STATISTICAL ANALYSIS PLAN
PHASE III

AMENDED VERSION: 2.0
DATE OF PLAN: APRIL 27, 2018

BASED ON: PROTOCOL DATED MAY 5, 2016

STUDY DRUG:

TAS-102

PROTOCOL NUMBER: TO-TAS-102-302

STUDY TITLE:

RANDOMIZED, DOUBLE-BLIND, PHASE 3 STUDY EVALUATING TAS-102 PLUS BEST SUPPORTIVE CARE (BSC) VERSUS PLACEBO PLUS BSC IN PATIENTS WITH METASTATIC GASTRIC CANCER REFRACTORY TO STANDARD TREATMENTS

SPONSOR AND SPONSOR CONTACT:

Taiho Oncology, Inc.;	Taiho Pharmaceutical Co., Ltd.
101 Carnegie Center, Suite 101 Princeton, NJ 08540, USA	1-27 Kandanishiki-Cho Chiyoda-ku, Tokyo, 101-8444, Japan

PPD, MD
PPD, PPD
Taiho Oncology, Inc.
Tel: PPD
Mobile: PPD
Fax: PPD
PPD

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

This document has been prepared and/or reviewed by

PPD

PPD Ph.D.
PPD
Date

PPD
PPD Ph.D.
PPD PPD PPD
Signature PPD
Date

This document has been reviewed and approved

PPD
PPD M.D.
PPD PPD
Taiho Oncology, Inc.
Date

PPD Ph.D.
PPD
Taiho Oncology, Inc.
Signature
Date

TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company Taiho Oncology, Inc.; Taiho Pharmaceutical Co., Ltd.	**Individual Study Table Referring to Part of the Dossier:** **Volume:**	***(For National Authority Use Only)*:**
Name of Finished Product: {LONSURF}	**Page:**	
Name of Active Ingredient: trifluridine (FTD) and tipiracil hydrochloride (TPI)	**Protocol:** TO-TAS-102-302	
Title Of Study: **RANDOMIZED, DOUBLE-BLIND, PHASE 3 STUDY EVALUATING TAS-102 PLUS BEST SUPPORTIVE CARE (BSC) VERSUS PLACEBO PLUS BSC IN PATIENTS WITH METASTATIC GASTRIC CANCER REFRACTORY TO STANDARD TREATMENTS**		
Investigators: Study Center(s): At least 120		
Studied period (years): 18 months	**Phase of development: Phase 3**	
Objectives: Primary: The primary objective of this study is to evaluate overall survival in patients with refractory metastatic gastric cancer receiving TAS-102 plus BSC or placebo plus BSC Key Secondary: The key secondary objective of this study is to evaluate progression-free survival in patients with refractory metastatic gastric cancer receiving TAS-102 plus BSC or placebo plus BSC. Other Secondary: Other secondary objectives of this study are to evaluate overall response rate, disease control rate, time to deterioration of ECOG performance and quality of life in patients with refractory metastatic gastric cancer receiving TAS-102 plus BSC or placebo plus BSC.		
Methodology: Double blind comparative study (investigational drug vs placebo)		
Number of Subjects (planned and analyzed): Approximately 500 patients will be randomized using a treatment allocation of 2:1 (TAS-102 plus BSC: placebo plus BSC). A target of 384 events (deaths) will be required for the primary analysis.		

Diagnosis and main criteria for inclusion (see protocol Section 2):

Male and female patients age 18 years or older (20 years or older for patients enrolled in Japan) with histologically confirmed, non-resectable, metastatic gastric adenocarcinoma including adenocarcinoma of the gastroesophageal junction, and an ECOG performance status of 0 or 1, who have received at least 2 prior regimens (at least 1 cycle per regimen) for advanced disease, and were refractory to or unable to tolerate their last prior therapy.

- Prior regimens must have included a fluoropyrimidine, platinum, and either a taxane- and/or irinotecan-containing regimen; patients whose tumors are known to be HER2-neu-positive (HER2+) must have received prior anti-HER2+ therapy if available.
- Patients have progressed based on imaging during or within 3 months of the last administration of their last prior regimen.
- Patients who have withdrawn from their last prior regimen due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will also be eligible to enter the study.
- Patients who have received postoperative adjuvant chemotherapy and radiotherapy, and had recurrence during or within 6 months of completion of the adjuvant chemotherapy are allowed to count the adjuvant therapy as one prior regimen for advanced disease. Patients who have received pre- and post-operative adjuvant chemotherapy, and had recurrence during or within 6 months of completion of the adjuvant chemotherapy are allowed to count the adjuvant therapy as one prior regimen only if the same regimen was administered both pre- and post-operatively.

Test product, dose and mode of administration:

TAS-102 (starting dose of 35 mg/m^2/dose) will be administered orally twice daily (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. Patients will receive blinded study medication until a discontinuation criterion is met or until completion of the primary endpoint analysis, whichever is sooner.

