these first 6 patients after they have undergone Cycle 1 treatment. If 2 or more patients experience a dose-limiting toxicity (DLT), then the dose of TAS-102, will be reduced (after discussion between the investigator and Sponsor) and an additional 6 patients will be enrolled. If the DLT is considered related to TAS-102 the investigator should follow the recommended dose modifications in Section 8.2.4. If the DLT is considered related to nivolumab, the investigator should follow the discontinuation/withhold criteria listed in Section 8.2.6. If the DLT relationship is unclear to either TAS-102 or nivolumab, but is not disease related, then both TAS-102 and nivolumab should be interrupted and the TAS-102 dose should be reduced at the next dose cycle. Accrual will not be halted while the review is being conducted if no DLTs are identified. Any outcome of this safety review will be communicated in a timely manner to the participating investigators so that they may notify their Institutional

	Review Boards. Assuming a tolerated dose is confirmed (up to 1 DLT in 6 patients), at least 9 additional patients evaluable for response will be enrolled and followed for a minimum of 6 months. At the point that the ninth patient is enrolled (or a total of at least 15 patients evaluable for response assessment at the target dose), enrollment will stop, and there will be an assessment of safety and efficacy to determine whether Stage 2 will open for enrollment. To proceed to Stage 2, two or more patients out of the 15 patients in Stage 1 will need to demonstrate a partial response or complete response within a 6-month tumor follow-up period. If there are fewer than 2 responders in Stage 1, then the study will be stopped. Stage 2 – An additional 10 patients evaluable for response assessment will be enrolled and followed for a minimum of 6 months. The combination of TAS-102 and nivolumab is expected to trigger immune-mediated responses, which require activation of the immune system before the observation of clinical responses. Such immune activation may take weeks to months to become evident. Some patients may have an objective volume increase of CCI
Number of Patients Planned:	Approximately 30 to 35 evaluable patients will be enrolled in a Simon's 2-stage design.
Criteria for Inclusion and Exclusion:	**Inclusion Criteria** 1. Has provided written informed consent. 2. Patient with confirmed histologically proven metastatic or locally advanced colorectal adenocarcinoma who are MSS (ie, not MSI) based on either an analysis of tissue from a prior biopsy or based on tissue from a new biopsy. 3. Patient with the presence of at least 1 lesion with measurable disease as defined by 10 mm in the longest diameter for a soft tissue lesions or 15 mm in the short axis for a lymph node by RECIST and irRC criteria for a response assessment. 4. Patient has received at least 2 prior lines of standard chemotherapies for mCRC and is refractory to or failing those chemotherapies. a. Standard chemotherapy must include ALL of the following agents: i. Fluoropyrimidines, irinotecan, and oxaliplatin ii. An anti-VEGF biological therapy (eg, bevacizumab or aflibercept or ramucirumab) iii. At least 1 of the anti-EGFR monoclonal antibodies (mAbs) (cetuximab or panitumumab) for *RAS* wild-type patients. 5. Age ≥ 18 years. 6. Eastern Cooperative Oncology Group performance status of 0 to 1 at the time of enrollment. 7. Life expectancy of ≥ 4 months. 8. Has adequate organ function as defined by the following criteria: a. Absolute neutrophil count of ≥ 1500/mm^3 (ie, ≥ 1.5 × 10^9/L by International Units [IU]). b. Platelet count of ≥ 100,000/mm^3 (IU: ≥ 100 × 10^9/L). c. Hemoglobin value of ≥ 9.0 g/dL (If patient required previous blood transfusions, a hemoglobin value must be obtained > 2 weeks after the last blood transfusion.) d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) value of ≤ 3.0 × upper limit of normal (ULN). e. Total serum bilirubin value of ≤ 1.5 × ULN. f. Serum creatinine value of ≤ 1.5 mg/dL.

	9. Women of childbearing potential must have a negative pregnancy test (urine or serum) within 7 days before starting study drugs. Both males and females must agree to use effective birth control during the study (before the first dose and for 6 months after the last dose of study drugs) if conception is possible during this interval. Female patients are considered to not be of childbearing potential if they have a history of hysterectomy, or are postmenopausal defined as no menses for 12 consecutive months without an alternative medical cause. For both males and females, see Section 7.7.3 for definitions of contraceptive methods considered effective for this protocol. 10. Is able to take medications orally (ie, study drug must not be administered via a feeding tube). 11. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures. **Exclusion Criteria** 1. Has a serious illness or medical condition including, but not limited to the following: a. Other concurrently active malignancies excluding malignancies that are disease-free for more than 3 years or carcinoma-in-situ deemed cured by adequate treatment. b. Known brain metastasis or leptomeningeal metastasis. c. Active infection (ie, body temperature ≥ 38°C because of infection) including active or unresolved pneumonia/pneumonitis. d. Intestinal obstruction, pulmonary fibrosis, renal failure, liver failure, or clinically significant cerebrovascular disorder and evidence of interstitial lung disease. e. Uncontrolled diabetes. f. Myocardial infarction within 12 months before enrollment severe/unstable angina, symptomatic congestive heart failure New York Heart Association class III or IV [redacted] g. Gastrointestinal hemorrhage (grade ≥ 3) within 2 weeks before enrollment. h. Known human immunodeficiency virus or acquired immunodeficiency syndrome-related illness, or chronic or acute hepatitis B or hepatitis C. i. Psychiatric disease that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results. j. History of any autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (eg, rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [eg, Wegener's Granulomatosis]); central nervous system or motor neuropathy considered of autoimmune origin (eg, Guillain-Barre Syndrome and Myasthenia Gravis, multiple sclerosis). Patients with Graves' disease will be allowed. k. Patients with a condition requiring systemic treatment with either corticosteroids (> 20 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of Cycle 1 Day 1. Inhaled or topical steroids, and adrenal replacement steroids doses ≤ 20 mg daily prednisone or equivalent, are permitted in the absence of active autoimmune disease. 2. Treatment with any of the following within the specified time frame before enrollment: a. Major surgery within the past 4 weeks (the surgical incision should be fully healed before study drug administration). b. Any anticancer therapy within the past 3 weeks before enrollment. c. Extended field radiation within the past 4 weeks or limited field radiation

	within the past 2 weeks before enrollment. d. Any investigational drug/device received within the past 4 weeks or 5 times the half-life (whichever is shorter) before enrollment. 3. Previous treatment with TAS-102. 4. Prior treatment with anti-PD-1, anti- PD-L1, anti- programmed cell death ligand-2, anti-CD137, anti-OX-40, anti-CD40, anti-cytotoxic T lymphocyte-associated antigen-4 antibodies, or any other immune checkpoint inhibitors. 5. Unresolved toxicity of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 ≥ grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity). 6. Prior events of immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis and renal dysfunction, immune-mediated rash, immune-mediated encephalitis, and history of infusion reactions to nivolumab. 7. Known or assumed hypersensitivity to TAS-102 or nivolumab or any of its ingredients, including polysorbate 80-containing infusion. 8. Previous severe hypersensitivity reaction to treatment with another mAb. 9. Pregnant or lactating female. 10. Inappropriate for entry into this study in the judgment of the investigator.
Treatment Regimens:	TAS-102 (starting dose of 35 mg/m^2/dose) will be administered orally BID, within 1 hour after completion of the morning and evening meals, for 5 days a week with 2 days of rest for 2 weeks, followed by a 14-day rest, repeated every 4 weeks. In addition, patients will receive nivolumab 3 mg/kg intravenously over 60 minutes every 2 weeks on Day 1 and Day 15 of each cycle. The investigator will attempt to keep the nivolumab schedule on the same schedule as TAS-102, even if there is a delay in dosing of TAS-102.
Study Duration:	Patients will be treated until the patient meets the discontinuation criteria (Section 7.5.1). For the purpose of final analyses, the study will be considered completed when all patients have discontinued from treatment or 12 months after the first day of treatment with TAS-102 plus nivolumab of the last patient enrolled, whichever occurs first. Upon data cutoff, patients ongoing with study treatment may continue with their treatment and be followed for safety. Measurements of efficacy and data collection may be reduced.
Efficacy Criteria for Evaluation:	Computed tomography scans will be performed at baseline and then every 2 cycles. On-site tumor assessments will be performed by the investigator/local radiologist. Tumor scans will be assessed using irRC and RECIST criteria. Overall response rate, DCR, PFS, and OS will be determined for all patients. CCI [redacted]
Safety Criteria for Evaluation:	Adverse events (AEs) will be graded using the NCI CTCAE.

Statistical Methods:	**Study Populations** The study populations for all analyses are defined as follows: • Safety Population: Includes all patients who received at least 1 dose of study drug. It will be the primary population for safety analyses. • DLT Evaluable Population: Includes all patients in the safety population in Stage 1, prior to confirming the recommended dose, who completed at least 1 cycle (28 days) of study treatment with at least 80% of the study treatment administered, unless the treatment was interrupted because of a DLT. • Efficacy Population: Includes all patients in the safety population who completed at least 6 months of tumor follow-up (evaluable irRC and/or RECIST assessments), unless the patient progressed or died before the 6-month follow-up. **Efficacy Analyses** Tumor response assessments and disease progression will be evaluated in this study using the irRC and RECIST criteria. The RECIST and irRC response assessments will be performed by the investigators for the study. Descriptive statistics, such as incidence of responses (ORR and DCR), Kaplan-Meier estimates for PFS and OS, and associated 95% confidence intervals will be provided. **Safety Analyses** Simple descriptive statistics will be provided for safety endpoints, demographic/baseline characteristics, and study drug exposure. Safety endpoints will primarily include incidence of AEs and changes from baseline (grade changes) in clinical laboratory tests.
Sample Size Justification:	Sample size considerations are based on a 2-stage minimax Simon design, testing a null hypothesis (poor response) of 10% or less immune-related overall response (irOR) versus an alternative hypothesis (promising response) of 30% or greater irOR at an approximate 5% 1-sided significance level and 80% power. In Stage 1 (futility assessment), enrollment will include 15 evaluable patients for irOR assessment and accrual will continue to Stage 2, if at least 2 of 15 (13%) patients respond (partial response or complete response). The probability of early stopping assuming poor response is about 55%. In Stage 2, if the Stage 1 futility boundary is exceeded, an additional 10 patients evaluable for irOR assessment will be enrolled, for a total of at least 25 evaluable patients. Further development will be considered promising if at least 6 of 25 (24%) patients respond. If the initial dose is not tolerated in the first 6 patients in Stage 1, an additional 6 DLT-evaluable patients will be enrolled at the reduced dose. Assuming a 10 to 15% nonevaluability for DLT and/or irRC assessment rate, a total of 30 to 35 patients is expected to be enrolled in the study.
Interim Analyses:	The first 6 patients will be enrolled and will be evaluated for the safety and tolerability of the combination therapy after Cycle 1. In Stage 1, at the point that the ninth patient is enrolled (or a total of at least 15 patients evaluable for response assessment at the target dose), enrollment will stop, and there will be an assessment of safety and efficacy to determine whether the second stage will open for enrollment.

2. STUDY SCHEDULE

Table 1: Study Schedule

	Baseline Period		On-Treatment Period								End of Treatment/ End of Study Period		
	Baseline Day		CYCLE 1 Day of Cycle[2]				SUBSEQUENT CYCLES Day of Cycle[2]						
Visit ID / Procedure	**-28 to -1**	**-7 to -1**	**1**	**12**	**15**	**End of Recovery**	**1**	**12**	**15**	**End of Recovery**	**End of Treatment[1]**	**30-Day Safety Follow-up Visit[2]**	**Survival Follow-up**
Sign ICF	X[3]												
Enrollment	X[4]												
Medical History	X												
Histological Confirmation	X												
Physical Examination[5]		X					X[6]				X	X	
Baseline Signs and Symptoms		X											
Height		X											
Vital Signs[7]		X					X[6]				X	X	
Weight		X			X		X[6]		X		X	X	
ECOG Performance Status[8]	X		X		X		X[6]		X		X	X	
Hematology[9]		X			X		X[6]		X		X	X	
Serum Chemistry[9]		X			X		X[6]		X		X	X	
Urinalysis[9]		X											
Pregnancy Test[10]		X									X	X	
Tumor Measurements[11]	X									X[11]	X[11]		X[11]
Concomitant Medications[12]	X	→	→	→	→	→	→	→	→	→	→	→	X[13]
AE/SAE Assessment[14]	X	→	→	→	→	→	→	→	→	→	→	→	
TAS-102 Treatment[15]			X D 1-5	X D 8-12			X D 1-5	X D 8-12					
Nivolumab –every 2 weeks			X		X		X		X				
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Table 1: Study Schedule (Continued)

Visit ID / Procedure	Baseline Period		On-Treatment Period								End of Treatment/ End of Study Period		
			CYCLE 1				SUBSEQUENT CYCLES						
	Baseline Day		Day of Cycle[2]				Day of Cycle[2]						
	-28 to -1	-7 to -1	1	12	15	End of Recovery	1	12	15	End of Recovery	End of Treatment[1]	30-Day Safety Follow-up Visit[2]	Survival Follow-up
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Survival Status			→				→				→		X[18]

[1] End of Treatment: Assessments will be performed at time of treatment discontinuation of both study drugs (TAS-102 and nivolumab). If the decision to discontinue study drugs is made within 2 weeks after the patient's last treatment visit, an End of Treatment visit is not required unless deemed clinically necessary by the investigator. If the decision to discontinue study drugs is made more than 2 weeks after the last treatment visit, an End of Treatment Visit is required. If this visit occurs within 2 weeks of the 30-day Safety Follow-up visit, the 2 visits can be combined and the information at the End of Treatment visit will be entered into the 30-day Safety Follow-up visit.

[2] Assessment Windows: A window of ± 3 days is allowable for study procedures (± 7 days allowable for computerized tomography [CT] scans), as long as the proper order is maintained.

[3] Sign Informed Consent Form (ICF): Written informed consent should be obtained before the performance of any study procedure.

[4] Enrollment: Enroll patient by entering baseline data into the electronic case report form in order to receive a unique 6-digit patient number.

[5.] Physical Examination: Beginning with Cycle 2, and for all subsequent cycles, perform a physical examination within 24 hours before Day 1 study drug administration.

[6.] Subsequent Cycles ≥ 2: Obtain within 24 hours before Day 1 study drug administration. Before starting subsequent cycles, verify that patients with toxicities have met resumption criteria before administering study drug.

[7.] Vital Sign Measurements: Blood pressure, heart rate, body temperature, respiratory rate; beginning with Cycle 2, and for all subsequent cycles; collect within 24 hours before Day 1 study drug administration.

[8.] ECOG Performance Status: Collect within 24 hours before Day 1 and Day 15 study drug administration for all cycles.

[9.] Hematology, Serum Chemistry, Urinalysis: Hematology and serum chemistry will be performed at baseline (within 7 days before Day 1 of Cycle 1), Day 15 Cycle 1 and Day 1 and Day 15 of each subsequent cycle before administration of study drug. Urinalysis is required at Baseline and thereafter as clinically indicated. Laboratory test results obtained before signing ICF may be used if the results were obtained within 7 days before Day 1 of Cycle 1.

[10.] Pregnancy Test: A pregnancy test is required at Baseline (within 7 days before Day 1 of Cycle 1) and at either the End of Treatment or 30-day Safety Follow-up visit. More frequent pregnancy assessments may be performed as required by local law.

[11.] Tumor Measurements: Obtain a contrast-enhanced CT scan of the chest and abdomen (and pelvis, if clinically indicated) within 28 days before Day 1 of Cycle 1 and every 2 cycles thereafter during study treatment. If a patient discontinues treatment because of radiologic disease progression, additional tumor assessment is not required at the End of Treatment visit. For patients who discontinue treatment for reasons other than radiologic disease progression, every effort should be made to perform an end-of-treatment tumor assessment before the start of new anticancer therapy. Patients that discontinued treatment for reasons other than disease progression should continue to be followed for tumor response every 2 cycles until the patient develops radiologic disease progression (or death) or initiation of new anticancer therapy (whichever occurs first). Tumor assessments should be performed according to Response

Evaluation Criteria in Solid Tumors [RECIST] (version 1.1) as well as immune-related response criteria (irRC). Computerized tomography scans obtained before signing the ICF may be used if the date of the scan is within 28 days before Day 1 of Cycle 1.

12. Concomitant Medications: Collect concomitant medications from time of signed ICF through the 30-day Safety Follow-up visit, including any medications used to treat adverse events (AEs) or serious AEs (SAEs). At the 30-day safety follow-up period, collect date of initiation of any new anticancer therapy.
13. Concomitant Medications: Collect anticancer therapies.
14. AE/SAE Assessment: Monitor patients for any untoward medical events from the time of signed ICF through the 30-day safety follow-up period or until initiation of new anticancer treatment, whichever comes first.
15. Study Drug Treatment: Patients will be dispensed with sufficient quantities of TAS-102 to self-administer twice daily on Days 1 through 5 and 8 through 12 of each cycle. Patients will be instructed to return all unused TAS-102 and used kits to their next clinic visit. Nivolumab will be administered intravenously once every 2 weeks on Day 1 and Day 15 of each cycle. This schedule should be maintained, even if there are delays in the dosing of TAS-102.

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Survival Status: Obtain survival status (alive/dead) at scheduled 8-week time intervals until study discontinuation criteria are met.

Abbreviations: AE = adverse event; ECOG = Eastern Cooperative Oncology Group; ICF = informed consent form; SAE = serious adverse event.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-FU	5-fluorouracil
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase (SGOT)
BID	Twice daily
BSA	Body surface area
BSC	Best supportive care
CI	Confidence interval
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
FDG-PET	fluorodeoxyglucose positron emission tomography
FTD	Trifluridine
G-CSF	Granulocyte colony-stimulating factor
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
irCR	Immune-related complete response
irOR	Immune-related overall response

Abbreviation	Definition
irORR	Immune-related overall response rate
irPD	Immune-related progressive disease
irPR	Immune-related partial response
irRC	Immune-related response criteria
irSD	Immune-related stable disease
IU	International units
KRAS	GTPase KRas; V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
mAb	Monoclonal antibody
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSS	Microsatellite stable
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand-1
PFS	Progression free survival
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RECOURSE	**Re**fractory **Co**lo**re**ctal Cancer **S**tudy (TPU-TAS-102-301 Phase 3 study; NCT01607957)
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious Adverse Reaction
SD	Stable disease
SPD	Sum of the products of the 2 largest perpendicular diameters
TOI	Taiho Oncology, Inc.
TP	Thymidine phosphorylase

Abbreviation	Definition
TPI	Tipiracil hydrochloride
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor

5. INTRODUCTION

5.1. TAS-102

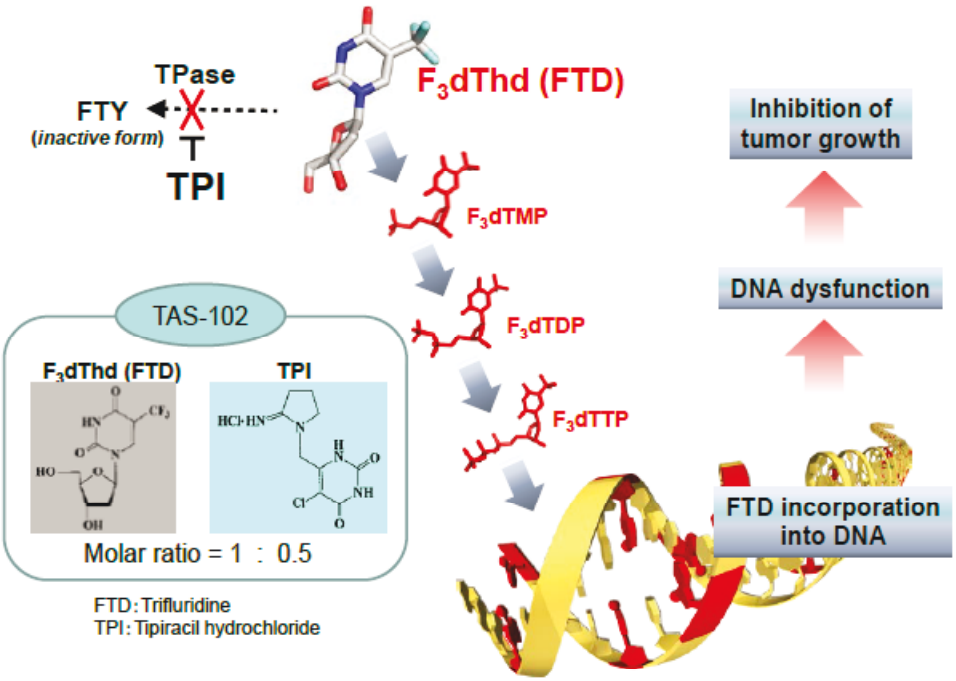
Detailed information on the nonclinical and clinical experience with TAS-102 is provided in the Investigator's Brochure (IB).

5.1.1. Mechanism of Action

TAS-102 is an oral combination drug of an antineoplastic thymidine-based nucleoside analogue, trifluridine (FTD) and a thymidine phosphorylase (TP) inhibitor, tipiracil hydrochloride (TPI). After uptake into cancer cells, FTD is phosphorylated by thymidine kinase, further metabolized in cells to a deoxyribonucleic acid (DNA) substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation. When orally administered, FTD is rapidly degraded to an inactive form by TP. Co-administration of TPI, an inhibitor of TP, with FTD prevents the rapid degradation of FTD, resulting in a significant increase in systemic exposure to FTD.

Trifluridine incorporation into DNA is markedly higher than that of other nucleoside analogues. The degree of incorporation of FTD into DNA ranges from approximately 10-fold up to 700-fold greater in comparison with that of 2'-deoxy-5-fluorouridine. Trifluridine also exhibits thymidylate synthase inhibition.[1-6] Results of in vivo studies showed FTD incorporation into DNA to be the primary mechanism of antitumor activity with oral administration. Trifluridine alone, when orally administered, is rapidly degraded to an inactive form, 5-trifluoromethyluracil by TP. Co-administration of TPI with FTD increases the concentration of FTD in the body leading to augmentation of cytotoxicity by FTD.[7] In preclinical studies, FTD incorporation into DNA in tumor was shown to increase with divided daily administration compared with once daily administration. Figure 1 shows the mechanism of antitumor activity of TAS-102.

Figure 1: Mechanism of Antitumor Activity of TAS-102



5.1.2. TAS-102 in Colon Cancer

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5.1.2.2. TAS-102 Clinical Experience

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5.1.2.2.2. Phase 2 Clinical Studies

One double-blind, randomized Phase 2 study (Study J003-10040030) has been conducted in patients with colorectal cancer to compare TAS-102 plus best supportive care (BSC) to placebo plus BSC. TAS-102 was administered at a dose of 35 mg/m^2/dose BID. The most frequently reported treatment-emergent adverse events (AEs) were neutrophil count decreased, white blood cell count decreased, hemoglobin decreased, lymphocyte count decreased, platelet count decreased, nausea, diarrhea, fatigue, and decreased appetite.

The median overall survival (OS) was 9.0 months in the TAS-102 group and 6.6 months in the placebo group. The median progression-free survival (PFS) assessed by an independent review committee was 2.0 months for the TAS-102 group and 1.0 month for the placebo group. Using the Response Evaluation Criteria in Solid Tumors (RECIST), the best tumor response assessed by an independent review committee for partial response (PR) was reported for 1 patient, stable disease (SD) was reported for 48 patients, progressive disease (PD) was reported for 53 patients, and 10 patients were not evaluable in the TAS-102 group. In the placebo group, SD was reported for 6 patients, PD was reported for 44 patients, and 7 patients were not evaluable. The response rate was 0.9% in the TAS-102 group and 0% in the placebo group. The disease control rate (DCR) was 43.8% in the TAS-102 group and 10.5% in the placebo group.

5.1.2.2.3. Phase 3 Clinical Studies

Study TPU-TAS-102-301 was a double-blind, global study comparing TAS-102 plus BSC and placebo plus BSC in refractory colorectal cancer (Refractory Colorectal Cancer Study [RECOURSE]).[8] Patients were randomly assigned in a 2:1 ratio and stratified by *KRAS* status (wild, mutant); time since diagnosis of first metastasis (< 18 months, ≥ 18 months); and region (Region 1: Asia [Japan]; Region 2: Western [US and Europe]). As of 31 January 2014, (cutoff date), 534 patients were randomized to TAS-102 and 266 patients were randomized to placebo. Two patients (1 in each treatment group) did not receive study drug; thus 798 patients were treated (533, TAS-102; 265, placebo). A total of 759 (95.1%) patients had discontinued study treatment and 39 patients (37, TAS-102; 2, placebo) were continuing to receive treatment. Overall, 88.0% of patients were discontinued because of clinical or radiologic disease progression.

The incidence of treatment-related AEs was higher in the TAS-102 group than in the placebo group (85.7% and 54.7%, respectively) as was the incidence of grade ≥ 3 AEs (69.4% and 51.7%, respectively). In the TAS-102 group, the most frequently reported grade 3 AEs were anemia (15.9%), neutropenia (13.7%), neutrophil count decreased (11.8%), and white blood cell decreased (9.2%). The most frequently reported grade 4 AEs were neutropenia (6.4%) and neutrophil count decreased (4.1%).

In the placebo group, the most frequently reported grade 3 AEs were fatigue (5.7%), decreased appetite (4.9%), and blood alkaline phosphatase increased (4.9%). The most frequently reported grade 4 AEs were gamma-glutamyl transferase increased (1.5%) and blood bilirubin increased (1.1%).

The most frequently reported AEs leading to discontinuation in the TAS-102 group (10.3%) were general physical health deterioration (2.3%), fatigue (1.1%), and dyspnea (0.6%). The most frequently reported AEs leading to discontinuation in the placebo group (13.6%) were blood bilirubin increased (2.3%), general physical health deterioration (1.9%), ascites (1.9%), decreased appetite (1.5%), hepatic failure (1.1%), abdominal pain (1.1%), and asthenia (1.1%).

As of the cutoff date, deaths were reported in 68.9% of patients in the TAS-102 group and 79.9% of patients in the placebo group. The only treatment-related death was a TAS-102 patient who died because of septic shock.

The frequency of serious AEs (SAEs) (including fatal) was 29.6% in the TAS-102 group and 33.6% in the placebo group. The most frequently reported SAEs in the TAS-102 group were general physical health deterioration, febrile neutropenia, and anemia.

The addition of TAS-102 to BSC resulted in a statistically significant improvement in OS compared with placebo plus BSC. The median OS was 7.1 months for the TAS-102 group versus 5.3 months for the placebo group (1- and 2-sided $P < .0001$). The percentage of patients surviving at 1 year was 27.0% in the TAS-102 group and 18% in the placebo group. CCI [redacted] Consistent with the primary mechanism of action of TAS-102, a significant increase in OS was demonstrated in patients who were refractory for 5-FU received as part of their last regimen before randomization.

5.2. Rationale for Study and Selection of Dose

5.2.1. Unmet Medical Need

Colorectal cancer is the third most common type of cancer among both men and women in the US, and is the second most deadly. It is estimated that 1 in every 20 people will develop colorectal cancer. In 2016, it is projected that there will be 95,270 new cases of colon cancer and 39,220 new cases of rectal cancer in the US. Approximately 49,190 deaths are expected in the US.[9]

TAS-102 is an oral combination of 1M FTD and 0.5M TPI. The primary mechanism of action of FTD, an antineoplastic thymidine-based nucleoside analog, is incorporation into DNA via

phosphorylation, resulting in a different cytotoxic mechanism from 5-FU and 2'-deoxy-5-fluorouridine (uracil-based thymidylate synthase inhibitors).

TAS-102 has been shown to significantly improve OS in patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not candidates for fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) biological therapy, and an anti-epidermal growth factor receptor (EGFR) therapy.[8] However, TAS-102 is not curative and the vast majority of patients will eventually progress. Hence, there are limited therapeutic options remain for patients in this setting.

Treatment with pembrolizumab (an anti-PD-1 antibody similar to nivolumab), showed that in mCRC patients with high microsatellite instability (MSI) tumors, pembrolizumab activity was much higher than in mCRC patients with microsatellite stable (MSS) tumors. The median PFS and OS were not reached in MSI-high mCRC patients. In contrast, the median PFS and OS were 2.2 and 5.0 months, respectively, in the cohort with MSS mCRC patients (hazards ratio for PFS was 0.10 [$P < .001$], and hazards ratio for OS was 0.22 [$P = .05$]). Moreover, the overall response rate (ORR) for mCRC patients with MSI-high and MSS was 40% and 0%, respectively. Therefore, an anti-PD-1 antibody therapeutic approach does not appear to be effective in MSS refractory colorectal cancer.[10]

5.2.2. Rationale for Study Design

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The proposed mechanism for the observed additive or synergistic effect is an increase in tumor immunogenicity after treatment with TAS-102, leading to better tumor response to anti-PD-1 antibody therapy. Increased tumor immunogenicity may be triggered by TAS-102 DNA incorporation. This Phase 2 study will examine this hypothesis. This present study is a multi-center, single arm, safety lead-in Phase 2 design evaluating the safety and efficacy of TAS-102 plus nivolumab in patients with MSS refractory mCRC.

Nivolumab is a PD-1 blocking antibody indicated for the treatment of unresectable or metastatic melanoma, metastatic non-small cell lung cancer, and advanced renal cell carcinoma. Although nivolumab has not been studied in the MSI mCRC patient population, it is considered to be in a similar class as pembrolizumab and will be used in this study. Nivolumab was selected for this combination therapy because it is administered every 2 weeks, whereas pembrolizumab is administered every 3 weeks. Therefore, nivolumab is appropriate to combine with TAS-102, which is administered on a 4-week regimen.

Overall response rate is one of the key efficacy evaluations utilized in oncology studies, in particular solid tumors, and is considered standard and well defined by several guidances (eg, European Marketing Authority and the Food and Drug Administration). Overall response rate is used in the evaluation and guidance of cancer treatments as well as in the prediction of clinical outcomes. In addition to ORR, patients will also be evaluated using the immune-related ORR

(irORR) because it is a modification of the ORR and is widely utilized in clinical trials evaluating treatments with immune-oncology products.

Regarding safety profiles of each drug as reflected in their respective US product inserts, TAS-102 treatment mainly caused myelosuppressive toxicities in the RECOURSE Phase 3 study, as well as other AEs at a frequency of ≥ 10% for anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia. Nivolumab treatment mainly caused rash in patients with melanoma with a frequency of ≥ 20% as well as other immune-mediated adverse reactions. Since there is no overlap between the 2 safety profiles, a dose-escalation design is not essential for this study but a safety lead-in period is necessary to determine the tolerability of TAS-102 in combination with nivolumab.

5.2.3. Selection of TAS-102 Dose

TAS-102 (35 mg/m^2/dose) will be administered orally BID, within 1 hour after completion of morning and evening meals, for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest. This treatment cycle will be repeated every 4 weeks.

The safety and tolerability of this TAS-102 regimen was demonstrated in a Phase 3, multinational, randomized, double-blind study (RECOURSE; TPU-TAS-102-301), in which TAS-102 was shown to significantly improve OS compared with placebo in patients with mCRC, who had been previously treated with, or were not candidates for fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy.[8]

In the RECOURSE study, the most common AEs associated with TAS-102 treatment were myelosuppressive toxicities. Up to 20% of patients receiving TAS-102 experienced grade 3 or grade 4 hematologic events related to anemia and neutropenia/leukopenia; however, the incidence of febrile neutropenia was low (3.8%). These events were generally manageable with reductions in dose, delays in cycle initiation and occasional use of granulocyte colony-stimulating factor (G-CSF). Only 3 patients discontinued treatment because of hematologic AEs, and there was only 1 treatment-related death because of neutropenia-related infection. Events of nausea, decreased appetite, diarrhea, and vomiting related to treatment were common in the TAS-102 group (20.1% to 39.4%); however, these AEs were rarely grade 3 or grade 4. The incidence of stomatitis among patients receiving TAS-102 was 7.9%; grade 3 or grade 4 events of stomatitis were rare (0.4%). In addition, hand-foot syndrome was reported in only 2.3% of patients receiving TAS-102 (all grade 1 or grade 2), which was the same percentage reported in the placebo arm.

Trifluridine, the active principal of TAS-102, is primarily metabolized by TP in the gastrointestinal tract and liver. Nivolumab is a therapeutic monoclonal antibody (mAb), expected to be catabolized into amino acids by general degradation process. As nivolumab is not a cytokine modulator, it is unlikely to have an effect on drug metabolizing enzymes or transporters in terms of inhibition or induction. There are no potential mechanisms of pharmacokinetic drug interactions for the combination of TAS-102 and nivolumab. Furthermore, the mechanism of action and the safety profiles of TAS-102 and nivolumab are also quite different. Therefore, the recommended dosage of each agent, 35 mg/m^2 for TAS-102 and 3 mg/kg for nivolumab is selected as the starting dose.

6. STUDY OBJECTIVES

The study will evaluate the following objectives in patients with mCRC receiving TAS-102 in combination with nivolumab:

Primary Objective

- To estimate the irORR of TAS-102 and nivolumab combination therapy in mCRC patients

Secondary Objectives

- To confirm the recommended Phase 2 dose for the combination therapy of TAS-102 and nivolumab
- To assess the safety of TAS-102 and nivolumab given as combination therapy
- To estimate the ORR using RECIST version 1.1
- To estimate the PFS based on immune-related response criteria (irRC) and RECIST
- To estimate the DCR using irRC and RECIST
- To estimate the OS

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7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a multi-center, single arm, safety lead-in, Phase 2 study evaluating the safety and efficacy of TAS-102 plus nivolumab in patients with MSS refractory mCRC.

Patients will undergo screening to assure eligibility. Screening will include confirmation of MSS status based on an analysis of either archived or fresh biopsy tissue.

Microsatellite instability testing is standardized and performed in Clinical Laboratory Improvement Amendments-certified laboratories without need for assay development. Archived tumor samples or newly obtained biopsies will be used for determining MSI. The test will be performed using certified immunohistochemistry or polymerase chain reaction-based tests for eligibility.

The study is a Simon's 2-stage design. Patients who are eligible will be enrolled sequentially in the following stages:

Stage 1: The first 6 patients will be enrolled and after Cycle 1 treatment, they will be evaluated for the safety and tolerability of the combination therapy. TAS-102 and nivolumab are not expected to have significant overlapping toxicities. A safety team comprised of the medical monitor and treating investigators will review safety data from these first 6 patients after they have undergone Cycle 1 treatment. If 2 or more patients experience a dose-limiting toxicity

(DLT), then the dose of TAS-102 will be reduced (after discussion between the investigator and Sponsor) and an additional 6 patients will be enrolled. If the DLT is considered related to TAS-102, the investigator should follow the recommended dose modifications in Section 8.2.4. If the DLT is considered related to nivolumab, the investigator should follow the discontinuation/withhold criteria listed in Section 8.2.6. If the DLT relationship is unclear to either TAS-102 or nivolumab, but is not disease related, then both TAS-102 and nivolumab should be interrupted and the TAS-102 dose should be reduced at the next dose cycle.

Accrual will not be halted while the review is being conducted if no DLTs are identified. Any outcome of this safety review will be communicated in a timely manner to the participating investigators so that they may notify their Institutional Review Boards (IRBs).

Assuming a tolerated dose is confirmed (up to 1 DLT in 6 patients), at least 9 additional patients evaluable for response will be enrolled and followed for a minimum of 6 months. At the point that the ninth patient is enrolled (or a total of at least 15 patients evaluable for response assessment at the target dose), enrollment will stop, and there will be an interim analysis to assess the safety and efficacy to determine whether the second stage will open for enrollment. To proceed to Stage 2, two or more patients out of the 15 patients in Stage 1 will need to demonstrate a PR or complete response (CR) within a 6-month tumor follow-up period. If there are fewer than 2 responders in Stage 1, then the study will be stopped.

Stage 2: An additional 10 patients evaluable for response assessment will be enrolled and followed for a minimum of 6 months.

The following TAS-102 related AEs will be considered DLTs (only AEs occurring in Cycle 1 will be DLT evaluable):

Hematological toxicities

1. Grade 4 neutropenia lasting > 7 days
2. Grade 4 febrile neutropenia and fever ≥ 38°C for over 1 hour
3. Grade 4 thrombocytopenia or grade 3 thrombocytopenia associated with bleeding or requiring transfusions

Non-hematological toxicities

1. Grade 3 or grade 4 non-hematologic toxicity (excluding alopecia, nausea, vomiting, diarrhea)
2. Grade 3 or grade 4 nausea/vomiting lasting > 48 hours and uncontrolled by aggressive anti-emetic therapy, including serotonin 5-HT3 receptor antagonists (eg, ondansetron)
3. Grade 3 or grade 4 diarrhea lasting > 48 hours and unresponsive to antidiarrheal medication

Drug-related toxicities

1. Any drug-related toxicity resulting in > 2 weeks delay in initiation of Cycle 2 (ie, cannot start Cycle 2 until Day 43 or later)
2. Any drug-related toxicity that prevents completion of 80% compliance for either drug in Cycle 1

The combination of TAS-102 and nivolumab is expected to trigger immune-mediated responses, which require activation of the immune system before the observation of clinical responses. Such immune activation may take weeks to months to become evident. Some patients may have an objective volume increase of tumor lesions or other disease parameters within weeks after the start of dosing. Such patients may not have had sufficient time to develop immune system activation or, in some patients, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor. Therefore, tumors will be evaluated with both RECIST and irRC to determine objective responses.

TAS-102 (35 mg/m^2/dose) will be administered orally BID, within 1 hour after completion of morning and evening meals, for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest, repeated every 4 weeks. Nivolumab (3 mg/kg/dose) will be administered intravenously over 60 minutes every 14 days on Day 1 and Day 15.

A contrast-enhanced computed tomography (CT) scan of the chest and abdomen (pelvis if clinically indicated) within 28 days before Day 1 of Cycle 1 and every 2 cycles thereafter will be performed during study treatment. On-site tumor assessments will be performed by the investigator or local radiologist. Tumor assessments will be analyzed using RECIST and irRC. For patients who discontinue treatment for reasons other than radiologic disease progression, every effort should be made to perform an end-of-treatment tumor assessment before the start of new anticancer therapy. Patients that discontinue treatment for reasons other than disease progression should continue to be followed for tumor response every 2 cycles until the patient develops radiologic disease progression (or death) or initiation of new anticancer therapy (whichever occurs first). Tumor assessments should be performed according RECIST and irRC. If the CT scan was obtained before the patient signed the informed consent form (ICF), the CT scan may be used if the date of the scan is within 28 days before Day 1 of Cycle 1.

Survival status (alive or dead) should be obtained at scheduled 8-week time intervals until study discontinuation criteria are met.

Standard safety monitoring will be performed and AEs will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

7.2. Study Duration

Patients will be treated until the patient meets the discontinuation criteria (see Section 7.5).

For the purpose of final analyses, the study will be considered completed when all patients have discontinued from treatment or 12 months after the first day of treatment with TAS-102 plus nivolumab of the last patient enrolled, whichever occurs first. Upon data cutoff, patients ongoing with study treatment may continue with their treatment and be followed for safety. Measurements of efficacy and data collection may be reduced.

7.3. Study Population

Approximately 30 to 35 male and female patients with mCRC will be enrolled in a Simon's 2-stage design.

7.3.1. Inclusion Criteria

A patient must meet all of the following inclusion criteria to be eligible for enrollment in this study:

1. Has provided written informed consent.
2. Patient with confirmed histologically proven metastatic or locally advanced colorectal adenocarcinoma who is MSS (ie, not MSI) based on either an analysis of tissue from a prior biopsy or based on tissue from a new biopsy.
3. Patient with the presence of at least 1 lesion with measurable disease as defined by 10 mm in the longest diameter for a soft tissue lesion or 15 mm in the short axis for a lymph node by RECIST and irRC criteria for a response assessment.
4. Patient has received at least 2 prior lines of standard chemotherapies for mCRC and is refractory to or failing those chemotherapies.
    a. Standard chemotherapy must include ALL of the following agents:
        i. Fluoropyrimidines, irinotecan, and oxaliplatin
        ii. An anti-VEGF biological therapy (eg, bevacizumab or aflibercept or ramucirumab)
        iii. At least 1 of the anti-EGFR mAbs (cetuximab or panitumumab) for *RAS* wild-type patients.
5. Age ≥ 18 years.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 at the time of enrollment.
7. Life expectancy of ≥ 4 months.
8. Has adequate organ function as defined by the following criteria:
    a. Absolute neutrophil count of ≥ 1500/mm^3 (ie, ≥ 1.5 × 10^9/L by International Units [IU]).
    b. Platelet count of ≥ 100,000/mm^3 (IU: ≥ 100 × 10^9/L)
    c. Hemoglobin value of ≥ 9.0 g/dL (If patient required previous blood transfusions, a hemoglobin value must be obtained > 2 weeks after the last blood transfusion.)
    d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) value of ≤ 3.0 × upper limit of normal (ULN).
    e. Total serum bilirubin value of ≤ 1.5 × ULN
    f. Serum creatinine value of ≤ 1.5 mg/dL.
9. Women of childbearing potential must have a negative pregnancy test (urine or serum) within 7 days before starting study drugs. Both males and females must agree to use effective birth control during the study (before the first dose and for 6 months after the last dose of study drugs) if conception is possible during this interval. Female patients are considered to not be of childbearing potential if they have a history of hysterectomy, or are postmenopausal defined as no menses for 12 consecutive months without an alternative medical cause. For both males and females, see Section 7.7.3 for definitions of contraceptive methods considered effective for this protocol.

10. Is able to take medications orally (ie, study drug must not be administered via a feeding tube).
11. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

7.3.2. Exclusion Criteria

1. Has a serious illness or medical condition including, but not limited to the following:
    a. Other concurrently active malignancies excluding malignancies that are disease-free for more than 3 years or carcinoma-in-situ deemed cured by adequate treatment.
    b. Known brain metastasis or leptomeningeal metastasis.
    c. Active infection (ie, body temperature ≥ 38°C because of infection) including active or unresolved pneumonia/pneumonitis.
    d. Intestinal obstruction, pulmonary fibrosis, renal failure, liver failure, or clinically significant cerebrovascular disorder and evidence of interstitial lung disease.
    e. Uncontrolled diabetes.
    f. Myocardial infarction within 12 months before enrollment, severe/unstable angina, symptomatic congestive heart failure New York Heart Association class III or IV [redacted].
    g. Gastrointestinal hemorrhage (grade ≥ 3) within 2 weeks before enrollment.
    h. Known human immunodeficiency virus or acquired immunodeficiency syndrome-related illness, or chronic or acute hepatitis B or hepatitis C.
    i. Psychiatric disease that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results.
    j. History of any autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (eg, rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [eg, Wegener's Granulomatosis]); central nervous system or motor neuropathy considered of autoimmune origin (eg, Guillain-Barre Syndrome and Myasthenia Gravis, multiple sclerosis). Patients with Graves' disease will be allowed.
    k. Patient with a condition requiring systemic treatment with either corticosteroids (> 20 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of Cycle 1 Day 1. Inhaled or topical steroids, and adrenal replacement steroids doses ≤ 20 mg daily prednisone or equivalent, are permitted in the absence of active autoimmune disease.
2. Treatment with any of the following within the specified time frame before enrollment:
    a. Major surgery within the past 4 weeks (the surgical incision should be fully healed before study drug administration).
    b. Any anticancer therapy within the past 3 weeks before enrollment.
    c. Extended field radiation within the past 4 weeks or limited field radiation within the past 2 weeks before enrollment.
    d. Any investigational drug/device received within the past 4 weeks or 5 times the half-life (whichever is shorter) before enrollment.

3. Previous treatment with TAS-102.
4. Prior treatment with anti-PD-1, anti-PD-L1, anti- programmed cell death ligand-2, anti-CD137, anti-OX-40, anti-CD40, anti-cytotoxic T lymphocyte-associated antigen-4 antibodies, or any other immune checkpoint inhibitors.
5. Unresolved toxicity of NCI CTCAE ≥ grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity).
6. Prior events of immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis and renal dysfunction, immune-mediated rash, immune-mediated encephalitis, and history of infusion reactions to nivolumab.
7. Known or assumed hypersensitivity to TAS-102 or nivolumab or any of its ingredients, including polysorbate 80-containing infusion.
8. Previous severe hypersensitivity reaction to treatment with another mAb.
9. Pregnant or lactating female.
10. Inappropriate for entry into this study in the judgment of the investigator.

7.4. Treatment Assignment

7.4.1. Patient Numbering

Study sites will enter patient demographic and baseline data into the electronic case report form (eCRF) in order to receive a patient number.

The eCRF will assign each patient a unique patient number. All patient numbers will be 6 digits; the first 3 digits will be the site number and the last 3 digits will be the patient's number. This patient number will be maintained throughout the study and will not be reassigned. Patients who withdraw consent or discontinue from the study after being assigned a patient number will retain their initial number.

Study drug administration should begin within 3 calendar days after enrollment as described in Section 8.

For patients who sign an ICF but are not enrolled and patients who are enrolled but never dosed, see the eCRF Completion Guidelines for instruction on which eCRF pages to complete.

7.4.2. Randomization

This is not a randomized study design.

7.4.3. Blinding

This is an open-label design study.

7.4.4. Replacement of Patients

Patients will not be replaced. An adequate number of patients will be enrolled until the pre-specified number of evaluable patients at each stage is met.

7.5. Discontinuation of Study Treatment

Patients will receive study drug until a discontinuation criterion is met.

A patient is considered discontinued from study treatment when the decision to permanently stop both study treatments is made, including those decisions made during study drug interruptions and recovery periods.

Study drugs should be continued whenever possible. In case study drug is stopped, it should be determined if the stop can be made temporarily; permanent study drug discontinuation should be a last resort. Any study drug discontinuation should be fully documented.

7.5.1. Treatment Discontinuation Criteria

The reason for discontinuation of treatment should be documented in the patient source documents.

Patients can be discontinued from treatment for the following reasons:

- Patient request at any time irrespective of the reason
- Patients with tumor progression by irRC
- Clinical progression
- Patient experiences an irreversible, treatment-related, grade 4, clinically relevant, non-hematologic event
- Unacceptable AEs, or change in underlying condition such that the patient can no longer tolerate therapy, including:
    a. A maximum dose delay > 28 days from the scheduled start date of the next cycle
    b. Need for more than 3 dose reductions of TAS-102 (or minimum 20 mg/m^2/dose BID)
    c. Discontinuation of both TAS-102 and nivolumab; patient may be considered for continuation of nivolumab or TAS-102 single therapy at the investigator's discretion
- Physician's decision including need for other anticancer therapy not specified in the protocol or surgery or radiotherapy to the only site(s) of disease being evaluated in this protocol
- Pregnancy

7.5.2. End of Treatment Procedures

Upon discontinuation of treatment the investigator must:

- Notify the clinical research associate immediately
- Complete the Study Treatment Discontinuation Form in the eCRF, specifying the reason for the patient's withdrawal from treatment
- If a patient is discontinued because of clinical progression, associated nonserious AEs should be reported on the treatment discontinuation page of the eCRF

7.6. Discontinuation from Study Follow-up

For patients who discontinue study treatment for irRC disease progression, additional tumor assessments are not required at the End of Treatment visit. CCI [redacted]. For patients who discontinue treatment for reasons other than irRC disease progression (eg, intolerable side effects), every effort should be made to perform an end of treatment tumor assessment before the start of new anticancer therapy. Patients that discontinue treatment for reasons other than disease progression should continue to be followed for tumor response every 2 cycles until the patient develops irRC disease progression (or death) or initiation of new anticancer therapy (whichever occurs first).

All treated patients will be followed for survival every 8 weeks until study discontinuation criteria are met, unless the patient has withdrawn consent from the trial. Patients may request discontinuation of study treatment but agree to survival follow-up (this is not considered withdrawal of consent from the trial). The investigator should make every effort to contact the patient or primary caregiver to determine the patient's survival status. Times and dates of contact must be documented in the patient's records.

A patient will be considered discontinued from study follow-up when 1 of the following occurs:

- Patient dies
- Twelve months after the last patient is enrolled and the final analysis is performed
- Study is terminated by the Sponsor or regulatory agencies

7.7. Other Medications and Therapies

7.7.1. Prohibited Medications and Therapies

Patients are not permitted to receive any other investigational or any other anticancer therapy, including chemotherapy, immunotherapy, immunosuppressive agents, biological response modifiers, or endocrine therapy (except for megestrol acetate and steroids at doses less than or equal to 20 mg of prednisone equivalent per day for ≤ 2 weeks) during the study treatment period.

Palliative radiotherapy is not permitted while the patient is receiving study treatment.

7.7.2. Concomitant Medication Therapies

Caution is required when using drugs that are human thymidine kinase substrates, eg, zidovudine. Such drugs, if used concomitantly with TAS-102, may compete with the effector, FTD, for activation via thymidine kinases. Therefore, when using antiviral drugs that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral agent, and consider switching to an alternative antiviral agent that is not a human thymidine kinase substrate, such as lamivudine, zalcitabine, didanosine, and abacavir.

The following medications may be given concomitantly under the following guidelines:

Hematologic Support

Administer hematologic support as medically indicated (eg, blood transfusions, G-CSF, erythropoietin) according to the institutional site standards. If there are no standard procedures for the use of growth factors, follow American Society of Clinical Oncology (ASCO) 2015 Guidelines for Use of Hematopoietic Colony-Stimulating Factors, available at http://www.instituteforquality.org/practice-guidelines.

Management of Diarrhea

Educate both patients and patients' families regarding the potential seriousness of chemotherapy-induced diarrhea. Instruct patients to immediately contact the clinical site staff at the first sign of loose stools.

Provide patients with loperamide or other standard antidiarrheal therapy and instruct the patient on how to use it at the first sign of diarrhea.

Monitor the patient's fluid and electrolyte balance, with appropriate intervention as clinically indicated with fluids and electrolyte replacement, antibiotics, and antiemetics.

Infection prophylaxis with oral antibiotics must be considered for patients with persistent diarrhea beyond 24 hours, or coincident with grade ≥ 3 neutropenia.

Administer prophylactic treatment for diarrhea as clinically indicated.

If there are no institutional standards, refer to the guidelines published by Benson AB et al in Journal of Clinical Oncology.[11]

Management of Nausea and Vomiting

Administer antiemetics as clinically indicated. If there are no institutional standards refer to the ASCO Guidelines for Antiemetics in Oncology.[12]

7.7.3. Effective Contraception During the Study

Both males and females must agree to use effective birth control during the study (before the first dose and for 6 months after the last dose) if conception is possible during this interval. Female patients who are considered not to be of childbearing potential must have a history of being postmenopausal (no menses for 12 consecutive months without an alternative medical cause), or hysterectomy that is clearly documented in the patient's source documents.

For women of childbearing potential, including female study participants and partners of male participants, effective contraception is defined as follows:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen -only hormonal contraception associated with inhibition of ovulation:
  - Oral

  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner with documentation of the success of the vasectomy
- Complete abstinence from heterosexual intercourse (periodic abstinence is not a safe method)

Male patients with partners who are women of childbearing potential should use a combination of male condom with a cap, diaphragm, or sponge with spermicide during the trial and for 6 months after the last dose of study drug.

7.8. Dietary Restrictions

TAS-102 should be taken with a glass of water within 1 hour after completion of the morning and evening meals. There are no dietary restrictions for nivolumab.

8. STUDY TREATMENT

At the beginning of each patient treatment cycle, study sites will weigh the patient and calculate the patient's body surface area (BSA), and determine the recommended study drug dosage. No increase in dose because of an increase in BSA is permitted.

The BSA will be calculated using the following DuBois formula (all BSA calculations are rounded to 2 decimal places) or institutional standards at the respective study site.

$$BSA\ (m^2) = ([Body\ Weight\ (kg)]^{0.425} \times [Height\ (cm)]^{0.725}) \times 0.007184$$

Please note the following:

- Dose escalations (for TAS-102, on a mg/m^2 basis) of study drugs are not permitted at any time
- Only 3 dose reductions of TAS-102 are permitted. There will be no dose reductions for nivolumab.
- Only a ≤ 28-day delay in the start of the next treatment cycle for TAS-102 is permitted (see Section 8.2.4.4).

Study treatment should be started within 3 calendar days after enrollment and should be administered as outlined in the following sections of the protocol. The investigator always has the right to deviate from the established rules for dose modification at her/his discretion if he or she believes a more conservative approach is needed in the management of related or unrelated AEs. However, doses must be modified at least to the extent specified in Section 8.2.4. All deviations from protocol-specified dose modifications must be documented.

Patients will receive study drugs until one of the discontinuation criteria listed in Section 7.5.1 is met.

8.1. Description and Labeling

8.1.1. TAS-102

A description of the study drug and the recommended storage conditions are provided in Section 8.1.1.1 and Section 8.1.1.2, respectively. CCI [redacted]

Patients will be dispensed TAS-102 at the beginning of each cycle. Each kit will be labeled with information including the following:

- Protocol Number
- Sponsor name
- Storage conditions
- Directions for use
- Investigational caution statement

Additional statements will be printed on the label(s) as required by local regulation. Study drug will be shipped from a regional distribution center directly to clinical sites.

8.1.1.1. Description

CCI [redacted]

TAS-102 is formulated as an immediate-release film-coated tablet, which is supplied in 2 strengths (expressed as FTD content):

- The 15 mg white, round, biconvex tablet contains 15 mg FTD and 7.065 mg TPI as active ingredients
- The 20 mg pale-red, round, biconvex tablet contains 20 mg FTD and 9.42 mg TPI as active ingredients
- Both tablet strengths contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, titanium dioxide, polyethylene glycol, and magnesium stearate
- The 20-mg tablet contains the following additional inactive ingredient: red ferric oxide

8.1.1.2. Storage

CCI [redacted]

All study drug must be kept in a locked area with access restricted to specific study personnel.

8.1.2. Nivolumab

Commercially available nivolumab (OPDIVO®) is available as:

- 40 mg/4 mL single-dose vial 0003-3772-11
- 100 mg/10 mL single-dose vial 0003-3774-12

will be used for the TO-TAS-102-203 study. The drug description and storage information can be found in the Patient Package Insert of the commercial label.

Nivolumab, which will be supplied in an approved commercial package (single vials in individual cartons), will be labeled with information including the following:

- Protocol Number
- Sponsor name
- Investigational caution statement

Additional statements will be printed on the label(s) as required by local regulation. Study drug will be shipped from a regional distribution center directly to clinical sites.

All study drug must be kept in a locked area with access restricted to specific study personnel.

8.2. Study Drug Administration

8.2.1. TAS-102 Treatment Regimen

Each treatment cycle will be 28 days in duration. TAS-102 dosage is calculated according to BSA.

One TAS-102 treatment cycle consists of the following:

- Days 1 through 5: TAS-102 (35 mg/m^2/dose) orally BID
- Days 6 through 7: rest
- Days 8 through 12: TAS-102 (35 mg/m^2/dose) orally BID
- Days 13 through 28: rest

Study drug should be taken only on Days 1-5 and 8-12 of each cycle. If doses are missed or held on those days, the patient should not make up for missed doses.

Patients should begin taking TAS-102 (Day 1) with the morning dose. Both the morning and evening doses should be taken at approximately the same time every day. TAS-102 should be taken with a glass of water within 1 hour after completion of the morning and evening meals.

8.2.2. Number of Tablets per TAS-102 Dose

TAS-102 tablet calculation is presented in Table 2, which shows the number of tablets that are needed per calculated BSA.

- Study drug should only be given on Days 1 through 5 and Days 8 through 12 of each cycle even if doses are missed or held for any reason during Days 1 through 12.
- Extension of study treatment into Days 6 and 7 or into the rest period (Days 13 through 28) is not permitted.

Table 2: Number of Tablets Per Dose

TAS-102 Dose (2 × daily)	BSA (m^2)	Dosage in mg (2 × daily)	Total daily dose (mg)	Tablets Per Dose	
				15 mg	20 mg
35 mg/m^2	< 1.07	35	70	1	1
	1.07 - 1.22	40	80	0	2
	1.23 - 1.37	45	90	3	0
	1.38 - 1.52	50	100	2	1
	1.53 - 1.68	55	110	1	2
	1.69 - 1.83	60	120	0	3
	1.84 - 1.98	65	130	3	1
	1.99 - 2.14	70	140	2	2
	2.15 - 2.29	75	150	1	3
	≥ 2.30	80	160	0	4

Abbreviation: BSA=body surface area (calculate to 2 decimal places).

8.2.3. Instructions for Patients for Handling TAS-102

The patient must be instructed in the handling of TAS-102 as follows:

- To store the study drug at room temperature
- To only remove from the study drug kit the amount of tablets needed at the time of dosing
- To wash their hands after handling study drug
- Not to remove doses in advance of the next scheduled dosing
- To make every effort to take doses on schedule
- To report any missed doses
- To take study drug within 1 hour after completing a meal (morning and evening meal) with a glass of water
- If the patient vomits after taking study drug, the patient should not take another dose
- To keep study drug in a safe place and out of reach of children
- To bring all used and unused study drug kits to the site at each visit

8.2.4. TAS-102 Dose Modifications

8.2.4.1. Dose Reduction Levels

TAS-102 dose reductions to be applied in case of toxicity and the number of tablets for each calculated BSA are described in Table 3. Patients are permitted dose reduction(s) to a minimum dose of 20 mg/m^2 (40 mg/m^2/day) in 5 mg/m^2 steps.

Table 3: TAS-102 Dose Reduction Levels and Number of Tablets per Dose

TAS-102 Dose (2 × daily)	BSA (m^2)	Dosage in mg (2 × daily)	Total daily dose (mg)	Tablets per Dose	
				15 mg	20 mg
Level 1 Dose Reduction: From 35 mg/m^2 to 30 mg/m^2					
30 mg/m^2	< 1.09	30	60	2	0
	1.09 - 1.24	35	70	1	1
	1.25 - 1.39	40	80	0	2
	1.40 - 1.54	45	90	3	0
	1.55 - 1.69	50	100	2	1
	1.70 - 1.94	55	110	1	2
	1.95 - 2.09	60	120	0	3
	2.10 - 2.28	65	130	3	1
	≥ 2.29	70	140	2	2
Level 2 Dose Reduction: From 30 mg/m^2 to 25 mg/m^2					
25 mg/m^2	< 1.10	25[a]	50[a]	2 (PM)[a]	1 (AM)[a]
	1.10 - 1.29	30	60	2	0
	1.30 - 1.49	35	70	1	1
	1.50 - 1.69	40	80	0	2
	1.70 - 1.89	45	90	3	0
	1.90 - 2.09	50	100	2	1
	2.10 - 2.29	55	110	1	2
	≥ 2.30	60	120	0	3
Level 3 Dose Reduction: From 25 mg/m^2 to 20 mg/m^2					
20 mg/m^2	< 1.14	20	40	0	1
	1.14 – 1.34	25[a]	50[a]	2 (PM)[a]	1 (AM)[a]
	1.35 – 1.59	30	60	2	0
	1.60 – 1.94	35	70	1	1
	1.95 – 2.09	40	80	0	2
	2.10 – 2.34	45	90	3	0
	≥ 2.35	50	100	2	1

Abbreviations: AM = morning; BSA=body surface area (calculate to 2 decimal places); PM = evening.
[a] At a total daily dose of 50 mg, patients should take 1 x 20-mg tablet in the morning and 2 x 15-mg tablets in the evening.

If dose modification fails to result in achieving minimal criteria to resume treatment, the investigator should discontinue study drug.

Should the toxicities that require dose reduction recur after dose reduction to 20 mg/m^2, study drug should be discontinued.

8.2.4.2. Dose Modifications in Response to Non-hematologic Toxicities

Rules for study drug dosing modifications for treatment-related non-hematologic AEs are provided in Table 4. At the discretion of the investigator, patients may continue on study drug at the same dose without reduction or interruption for drug-related AEs (irrespective of grade) considered unlikely to become serious or life threatening (including, but not limited to, fatigue, alopecia, changes in libido, and dry skin).

Table 4: TAS-102 Dose Modification Criteria for Non-hematologic Toxicities

Grade[a]	Dose Hold/Resumption within a 28-day Treatment Cycle	Dose Adjustment for Next Cycle
Grade 1 or 2		
Any occurrence	Maintain treatment at the same dose level	None
Grade 3[a] or Higher		
First, second, or third occurrence	Suspend treatment until Grade 0 or 1	Reduce by 1 dose level from the previous level
Fourth occurrence	Discontinue treatment	Discontinue treatment

[a] Except for grade 3 nausea and/or vomiting controlled by aggressive antiemetic therapy or diarrhea responsive to antidiarrheal medication.

If there is any uncertainty about continuing therapy or resuming therapy in a patient with ≥ grade 3 non-hematologic drug-related AEs, the case must be discussed with the Sponsor's medical monitor before continuing therapy.

8.2.4.3. Dose Modifications in Response to Hematologic Toxicities

Criteria for dose hold and resumption in response to hematologic toxicities related to myelosuppression are described in Table 5 and Table 6, respectively.

NOTE: For all patients with decreases in neutrophils and/or platelets, the next cycle of study treatment should not be started until the resumption criteria in Table 6 are met; these resumption criteria apply to the start of the next cycle for all patients regardless of whether or not the hold criteria were met.

Table 5: TAS-102 Dose Hold Criteria for Hematologic Toxicities Related to Myelosuppression

Parameter	Hold Criteria	
	Conventional Units	SI Units
Neutrophils	$< 500/mm^3$	$< 0.5 \times 10^9/L$
Platelets	$< 50{,}000/mm^3$	$< 50 \times 10^9/L$

Abbreviation: SI = Standard International.

Table 6: TAS-102 Resumption Criteria for Hematologic Toxicities related to Myelosuppression

Parameter	Resumption Criteria[a]	
	Conventional Units	SI Units
Neutrophils	$\geq 1500/mm^3$	$\geq 1.5 \times 10^9/L$
Platelets	$\geq 75{,}000/mm^3$	$\geq 75 \times 10^9/L$

Abbreviation: SI = Standard International.

[a] These resumption criteria apply to the start of the next cycle for all patients regardless of whether or not the hold criteria were met.

Criteria for dose reduction in response to hematologic toxicities are as follows:

- Uncomplicated neutropenia or thrombocytopenia ≤ grade 3, do not require a reduction in dose of study drug.
- Patients who experience uncomplicated grade 4 neutropenia or thrombocytopenia that results in a ≤ 1 week delay of the start of the next cycle should start the next cycle at the same dose level.
- Patients who experience uncomplicated grade 4 neutropenia or thrombocytopenia that results in a > 1 week delay of the start of the next cycle should start the next cycle at one reduced dose level as described in Table 3.

Patients who experience complicated ≥ grade 3 neutropenia or thrombocytopenia should be considered for administration of hematopoietic growth factors, or for a dose reduction in the next cycle or both, dependent on the severity of the complication.

In the event of febrile neutropenia:

- Interrupt dosing until toxicity resolves to grade 1 or baseline
- When resuming dosing, decrease the dose level by 5 mg/m^2/dose from the previous dose level (as per Table 3).

8.2.4.4. TAS-102 Dose Resumption

If the patient recovers from toxicities requiring dose delay during the 2-week treatment period of a cycle (treatment Days 1 through 5 and Days 8 through 12), and no dose reduction is required, study drug may be resumed during that cycle. If a dose reduction is required, study drug should

be resumed at the start of the next cycle at the appropriate dose level as shown in Table 3. Do not increase the study drug dose after it has been reduced.

If the patient recovers from toxicities requiring dose delay during the recovery period (Days 13 through 28), start the next cycle on schedule at the appropriate dose level based on Section 8.2.4.2 and Section 8.2.4.3 above. If the toxicities that are defined above do not recover during the treatment or rest period, the start of the next cycle can be delayed for a maximum of 28 days from the scheduled start date of the next cycle. If resumption criteria are met by this maximum 28-day delay, start the next cycle at the appropriate dose level.

Patients who require more than a 28-day delay in the scheduled start date of the next cycle will have study drug discontinued. Discontinuation of both TAS-102 and nivolumab will lead to discontinuation from the study. Future treatment will then be at the discretion of the investigator.

8.2.5. Nivolumab Treatment Regimen

The dose of nivolumab is calculated according to the patient's weight. All doses of nivolumab will be administered to the patient by study site personnel on Days 1 and 15 of each cycle. The nivolumab should be administered on the same cycle as the TAS-102. Hence, if there is a delay in the TAS-102 dosing, the same delay should be applied to the nivolumab dosing.

One nivolumab treatment cycle consists of the following:

- Day 1: nivolumab (3 mg/kg/dose) intravenous over 60 minutes
- Days 2 through 14: rest
- Day 15: nivolumab (3 mg/kg/dose) intravenous over 60 minutes
- Days 16 through 28: rest

8.2.5.1. Nivolumab Preparation and Administration

Prepare nivolumab for administration according to the instructions in the package insert.

8.2.6. Nivolumab Dose Modifications

Recommendations for nivolumab dose modifications are listed in Table 7 . For patients who experience mild or moderate infusion reactions, the infusion should either be interrupted or the rate should be slowed. If a patient has a severe or life-threatening infusion reaction, the nivolumab should be discontinued. Discontinuation of both TAS-102 and nivolumab will lead to discontinuation from the study. Future treatment will then be at the discretion of the investigator.

Table 7: Recommended Dose Modifications for Nivolumab

Adverse Reaction	Severity[a]	Dose Modification
Colitis	Grade 2 or grade 3 diarrhea or colitis	Withhold dose[b]
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[b]
	Grade 3 or grade 4 pneumonitis	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 3 and up to 5 × the upper limit of normal (ULN) or total bilirubin more than 1.5 and up to 3 × the ULN	Withhold dose[b]
	AST or ALT more than 5 × the ULN or total bilirubin more than 3 × the ULN	Permanently discontinue
Hypophysitis	Grade 2 or grade 3 hypophysitis	Withhold dose[b]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[b]
	Grade 3 or grade 4 renal insufficiency	Permanently discontinue
Type 1 Diabetes	Grade 3 hyperglycemia	Withhold dose[b]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 × the ULN	Withhold dose[b]
	Serum creatinine more than 6 × the ULN	Permanently discontinue
Rash	Grade 3 rash	Withhold dose[b]
	Grade 4 rash	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[b]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other grade 3 adverse reaction, first occurrence	Withhold dose[b]
	Recurrence of same grade 3 adverse reaction	Permanently discontinue

Adverse Reaction	Severity[a]	Dose Modification
	Life threatening or grade 4 adverse reaction	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent grade 2 or grade 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

[a] Toxicity was graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.
[b] Resume treatment when the adverse reaction returns to grade 0 or 1.

8.3. Treatment Compliance

Compliance to all study drug administration should be documented in the patient's source documents.

8.4. Study Drug Accountability

In accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and local regulatory requirements, the investigator and/or the person responsible for dispensing investigational drug must be able at all times to account for all investigational product provided to the site.

Dose reductions, interruptions, and reason for these actions must be recorded in the patient's source documents.

All used and unused study drug shipped to the investigator must be returned to the Sponsor or its representative. If on-site destruction is required by site policy, such requirements must be documented in the institution's Standard Operating Procedure and provided to the Sponsor or its representative for review.

No study drugs are to be used outside of this study.

9. STUDY ASSESSMENTS

The study assessments are described by procedure in the following sections. All information required by the protocol must be recorded.

The study schedule must be followed; however, in unavoidable circumstances, (eg, holidays, weekends) a window of ± 3 days is allowable for study procedures, as long as the proper order of procedures and assessments is maintained. A window of ± 7 days is allowable for CT scans, and follow-up visits. These windows are not applicable during the Baseline Period (up to 28 days before enrollment). If any baseline assessments are repeated on Day 1 of Cycle 1, the site must ensure the patient meets the eligibility criteria listed in Section 7.3.1 and Section 7.3.2.

After confirmation of eligibility, patients should receive the first dose of study treatment (Day 1 of Cycle 1) within 3 calendar days after enrollment. The maximum screening period is 28 days; eligible patients must be enrolled by Day 28 of screening.

Enrolled patients will be assigned a unique 6-digit patient number.

9.1. All Study Procedures

9.1.1. Informed Consent

A signed and dated ICF will be obtained from the patient as required by the protocol before any baseline procedures are conducted. A signed copy of the ICF will be given to the patient.

9.1.2. Medical History

A complete medical history will be obtained during baseline within 28 days before the first study drug administration on Day 1 Cycle 1.

The patient's medical history should be recorded on the Medical History section of the eCRF.

Existing signs and symptoms will be obtained within 7 days before study drug administration on Day 1 Cycle 1.

9.1.3. Histologic Confirmation

Confirmation of MSS refractory mCRC via a pathology report should be obtained at baseline within 28 days before administration of the first dose of study drug on Day 1 Cycle 1 (pathology may be from primary tumor or metastasis). The pathology report should be available in the patient's source documents.

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9.1.6. Physical Examination

A complete physical examination will be performed at the time points listed below:

- Within 7 days before study drug administration on Day 1 of Cycle 1
- Beginning with Cycle 2, obtain within 24 hours before the start of study treatment on Day 1 of every cycle
- End of Treatment visit (if applicable)
- 30-day Safety Follow-up visit

9.1.7. Baseline Signs and Symptoms

Signs and symptoms present after signature of the ICF and within 7 days before study treatment on Day 1 of Cycle 1 should be recorded in the patient's source documents.

- Height, Vital Sign Measurements, and Weight
- The patient's height will be obtained only during baseline before study drug administration within 7 days before Day 1 of Cycle 1. The patient's vital sign measurements (blood pressure, heart rate, body temperature, and respiration rate) will be collected at the time points listed below. All the vital sign measurements are to be obtained with the patient in a position that is consistent for all time points for each patient.
- Beginning with Cycle 2, obtain within 24 hours before the start of study drug administration on Day 1 of every cycle
- End of Treatment visit (if applicable)
- 30-day Safety Follow-up visit
- Weight will be collected within 7 days of Day 1 Cycle 1, Cycle 1 Day 15, Day 1 and Day 15 of all subsequent cycles, End of Treatment visit, and at the 30-day Safety Follow-up visit.

9.1.8. Performance Status

An ECOG performance status score [redacted] will be obtained at the following time points:

- Within 28 days before study drug administration on Day 1 of Cycle 1
- Obtain within 24 hours before the start of study drug administration on Day 1 in every cycle and Day 15
- End of Treatment visit (if applicable)
- 30-day Safety Follow-up visit

9.1.9. Clinical Laboratory Evaluations

Samples for hematology, serum chemistry and urinalysis assessments will be collected and measured as described in Section 9.1.9.1, Section 9.1.9.2, and Section 9.1.9.3. Laboratory assessments obtained before the signing of the ICF may be used as screening laboratory values if

they were obtained within 7 days before administration of study drug administration on Day 1 of Cycle 1.

All laboratory results must be reviewed for clinically significant events. Any clinically significant event must be followed and reported as required by the protocol (see Section 11.1, Adverse Events/Serious Adverse Events and Section 11.2, Laboratory Evaluations). In addition, follow the criteria for repeat testing listed in Section 11.2.2 as needed.

9.1.9.1. Hematology

Blood samples for hematology assessments will be obtained at the following time points and when clinically indicated:

- Within 7 days before Day 1 of Cycle 1 (Laboratory results obtained before signing the ICF may be used if the results were obtained within 7 days before Day 1 of Cycle 1.)
- Day 15 of each cycle
- Beginning with Cycle 2, obtain blood samples within 24 hours before the start of study drug administration on Day 1 of every cycle
- End of Treatment visit (if applicable)
- 30-day Safety Follow-up visit

In addition, the criteria for repeat testing listed in Section 11.2.2, will be followed as needed. Hematology parameters that will be measured are listed in Table 8.

Table 8: Hematology Laboratory Parameters

Hemoglobin	White blood cell (WBC) count with differential (automated):
Hematocrit	Neutrophils
Platelets	Lymphocytes
Red blood cell count	Monocytes
	Eosinophils
	Basophils

9.1.9.2. Serum Chemistry

Blood will be collected at the following time points for serum chemistry assessments:

- Within 7 days prior to Day 1 of Cycle 1 (Laboratory results obtained before signing the ICF may be used if the results were obtained within 7 days before Day 1 of Cycle 1.)
- Day 15 of each cycle
- For all subsequent cycles, obtain within 24 hours before the start of study drug administration on Day 1 of every cycle
- End of Treatment Visit (if applicable)
- 30-day Safety Follow-up Visit.

In addition, follow the criteria for repeat testing listed in Section 11.2.2 as needed.

Table 9 lists the serum chemistry parameters that will be measured.

Table 9: Serum Chemistry Laboratory Parameters

ALT	Creatinine	Chloride
AST	Blood urea nitrogen	Calcium
Alkaline phosphatase	Sodium	Albumin
Bilirubin[a]	Potassium	Glucose
Thyroid stimulating hormone	Thyroxine 4 (T4)	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.
[a] In case of elevation in total bilirubin, fractionation (direct/indirect) should be performed.

9.1.9.3. Urinalysis

Collect urine samples for qualitative (dipstick) analysis, to include tests for protein, glucose, urobilinogen, red blood cell count, and white blood cell count, at the time points listed below:

- Within 7 days before Day 1 of Cycle 1 (Laboratory results obtained before signing the ICF may be used if the results were obtained within 7 days before Day 1 of Cycle 1.)

- As clinically indicated thereafter

If a new abnormality is identified, quantitative urinalysis should be performed.

In addition, follow the criteria for repeat testing listed in Section 11.2.2 as needed.

9.1.10. Pregnancy Testing

If the patient is female and of childbearing potential, pregnancy testing by assessment of serum or urine beta-human chorionic gonadotrophin will be conducted at the following time points and the date, time, and test results should be recorded in the patient's source documents (Note: More frequent pregnancy assessments should be performed if required by local law):

- Within 7 days prior to Day 1 of Cycle 1
- End of Treatment or 30-day Safety Follow-up Visit

Female patients who are considered not to be of child bearing potential must have a history of being post-menopausal (no menses for 12 consecutive months without an alternative medical cause), or hysterectomy that is clearly documented in the patient's source documents.

9.1.11. Tumor Measurements

Tumor assessments/contrast-enhanced CT scans of the chest and abdomen (and pelvis, if clinically indicated) must be obtained at each time point listed below for all patients:

- Within 28 days before Day 1 of Cycle 1. Scans obtained before the patient signs the ICF may be used if the date of the scan is within 28 days of enrollment.
- Every 2 cycles during study treatment
- For patients who discontinue treatment because of radiologic disease progression by irRC, an additional tumor assessment is not required at the End of Treatment visit.
- For patients who discontinued treatment for reasons other than radiologic disease progression by irRC, every effort should be made to perform an end of treatment tumor assessment before the start of new anticancer therapy and should be followed for tumor response every 2 cycles until the patient develops radiologic disease progression (or death) or initiation of new anticancer therapy (whichever occurs first).

On-site tumor assessments will be performed by the investigator or local radiologist according to RECIST criteria and irRC. Results of these assessments including response for target and non-target lesions and appearance of new lesions will be the basis for the continuation or discontinuation of study drug. Response definitions are provided in Section 10.3.1.

Patients with tumor progression determined by irRC or laboratory parameters before their 6-month evaluation but without rapid clinical deterioration or change in performance status who do not require additional immediate therapy, may continue to be treated with and clinically observed after the assigned imaging schedule to allow detection of a subsequent tumor response. Symptoms of clinical progression must be documented in the patient's source documents and must be reported as AEs. Every effort should be made to document objective progression even after discontinuation of treatment.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline, throughout the study, and during the follow-up period.

All patients' files and radiological assessments must be available for source verification and may be submitted for extramural review for initial assessment of antitumor activity.

Results of any unscheduled evaluations should be recorded in the patient's source documents.

9.1.12. Prior and Concomitant Medications

All therapies and medications, prescription and over-the-counter, will be collected from the time the ICF is signed through the 30-day Safety Follow-Up visit, including any medication used to treat AEs or SAEs during the Safety Follow-up Period. Use of concomitant medication should be documented in the patient's source documents.

The time of initiation of new anticancer therapy received during the 30-day Safety Follow-up Period will be collected.

During the survival follow-up period, only anticancer therapies will be collected.

9.1.13. Adverse Event Assessments

Patients will be monitored for any untoward medical events (AEs or SAEs) from the time of signed informed consent through 30 days after last dose of study drug or until the start of new antitumor therapy, whichever is earlier.

Serious AEs should be reported to Taiho Oncology, Incorporated (TOI) Pharmacovigilance or its designee. If serious medical occurrences or deaths **outside** the 30-day follow-up period are reported to or observed by the investigator that he/she believes are related to the administration of the study drug, it is the investigator's responsibility to report this occurrence to TOI Pharmacovigilance or its designee. See Section 11.1.1 and Section 11.1.2, respectively, for definitions and detailed reporting of AEs and SAEs.

9.2. Assessments by Visit

See Section 9.1 for details about specific assessments.

9.2.1. Baseline Procedures Before Enrollment

9.2.1.1. Day −28 through Day −1

- Signature of ICF
- Review of inclusion and exclusion criteria
- Medical history
- Histological confirmation of mCRC from either the primary or metastatic site of disease
- ECOG performance status
- Tumor measurement (by CT scan)
- Concomitant medication

- Tumor biopsies (from fresh tissue within 21 days of Cycle 1 Day 1)
- AE/SAE assessment

9.2.1.2. Day −7 through Day −1

- Review of inclusion and exclusion criteria
- Physical examination
- Baseline signs and symptoms
- Height
- Vital sign measurements (blood pressure, heart rate, body temperature, respiration rate) and body weight and calculate the patient's BSA
- Blood samples for hematology and serum chemistry

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- Urine sample for urinalysis
- Pregnancy test
- Concomitant medication
- AE/SAE assessment

9.2.2. On Treatment Period

9.2.2.1. Cycle 1 Day 1

Study treatment should be started within 3 calendar days after the patient has been enrolled in the study. The following will be assessed:

- Review of inclusion and exclusion criteria
- ECOG performance status (confirmation of eligibility)
- Administer intravenous nivolumab
- Dispense study drug (TAS-102)
- Concomitant medication
- AE/SAE assessment

9.2.2.2. Cycle 1 Day 15

- Blood samples for hematology and serum chemistry
- Obtain the patient's weight
- ECOG performance status
- Administer intravenous nivolumab
- Concomitant medication

- AE/SAE assessment

CCI [redacted]

9.2.2.3. Subsequent Cycles - Cycle X Day 1

Obtain within 24 hours before Day 1 study drug administration. Before starting subsequent cycles, verify that patients with toxicities have met resumption criteria before administering study drug.

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- Physical examination
- Vital sign measurements (blood pressure, heart rate, body temperature, respiration rate) and body weight
- ECOG performance status
- Blood samples for hematology and serum chemistry

CCI [redacted]

- Administer intravenous nivolumab
- Dispense study drug (TAS-102)
- Concomitant medication
- AE/SAE assessment

9.2.2.4. Subsequent Cycles – Cycle X Day 15

- Blood sample for hematology and chemistry
- Body weight
- ECOG performance status
- Administer intravenous nivolumab
- Concomitant medication
- AE/SAE assessment

9.2.2.5. Every 2 cycles from Start of Treatment

- Tumor measurement/assessment (CT scan)

9.2.3. End of Treatment Visit

If the decision to discontinue study drugs is made within 2 weeks after the patient's last treatment visit, an End of Treatment Visit is **not required** unless deemed clinically necessary by the investigator. If the decision to discontinue study drugs (because of proven radiologic disease progression or other reasons) is made more than 2 weeks after the last treatment visit, an End of Treatment visit is required. If this visit occurs within 2 weeks of the 30-day Safety Follow-up visit, the 2 visits can be combined and the information at the End of Treatment visit will be entered into the 30-day Safety Follow-up visit.

Perform the following assessments:

- Physical examination
- Vital sign measurements (blood pressure, heart rate, body temperature, respiration rate) and body weight
- ECOG performance status
- Tumor measurement/assessment (CT scan)
- Blood samples for chemistry and hematology

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- Pregnancy test
- For patients who discontinue treatment for radiologic disease progression, every effort should be made to perform an end of treatment tumor assessment before the start of new anticancer therapy. Patients that discontinued treatment for reasons other than disease progression should continue to be followed for tumor response every 2 cycles until the patient develops radiologic disease progression (or death) or initiation of new anticancer therapy (whichever occurs first)
- Concomitant medication, including any new anticancer therapy and time of initiation
- AE/SAE assessment

9.2.4. 30-Day Safety Follow-up Visit

A Safety Follow-up visit will be conducted 30 days after the patient's last dose of study drug. If the patient will be starting new anticancer therapy within the 30-day window after the last dose of study drug, the 30-day Safety Follow-up visit should be performed before the start of new anticancer therapy. If the patient is unable to return to the site before the initiation of new treatment, a follow-up phone call can be conducted by the site to collect any new safety information that occurred between the end of study treatment and the initiation of the new treatment.

Perform the following assessments:

- Physical examination

- Vital sign measurements (blood pressure, heart rate, body temperature, respiration rate) and body weight
- ECOG performance status
- Blood samples for chemistry and hematology
- Pregnancy test
- Concomitant medication, including any new anticancer therapy and time of initiation
- AE/SAE assessment

9.2.5. Survival Follow-up after 30-Day Safety Visit

The following assessments should be obtained at scheduled 8-week time intervals during the survival follow-up period (these may be telephonic):

- Tumor measurement (by CT scan, see Section 10) every 2 cycles until radiologic disease progression (for patients who discontinued treatment for reasons other than disease progression) or initiation of new anticancer therapy (whichever occurs first)
- Concomitant medications – collect antitumor therapies only
- Contact patient/caregiver to determine survival status (alive/dead)
- SAE collection only if the SAE is related to study drug

Patients will be followed for survival until the study discontinuation criteria are met. The investigators will be informed when these criteria are reached.

10. EFFICACY ASSESSMENT CRITERIA

The determination of antitumor efficacy will be based on objective tumor assessments made by the investigator/local radiologist according to the irRC[13] and revised RECIST criteria of unidimensional evaluation.[14] Treatment decisions by the investigator will also be based on these criteria.

Considering that the primary endpoint is response-related, a confirmation of response is required after a minimum of 4 weeks.

10.1. Method of Imaging

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of treatment. All measurements should be recorded in metric notation using a ruler or calipers.

Contrast-enhanced CT is the preferred method for tumor assessments. If contrast agent is contraindicated in a patient, obtain a non-contrast chest CT and enhanced magnetic resonance imaging (MRI) of the abdomen (and pelvis if clinically indicated). A spiral CT should be performed using a 5 mm or less contiguous reconstruction algorithm. Images must be acquired of the chest and abdomen (and pelvis if clinically indicated or obtained at baseline) at each time point. Only CT and MRI may be used for tumor measurement.

Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Ultrasound should not be used to measure tumor lesions that are clinically not easily accessible for objective response evaluation (eg, visceral lesions). Ultrasound is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

An additional fluorodeoxyglucose positron emission tomography (FDG-PET) scan may help confirm the diagnosis of suspicious lymph nodes as needed. A “positive” FDG-PET scan lesion is one that is FDG avid “with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.” However, this scan is not mandatory. A FDG-PET scan alone cannot replace a MRI or contrast-enhanced CT.

10.2. Immune-related Response Criteria

10.2.1. Immune-related Response Criteria Definitions

Measureable Disease: Neoplastic masses that can be precisely measured in 2 in-plane perpendicular diameters. Both its longest diameter and it longest perpendicular must be ≥ 10 mm. Lymph nodes must be measureable in 2 perpendicular diameters. Both its longest diameter and its longest perpendicular must be ≥ 15 mm. Malignant lymph nodes must be

measurable in 2 perpendicular diameters. Both its longest diameter and its longest perpendicular must be ≥ 15 mm. The quantitative endpoint will be defined as the product of the longest diameter with its longest perpendicular.

Non-measurable disease: Non-measurable diseases are those that are not suitable for quantitative assessment over time. These include:

- Neoplastic masses that are too small to measure, because their longest uninterrupted diameter or longest perpendicular are < 10 mm.
- Neoplastic masses whose boundaries cannot be distinguished. This includes masses that cannot be demarcated from surrounding tissue because of inadequate contrast, masses with overly complex morphology, or those with highly heterogeneous tissue composition.
- Other types of lesions that are confidently felt to represent neoplastic tissue, but difficult to quantify in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitis cutis/pulmonis cystic lesions, ill-defined abdominal masses, etc.

For irRC, only index lesions selected at baseline and measurable new lesions are taken into account.

10.2.2. Immune-related Response Criteria

At the baseline tumor assessment, the sum of the products of the 2 largest perpendicular diameters (SPD) of all index lesions (5 lesions per organ, up to 10 visceral lesions and 5 cutaneous index lesions) is calculated.

At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥ 5 × 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total time-point tumor burden:

$$\text{Tumor burden} = SPD_{\text{index lesions}} + SPD_{\text{new, measureable lesions}}$$

Overall responses using irRC are defined as follows and presented in Table 10:

- Complete Response (immune-related CR [irCR]): Complete disappearance of all tumor lesions (whether measurable or not, and no new lesions). Complete response must be confirmed by repeated, consecutive assessments made no less than 4 weeks from the date first documented.
- Partial Response (immune-related PR [irPR]): Decrease in SPD of 50% or greater by a consecutive assessment at least 4 weeks after first documentation.
- Stable Disease (immune-related SD [irSD]): Failure to meet criteria for irCR or irPR, in absence of progressive disease (irPD).
- Progressive Disease (immune-related PD [irPD]): At least 25% increase in SPD relative to nadir (minimum recorded tumor burden). Confirmation by a repeat, consecutive assess no less than 4 weeks from the date first documented.

Table 10: Derivation of irRC Overall Responses[13]

Measurable Response	Non-measurable Response		Overall Response
Index and New, Measurable Lesions (Tumor Burden) %[a]	**Non-index Lesions**	**New, Non-measurable Lesions**	**Using irRC**
↓ 100	Absent	Absent	irCR[b]
↓ 100	Stable	Any	irPR[b]
↓ 100	Unequivocal progression	Any	irPR[b]
↓ ≥ 50	Absent/stable	Any	irPR[b]
↓ ≥ 50	Unequivocal progression	Any	irPR[b]
↓ < 50 to < 25 ↑	Absent/stable	Any	irSD[b]
↓ < 50 to < 25 ↑	Unequivocal progression	Any	irSD[b]
≥ 25 ↑	Any	Any	irPD[b]

Abbreviations: irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irRC = immune-related response criteria; irSD = immune-related stable disease.
Note: Complete response and partial response must be confirmed by repeated, consecutive assessments made no less than 4 weeks from the date first documented.
[a] Assuming response (irCR and irPR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart.
[b] Decreases assessed relative to baseline, including measurable lesions only (> 5 × 5 mm).

If a patient is classified as having irPD at a postbaseline tumor assessment, then confirmation of irPD by a second scan in the absence of rapid clinical deterioration is required. The definition of confirmation of progression represents an increase in tumor burden ≥ 25% compared with the nadir at 2 consecutive time points at least 4 weeks apart. It is recommended that this be done at the discretion of the investigator because follow-up with observation alone may not be appropriate for patients with a rapid decline in performance irRC (Table 10), as most of these late responding patients have a trend toward response within 4 weeks after initial irPD. A patient may continue receiving study drug treatment if the patient is classified as having irPD at a postbaseline tumor assessment and shows no signs of clinical progression.

10.3. Response Evaluation Criteria in Solid Tumors

10.3.1. RECIST Tumor Definitions

Measurable Lesions:

- Measurable visceral lesions: Lesions that can be accurately measured in at least 1 dimension with the longest diameter (to be recorded) ≥ 10 mm by CT scan if using slice thickness of 5 mm or less, or at least double the slice thickness of the CT or MRI scan if the slice thickness is > 5 mm.

- Measurable pathological lymph nodes: A malignant lymph node must be considered pathologically enlarged with high suspicion of metastasis and measure ≥ 15 mm in the short axis when assessed by CT scan. The short axis is defined as the longest linear dimension perpendicular to the node's longest diameter as assessed within the same plane that the scan was acquired.

Only measurable lesions can be selected as target lesions.

Non-measurable Lesions: Non-measurable lesions include:

- Small visceral metastatic lesions that have a longest dimension less than 10 mm or if slice thickness is greater than 5 mm less than twice the slice thickness.
- Abnormal and suspected metastatic lymph nodes that are ≥ 10 mm to < 15 mm in the short axis.
- Truly non-measurable lesions (eg, ascites and peritoneal carcinomatosis).

All non-measurable lesions can only be selected as non-target lesions.

Target Lesions:

- All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs/tissues should be identified as target lesions.
- Target lesions should be selected on the basis of their size (visceral lesion with the longest diameter and lymph node with the measurement of short axis), be representative of all involved organs/tissues, but in addition should be those that lend themselves to reproducible repeated measurements.
- When recording tumor measurements, the longest diameter will be measured for each non-nodal target lesion. For measurable pathological lymph nodes that may be identified as target lesions, the short axis measurement will be combined with the measurements of non-nodal (ie, visceral lesion) target lesions. Therefore, in cases of CR when abnormal nodes have been used as target lesions, the sum of diameters will not reduce to a null value. Target lesions will be followed and measured at each subsequent time point.

The sum of the diameters for all target lesions will be calculated and recorded. The baseline sum will be used as a reference to further characterize any objective tumor assessment in the measurable dimension of the disease.

- Assign a measurement to all target lesions regardless of size. An option of "too small to measure" will be provided if a measurement cannot be assigned. A value of zero should only be assigned in the case of a CR.
- An option of "Not Assessable" for a lesion will only apply to lesions that cannot be read due to technical reasons, for example:
    1. CT artifact.
    2. Patient positioning where the lesions are obstructed or cannot be seen.
    3. Lesions that may not be seen in their entirety because of CT slice thickness.

- In cases where a lesion divides into 2 lesions, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.
- In cases where 2 lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Non-target Lesions:

- Non-target lesions include all non-measurable lesions and measurable lesions that have not been selected as target lesions
- Lymph nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded.
- Any equivocal lesion without clear diagnosis (eg, uncharacteristic solitary lung nodule without biopsy, uncharacteristic thyroid mass lesion without fine needle aspiration) may be considered a non-target lesion if it cannot be differentiated from a benign lesion.
- All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at Baseline. Measurements are not required, but their presence, absence, or unequivocal progression should be followed throughout the study.

It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (eg, multiple enlarged pelvic lymph nodes or multiple liver metastasis).

10.3.2. RECIST Response Criteria

On-site assessments will include the assessment of:

- Target and non-target tumor responses.
- Overall response.

The above assessments will be made as per the time points identified in Section 9.1.11.

10.3.2.1. RECIST Target and Non-target Response Assessments

10.3.2.1.1. RECIST Criteria for Assessment of Tumor Response

Assessments will be made based on the following definitions[14]:

TARGET LESIONS	
Lesions Response:	**Definition:**
Complete Response (CR)	The disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of the target lesions, taking as a reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of the target lesions, taking as a reference the smallest sum on study, including the baseline sum. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Definitive new lesion presence also indicates progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum diameters while on study.

NON-TARGET LESIONS	
Lesions Response:	**Definition:**
Complete Response (CR)	The disappearance of all non-target lesions. All lymph nodes must be non-pathological morphologically (ie, < 10 mm in short axis in size).
Non-CR/Non-PD	A persistence of ≥ 1 non-target lesion(s)/ not reaching the extent of "unequivocal progression".
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions (see definition below).

Progression in Non-target Disease:

There must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease; ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase in diameter in a measurable lesion).

10.3.2.1.2. Additional Criteria to Consider When Assessing Tumor Response

When effusions are known to be a potential adverse effect of treatment, cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or SD is not mandatory, but might be performed to differentiate between response (or SD) and PD when substantial change of effusion and or ascites is noted.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at

the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

10.3.2.2. RECIST Overall Response Assessment

Assessments will be made based on definitions[14] provided in Table 11.

Table 11: Time Point Response for Patients with Target (± Non-target) Disease

Target Lesions	Non-target Lesions	New Lesion	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD or Not all evaluated	No	PR
PR	Non-PD or Not all evaluated	No	PR
SD	Non-PD or Not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
PD	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

10.3.3. RECIST Best Overall Response Assessment

The best overall response as per RECIST criteria is the best response recorded from the start of the study treatment until the end of treatment.

11. REPORTING SAFETY INFORMATION

11.1. Adverse Events and Serious Adverse Events

11.1.1. Adverse Events

An **AE** is any untoward medical condition that occurs in a patient while participating in a clinical study and does not necessarily have a causal relationship with the use of the study drugs.

Treatment-emergent AEs are AEs that occur from the initiation of any study treatment administration, and do not necessarily have a causal relationship to the use of the study treatments.

Provide a complete and specific clinical diagnosis as an AE verbatim term. If a diagnosis is not available, then report signs and symptoms. The CTCAE terms are to be used to assess severity/provide the grade for each AE that is reported.

Refer to Section 11.1.5, Section 11.1.6, and Section 11.1.7 for definitions and reporting of pregnancy, medication errors, and overdose, respectively.

Any untoward medical event that occurs outside the period of patient follow-up (30 days after the last dose of study treatment or until the start of new antitumor therapy, whichever is earlier) is not considered an AE unless determined by the investigator to have a causal relationship with the study treatment.

If any SAEs are observed after the patient follow-up period has ended, only those SAEs determined to have a causal relationship with the study drugs will be recorded in the case report form.

Symptoms or laboratory or instrumental (eg, electrocardiographic) abnormalities of a pre-existing disease, such as cancer or other disease, should not be considered an AE. However, occurrences of new symptoms as well as worsening of pre-existing medical conditions are considered AEs. In addition, a new laboratory or instrumental abnormality that has a clinical impact on a patient (eg, resulting in study drugs dose reduction, treatment delay, treatment discontinuation, requires treatment due to abnormal values, or is considered medically important by the investigator) is considered an AE, unless it is considered part of clinical manifestations to a clinical diagnosis that is already reported as an AE.

Adverse events will be reported from the time of informed consent through the period of patient follow-up (30 days after the last dose of study drugs or until the start of new antitumor therapy, whichever is earlier). Document all AEs in the source documents. Documentation should include onset and resolution, severity/grade, relationship to study drugs, and outcome of the event.

Causal relationship:

When assessing AE causal relationship to study drugs, relationship to TAS-102 and nivolumab will be assessed independently.

1. Reasonably possible: The AE is related if it follows a reasonable temporal sequence from administration of study drugs and, one of the following conditions is true:
    - A positive de-challenge. This means that the event resolves when the drug is stopped.
    - A positive re-challenge. This means that the event reappears when the drug is restarted.
    - Or, the event cannot be reasonably explained by the patient's clinical state and/or other administered therapies.
2. Not reasonably possible: The AE is not related when there is no reasonable possibility that the study drugs caused the event. For the purposes of safety reporting, "no reasonable possibility" means there is no evidence to suggest a causal relationship between the drug and the AE.

    Reasonable possibility is provided by the following examples of types of evidence that would suggest a causal relationship between drug and AE:

    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson syndrome)

- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to drug (eg, tendon rupture)

Outcome:

- Resolved without sequelae
- Resolved with sequelae
- Resolving (can only be used for SAEs and cannot be a final outcome)
- Unresolved
- Death

Any unresolved AEs should be followed until the earliest occurrence of one of the following:

- AE has resolved.
- AE has stabilized. An AE cannot be considered stabilized while the patient is on study drug. Ongoing AEs must be assessed for stabilization 30 days post study drug discontinuation.
- The start of new antitumor therapy.

11.1.2. Serious Adverse Events

An **SAE** (experience) is any untoward medical occurrence that at any time:

a. Results in death (see Section 11.1.3).
b. Is life threatening.

   NOTE: The term "life threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization. The following are not considered hospitalizations for the purposes of assessing seriousness:

   – Emergency room visits less than 24 hours.

   – Hospitalizations for preplanned procedures.

   – Hospitalization for study-related treatment and procedures.

d. Results in persistent or significant incapacity or disability, where disability is defined as a substantial disruption of a person's ability to conduct normal life functions, either reported or defined as per clinical judgment.
e. Is a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child).
f. Is any other important medical event, eg, may not result in death, be life-threatening, or require hospitalization, but based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the points above. Examples of such events are: intensive

treatment in an emergency room or at home for allergic bronchospasm; and blood dyscrasias or convulsions that do not result in hospitalization.

Serious adverse events must be reported to Taiho Pharmacovigilance or designee **within 24 hours** from the time the investigator first becomes aware of the SAE. Comprehensive information available at the time of initial reporting (including narrative description, medical history and concomitant medications) needs to be provided with careful consideration regarding causality and serious criteria. The SAE reporting process and contact information for reporting the SAE are provided in the eCRF/SAE Completion Guidelines.

After the initial SAE notification to Taiho Pharmacovigilance or designee, follow-up SAE information will be submitted each time that important follow-up information (eg, diagnosis, outcome, causality assessment, results of specific investigations) becomes available.

All SAEs **within** the follow-up window (eg, within 30 days after the last dose of study drug or until the start of new antitumor therapy, whichever is earlier) established in the protocol will be reported to Taiho Pharmacovigilance or designee.

If serious medical occurrences including deaths **outside** the follow-up window established by the protocol are reported to or observed by the investigator that he/she believes are related to the administration of the investigational product, it is the investigator's responsibility to report this occurrence to Taiho Pharmacovigilance or designee.

A **serious adverse reaction** (SAR) is any event that meets the definition of an SAE and is considered related to the administration of study drugs. An unexpected SAR is defined as any SAR, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unauthorized investigational product or summary of product characteristics for an authorized product).

11.1.3. Reporting of Deaths

All deaths occurring through the 30-day follow-up period must be reported in the eCRF **within 24 hours**.

1. Death due to disease progression:

   Disease progression (radiologic or clinical) with the outcome of death will not be reported as an SAE. However, relevant signs, symptoms and complications of disease progression (radiologic or clinical) must be reported as an AE or SAE if it meets the serious criteria. It should be indicated that the signs, symptoms and complications are related to disease progression.

2. Death due to other causes:

   Deaths due to reasons other than disease progression must be reported as an SAE.

   Death is not an acceptable AE/SAE term. Death is an outcome of an SAE.

When reporting a death in the eCRF, the investigator will be required to identify which of the following best describes the category of death:

- Toxicity for study drugs
- Radiologic disease progression

- Clinical disease progression
- Other causes

11.1.4. Disease Progression

1. How to report events related to non-fatal disease progression:
   a. Disease progression is not an acceptable AE term. In cases of non-fatal disease progression, the relevant signs, symptoms and complications should be reported as an AE unless they meet the serious criteria. If any of the signs, symptoms and complications meets any of the serious criteria, they should be reported as an SAE. In both cases it should be indicated whether the signs, symptoms and complications are related to disease progression.
   b. Radiologic disease progression without relevant signs, symptoms and complications will not be reported as an AE or SAE.
2. How to report events related to fatal disease progression:
   a. See Section 11.1.3, Reporting of Deaths.

11.1.5. Pregnancy

If a patient becomes pregnant while in the study, the study treatment must be immediately discontinued. Pregnancy information for a female patient should be reported **within 24 hours** from the time the investigator first becomes aware of a pregnancy or its outcome. This should be performed by completing a Pregnancy Form and faxing it to Taiho Pharmacovigilance or designee.

New and/or corrected information regarding the pregnancy obtained after submitting the initial Pregnancy Form must be submitted by faxing an updated Pregnancy Form to Taiho Pharmacovigilance or designee.

If outcome of the pregnancy is a stillbirth, congenital anomaly/birth defect, or a serious event in the mother, report as an SAE to Taiho Pharmacovigilance or designee.

11.1.6. Medication Errors

A **medication error** is defined as any accidental incorrect administration of a medicinal product. The error may be related to the administration of a wrong medication, nature of the medication, route of administration, dosage or frequency of the treatment as specified in this protocol (including omission of one or more administrations).

- Medication errors with study drugs and concomitant medication treatment will not be recorded in the eCRF unless they result in an AE.
- Medication errors with study drugs that result in an overdose will be captured as an AE in the eCRF.
- Medication errors with study drugs that do not result in an AE should be handled as follows:
  - If it results in the omission of an administration, an incorrect dose (relative to that specified in this protocol), or the administration of more than the

prescribed dose (but does not meet the overdose criteria), it will be identified through the recording of study drug accountability data in the eCRF and does not need to be reported as an AE.

- If it results in an overdose, incorrect route of administration, or administration of an incorrect study drug, it will be reported as an AE.

Based on the above criteria, medication errors that are captured as an AE on the eCRF should be reported to Taiho Pharmacovigilance or designee **within 24 hours** from the time the investigator first becomes aware of its occurrence following the same process as described for the SAEs even if it does not meet any of the criteria of an SAE.

11.1.7. Overdose

An overdose with TAS-102 for this clinical trial is defined as:

- Taking a dose beyond the recommended dose in 1 day or beyond the recommended total dose in each cycle.

An accidental or intentional overdose with TAS-102 regardless of whether it is associated with an AE (even if not fulfilling a seriousness criterion) is to be captured as an AE on the eCRF and reported to Taiho Pharmacovigilance or designee **within 24 hours** from the time the investigator first becomes aware of its occurrence following the same process as described for the SAEs.

There is no known antidote available in case of TAS-102 overdose. Overdose should be managed aggressively with close monitoring and administration of prophylactic and symptomatic therapies to prevent or correct potential side effects.

Overdose with nivolumab is defined as administering quantities above the recommended/schedule dosage per the nivolumab label, large enough to overwhelm the homeostasis, disrupting wellbeing, or causing severe illness and/or death. Any overdose with nivolumab associated with AEs should be reported to Taiho Pharmacovigilance or designee **within 24 hours** from the time the investigator becomes aware of the overdose. Included in this category are intentional overdose and accidental overdose by medication error.

An accidental or intentional overdose for concomitant medication should only be reported if it is associated with an AE.

11.2. Laboratory Evaluations

11.2.1. Reporting and Evaluation of Laboratory Test Results

Laboratory tests are to be performed as required per protocol. All laboratory values that are out of the normal range are to be evaluated for their clinical significance before exposing the patient to the next dose of study drug.

The laboratory must provide normal reference ranges.

Any laboratory abnormality that has a clinical impact on the patient, eg, results in delay of study drug dosing, study discontinuation, requires treatment because of abnormal values, or is considered by the investigator to be medically important, must be reported as an AE, unless it is considered a supporting laboratory result to a clinical diagnosis that is already reported as an AE.

If there is a question or concern, please call the Sponsor's medical monitor. All laboratory data will be analyzed using NCI CTCAE grade criteria.

11.2.2. Repeat Testing

Repeat the evaluation of any clinically significant laboratory test, as clinically indicated, until the value returns to the baseline level or clinically stabilizes, or until another treatment is given.

11.3. Physical Examination and Performance Status

Perform physical examinations and performance status evaluations as described in the study procedures section of the protocol. If changes are observed, determine whether they meet the definition of an AE. All observations and evaluations should be documented.

11.4. Vital Sign Measurements and Body Weight

Verify and document vital sign measurements and body weight. If a clinically significant change is observed, repeat the measurement as clinically indicated and evaluate for its clinical relevance and whether it meets the definition of an AE.

12. STATISTICS

A Statistical Analysis Plan (SAP) that includes a more technical and detailed description (including templates for tables, listings, and figures) of the planned statistical summaries analyses will be prepared.

12.1. Study Populations

The study populations for all analyses are defined as:

- Safety Population: Includes all patients who received at least 1 dose of study drug. It will be the primary population for safety analyses.
- DLT Evaluable Population: Included all patients in the safety population in Stage 1, prior to confirming the recommended dose, who completed at least 1 cycle (28 days) of study treatment with at least 80% of the study treatment administered, unless the treatment was interrupted because of a DLT.
- Efficacy Population: Includes all patients in the safety population who completed at least 6 months of tumor follow-up (evaluable irRC and/or RECIST assessments), unless the patient progressed or died before the 6-month follow-up.

12.2. Study Endpoints

12.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is irORR which is defined as the incidence of complete (irCR) and partial (irPR) responses in the efficacy population.

12.2.2. Secondary Endpoints

Secondary efficacy endpoints include:

- DLTs of the combination therapy
- Incidence of AEs and laboratory test abnormalities
- RECIST ORR defined as the incidence of complete (RECIST CR) and partial (RECIST PR) responses in the efficacy population
- PFS defined as the time from the first dose of study drug to disease progression based on irRC and RECIST in the efficacy population
- DCR defined as the incidence of no-PD patients, based on the irRC and RECIST in the efficacy population
- OS defined as the time from the first dose to death in the safety population. Patients alive at the time of study discontinuation will be censored. Additional censoring rules will be defined in the SAP.

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12.3. Analytical Methods

12.3.1. Patient Disposition, Baseline and Treatment Characteristics

12.3.1.1. Patient Disposition

The number of patients in each study population and the reasons for exclusion will be summarized. In addition, patients that discontinue study treatment or study follow-up will also be summarized, along with reasons for study discontinuation.

12.3.1.2. Patient Baseline Characteristics

Patient demographic and disease characteristics at Baseline will be summarized in frequency tables or with summary statistics for continuous variables.

12.3.1.3. Study Treatment

Study drug administration profiles will be summarized descriptively for TAS-102 and nivolumab with respect to number of cycles taken, the cumulative dose, the dose intensity, the relative dose intensity, and dose modifications.

12.3.1.4. Non-Study Treatment in the Study Follow-up Period

The number, type, and extent of use of non-study cancer treatments after study treatment discontinuation will be summarized. Any use of non-study cancer treatments during the study treatment period will also be presented.

12.3.2. Efficacy Analysis

Descriptive statistics such as incidence of responses (ORR and DCR) for each set of criteria, and associated 95% confidence intervals (CIs) will be provided.

For the time to event endpoints, PFS (both sets of tumor response criteria), the Kaplan-Meier estimates will be derived and the associated 95% CIs will be provided.

12.3.3. Safety Analyses

The safety evaluations will focus on AEs and laboratory assessments. All patients included in the ITT Population will be evaluated in the safety analysis.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology and the severity of the toxicities will be graded according to the NCI CTCAE criteria, where applicable. Concomitant medications will be coded according to the World Health Organization Drug Dictionary. Hematological and chemistry laboratory parameters will be graded according to the NCI CTCAE criteria, where applicable.

All AEs will be summarized (incidence) and listed by the system organ class, preferred term, toxicity/severity grade, and causal relationship to study drugs. In addition, separate summaries of the DLTs, at each dose level as applicable, SAEs, and grade 3 and 4 AEs will be presented.

Absolute values, changes from baseline, and shifts for hematology and serum chemistry parameters will be summarized by cycle. In addition, worst severity grade, and time to event will also be summarized.

12.4. Justification of Sample Size

Sample size considerations are based on a 2-stage minimax Simon's design, testing a null hypothesis (poor response) of 10% or less immune-related overall response (irOR) versus an alternative hypothesis (promising response) of 30% or greater irOR at an approximate 5% 1-sided significance level and 80% power. In Stage 1 (futility assessment), enrollment will include 15 evaluable patients for irOR assessment and accrual will continue to Stage 2, if at least 2 of 15 (13%) patients respond (PR or CR). The probability of early stopping assuming poor response is about 55%. In Stage 2, if the Stage 1 futility boundary is exceeded, an additional 10 patients evaluable for irOR assessment will be enrolled, for a total of at least 25 evaluable patients. Further development will be considered promising if at least 6 of 25 (24%) patients respond.

If the initial dose is not tolerated in the first 6 patients in Stage 1, an additional 6 DLT-evaluable patients will be enrolled at the reduced dose. Assuming a 10-15% non-evaluability for DLT and/or irRC assessment rate, a total of 30 to 35 patients is expected to be enrolled in the study.

12.5. Interim Analyses

An interim analysis for efficacy and futility is planned for the study after Stage 1 enrollment is completed. At the point that the ninth patient is enrolled (or a total of at least 15 patients evaluable for response assessment at the target dose), enrollment will stop, and there will be an assessment of safety and efficacy to determine whether the second stage of an additional 10 patients evaluable for response will be enrolled.

13. ETHICS

13.1. Ethical Considerations

It is mandatory that all considerations regarding the protection of human subjects be carried out in accordance with the protocol, Good Clinical Practice (GCP), ICH Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements.

13.2. Informed Consent and Patient Information

Obtaining informed consent must be done according to the guidelines provided in the Declaration of Helsinki, ICH E6 Guideline for GCP, and local regulations.

The investigator (according to applicable regulatory requirements) or a person designated by the investigator and under the investigator's responsibility should fully inform patients of all pertinent aspects of the clinical trial. All participants should be informed to the fullest extent possible about the study in a language and in terms they are able to understand.

Before participation in the trial, the written ICF is to be signed and personally dated by the patient or by the patient's legal representative and by the person who conducted the ICF discussion. A copy of the signed and dated ICF will be provided to the patient. The ICF used must have had prior approval by the IRB/Independent Ethics Committee (IEC).

13.3. Institutional Review Board/Independent Ethics Committee Approval

The study must be approved by an appropriately constituted IRB/IEC, as required in Chapter 3 of the ICH E6 Guidelines.

The IRB/IEC must provide written approval of the study. The written approval/favorable opinion should include protocol (title, number and version number), list of documents reviewed (eg, protocol, ICF, IB, curriculum vitae), and the date of the review.

The investigator is required to submit a copy of the written and dated IRB/IEC approval/favorable opinion to the Sponsor or its representative prior to initiation of this study.

Investigational product will not be released to the trial site and the investigator will not start the trial until this written IRB/IEC approval/favorable opinion is received by the Sponsor or its representative.

The investigator is responsible for obtaining renewal of approval throughout the duration of the study. Timeframes for renewal will be based on IRB/IEC requirements, but renewal at least annually is required by regulations.

At the end of the trial, the IRB/IEC will be notified of the conclusion of the trial and its outcome.

14. ADMINISTRATIVE CONSIDERATIONS

14.1. Protocol Amendments

No change to the protocol may be made without the agreement of Taiho Oncology, Inc. Any amendment to the original protocol will be made by Taiho Oncology, Inc. and will be submitted to the IRB/IEC and appropriate regulatory authorities for approval or notification.

14.2. Curriculum Vitae

All investigators and any sub-investigator(s) must provide Taiho Oncology, Inc. with current (within 2 years) signed and dated copies of their own curriculum vitae listing the experience, qualifications, and training before the beginning of the study.

14.3. Administrative Structure

The administrative structure of the study (eg, Contract Research Organizations) will be provided to all sites.

14.4. Monitoring Procedures

14.4.1. Investigator's Responsibilities

The investigator agrees to conduct the study in accordance with the Clinical Trial Protocol, ICH guidelines E6 – GCP, Section 4 – Investigator's obligations and the applicable regulatory requirements.

The investigator is required to ensure compliance with the protocol and other procedures provided by the Sponsor. The investigator agrees to provide reliable data and all information required by the protocol, eCRF, SAE forms, and Data Resolution Forms or any other appropriate instrument. This information must be accurate, legible and according to instructions provided.

The investigator must ensure that the Sponsor, Sponsor's representatives and regulatory agencies will have access to such documentation.

The investigator may appoint sub-investigators to assist in the conduct of the trial. All sub-investigators shall be appointed and listed in a timely manner. They will be supervised and work under the responsibility of the investigator.

14.4.2. Sponsor's Responsibilities

The Sponsor is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol with regard to ethics, protocol compliance, and integrity and validity of the data recorded in the eCRFs. Thus, the main duty of the study site monitor (Clinical Research Associate) is to help the investigator and the Sponsor maintain a high level of ethical, scientific, technical, regulatory, and quality in all aspects of the trial.

At regular intervals during the trial, the site will be contacted, through monitoring visits, letters or telephone calls by the Sponsor or its representatives to review study progress, investigator and patient's compliance with requirements, and follow up on any issues to be addressed. During the

monitoring visits, source documents, informed consent, recruitment, SAE documentation and reporting, investigational product accountability, concomitant medications, AEs, eCRFs, and queries will be reviewed with the investigator.

14.4.3. Source Documents

According to ICH guidelines, the monitor will check the eCRF entries against the source documents. Source documents are original documents, data, and records (eg, hospital records, clinical and office charts, laboratory notes, memoranda, subject's evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, at laboratories, and at medical-technical departments involved in the clinical trial).

The informed consent will include a statement by which the patient allows the Sponsor's duly authorized personnel, the IRB/IEC, and regulatory authorities to have direct access to original records supporting eCRF data.

The use of pencil and correction fluids is not accepted for recording clinical research information. Corrections in source documents must be done by crossing out with a single line, then initialing and dating and recording the corrected information.

14.4.4. Case Report Form

Electronic case report forms will be provided by the Sponsor.

Investigators will be provided with detailed eCRF Completion Guidelines that will identify the required data points to be collected, how to document them, and when the data should be documented.

It is the responsibility of the investigator to maintain adequate and accurate eCRFs to record (according to the eCRF Completion Guidelines) all observations and other data pertinent to the clinical trial obtained during scheduled or unscheduled visits. All eCRFs should be fully completed to ensure accurate data interpretation.

The computerized handling of the data by the Sponsor after entry of data via eCRFs may generate additional requests via electronic queries or other means to which the investigator is obliged to respond by confirming or modifying the data questioned. These requests with their responses will be included in the eCRFs held by the investigator and Sponsor.

14.4.5. Sponsor's Audits and Regulatory Inspections

For the purpose of ensuring compliance with the protocol, GCP and applicable regulatory requirements, the investigator will permit auditing by the Sponsor or its representative and inspections by regulatory authorities.

The investigator agrees to allow the auditors and inspectors to have direct access to the study records for review. The people performing these activities will not disclose any personal identity or personal medical information assessed.

The investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data and documents pertaining to the clinical

trial. As soon as the investigator is notified of a planned inspection by the regulatory authorities or IRB/IEC, the investigator will inform the Sponsor. Any results arising from such inspections will be immediately communicated by the investigator to the Sponsor. The investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during audits and or inspections.

14.5. Archiving of Records

The investigator is responsible for the retention of all study documents according to institutional policies, local laws, ICH guidelines E6 – GCP, Sections 4.9.4 and 4.9.5 and, for studies conducted under an Investigational New Drug application, the US Code of Federal Regulations Title 21 part 312.62. For more information on USA requirements and ICH Guidelines, please go to http://www.fda.gov and http://www.ema.europa.eu.

The investigator agrees to inform the Sponsor in writing of the intention to remove or destroy any study-related records. Before contacting the Sponsor, the investigator must ensure that institutional and local requirements (for example, ICH Guidelines) have been satisfied. The Sponsor will evaluate the investigator's request and provide authorization for destruction of such records to the investigator in writing.

In the event that all retention of records requirements have been fulfilled, but the Sponsor requests that the investigator maintain the records for a longer period of time, additional arrangements will be made.

14.6. Final Report

Whether the study is completed or prematurely terminated, a final report of the study will be written by the Sponsor or its designee and submitted to the regulatory agency(ies), as required by the applicable regulations.

The final study report will be retained by the Sponsor or by any other subsequent owner of this drug, for 5 years beyond the lifetime of the product.

14.7. Use and Publication of Study Results

The investigator agrees that the Sponsor maintains the right to use the results of this study in their original form and/or in a global report for submission to governmental and regulatory authorities of any country. Data from this study must not be published without prior authorization from the Sponsor.

The results of the study may be presented during scientific symposia or published in a scientific journal only after review by the Sponsor in accordance with the guidelines set forth in the applicable publication or financial agreement.

14.8. Financial Disclosure

Financial disclosure for clinical investigators will be obtained and record keeping of financial records will be in accordance with local regulatory requirements and US Code of Federal Regulations Title 21 part 54.

14.9. Termination of the Study

If the Sponsor and/or the investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted. The Sponsor also reserves the right to discontinue this study for administrative reasons at any time.

15. CONFIDENTIALITY AND DATA PROTECTION

All information provided to the investigator by the Sponsor or Sponsor's representatives, information produced during the clinical trial including, but not limited to the protocol, eCRF, IB, and the results obtained during the course of the trial is confidential. The members of the research team agree not to discuss such information in any way without prior written permission from the Sponsor.

However, the submission of the protocol and necessary documentation to the IRB/IEC is permitted. The IRB/IEC members have the same obligation of confidentiality.

The patient's personal data and investigator's personal data that may be included in the Sponsor's database shall be treated in compliance with all applicable laws and regulations.

When processing and archiving personal data pertaining to the investigator and or to the patients, the Sponsor or its representatives shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

16. SIGNATURES OF SPONSOR AND INVESTIGATOR

Protocol TO-TAS-102-203: A PHASE 2 STUDY WITH SAFETY LEAD-IN EVALUATING TAS-102 PLUS NIVOLUMAB IN PATIENTS WITH MICROSATELLITE-STABLE REFRACTORY METASTATIC COLORECTAL CANCER

a. Declaration of Sponsor

This study protocol was subject to critical review and has been approved by the sponsor. The information it contains is consistent with:

- The current risk-benefit evaluation of the investigational product
- The moral, ethical, and scientific principles governing clinical research as set out in the protocol, Good Clinical Practice (GCP), International Council for Harmonisation (ICH) Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements

The investigator will be supplied with details of any significant or new findings, including adverse events (AEs), relating to treatment with the investigation product.

Date PPD _Signature:_____ PPD _____

b. Declaration of Investigator

I have read the above protocol, appendices, and referenced documents. I understand the contents and intend to fully comply with all requirements. No changes will be made without formal authorization by Taiho Oncology, Inc./Taiho Pharmaceutical Co., Ltd. in the form of a protocol amendment. I will work according to the moral, ethical, and scientific principles governing clinical research as set out in the protocol, Good Clinical Practice (GCP), International Council for Harmonisation (ICH) Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements.

I confirm that I am not banned from conducting clinical research and I will immediately contact Taiho Oncology, Inc. if I cannot fulfill my obligations to complete this protocol.

Investigator:

Date:_____ Signature:_____

Name (block letters):_____

17. LIST OF REFERENCES

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