Duration of treatment:

After the end of treatment, all patients will be followed for survival every 4 weeks until death or until the target number of events (deaths) is met. If the primary endpoint of the study is met and efficacy as well as safety support a favorable benefit/risk ratio for TAS-102, patients currently or previously treated with placebo who continue to meet study eligibility criteria will be offered the option to crossover to open-label TAS-102. Patients receiving TAS-102 will also be switched to open-label TAS-102 at that time. Patients who receive open-label TAS-102 treatment after conclusion of survival follow-up will be followed for safety and tumor response according to the site standard of care.

Reference therapy, dose and mode of administration:

Placebo (starting dose of 35 mg/m^2/dose) will be administered orally twice daily (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.

Criteria for evaluation (see protocol section x.n):

Efficacy:

Computed tomography (CT) scans will be performed every 8 weeks. On-site tumor assessments will be performed by the Investigator/local radiologist. Tumor assessments will be analyzed using Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Version 1.1, 2009). Progression-free survival will be determined for all patients. Quality of Life assessments will be performed prior to start of dose administration in each cycle

Safety:

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

Statistical methods:

Study Populations

The study populations for all analyses are defined as follows.

• Intent-to-Treat (ITT) population: This population includes all randomized patients and is the primary population for all efficacy parameters. All analyses using this population will be based on the treatment assigned by IXRS.

• As-Treated (AT) population: This population includes all patients who took at least one dose of study treatment. This population is for safety analyses. All analyses using this population will be based on the treatment actually received.

• Tumor Response (TR) Population: All patients in the ITT population with measurable disease (at least one target lesion) at baseline and with at least one tumor evaluation while on treatment. (Patients who have disease progression or a cancer-related death prior to their first on treatment tumor evaluation will also be considered evaluable.) All analyses using this population will be based on the treatment assigned by IXRS.

Primary Efficacy Endpoint (OS)

OS is defined as the time from the date of randomization to the date of death. If death is not observed during the study, the time will be censored at the last date the patient is known to be alive or the cut-off date, whichever is earlier. For the primary analysis of OS, the two treatment arms will be compared using the stratified log-rank test using the 3 stratification factors in the randomization as per IXRS assignment. The hazard ratio will be estimated, along with the associated 2-sided 95% confidence intervals (CI), using a stratified Cox's proportional hazard (CPH) model. Survival for each arm will be summarized using Kaplan Meier curves and further characterized in terms of the median and survival probability at 3, 6, 9 and 12 months, along with the corresponding 2-sided 95% CI for the estimates.

Key Secondary Efficacy Endpoint (PFS)

PFS will be evaluated from date of randomization to the first occurrence of radiologic progression or death. Treatment comparisons for PFS will use similar analytical methods as the OS endpoint.

Other Secondary Efficacy Endpoints

ORR and DCR will be compared between treatment arms using Fisher's exact test and associated 95% CIs will also be derived. Time to deterioration of ECOG performance status to a score of 2 or higher will be analyzed as described for PFS. Change in QoL scores prior to cycles 2, 3 and 4 will be determined for the summary, all domains and single items by subtracting each patient's score from their corresponding baseline score. For each domain, the proportion of patients with deteriorating (vs stable or improving) scores prior to cycles 2, 3 and 4 will be compared using Fisher's exact test. Time to QoL deterioration will be evaluated for each arm using Kaplan-Meier estimates and compared using the log-rank test.

Safety Analyses

Simple descriptive statistics will be provided for safety endpoints and demographic/baseline characteristics.

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LIST OF TABLES

1. LIST OF ABBREVIATIONS

In order to facilitate the interpretation of abbreviations used in this SAP, a comprehensive list (sorted alphabetically) of abbreviations was created for reader's convenience and references.

Table 1: List of Abbreviations

Abbreviation	Term
μmol or mkmol	Micromole
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AT	As-Treated Population (⇔ Safety Population)
AST	Aspartate Aminotransferase
b.i.d.	Twice Daily
BSA	Body Surface Area
BSC	Best Supportive Care
BP	Blood Pressure
bpm	Beats per Minute
BUN	Blood Urea Nitrogen
C	Center
°C	Degrees Celsius
Ca	Calcium
Cl	Chloride
CrCl	Creatinine Clearance
CMH	Cochran Mantel-Haenszel
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DL	Deciliter

DMC	Data Monitoring Committee
DOB	Date of Birth
dy	Days
ECOG	Eastern Cooperative Oncology Group
ºF	Degrees Fahrenheit
FTD	Trifluridine
g	Grams
GCP	Good Clinical Practices
GGT	Gamma-Glutamyl Transferase
HGB	Hemoglobin
HR	Hazard Ratio
ICD-9	International Classification of Diseases – 9th Edition
ICF	Informed Consent Form
In	Inches
IR	Immediate Release
IRB	Institutional Review Board
ITT	Intent-to-Treat Population
IU	International Units
K	Potassium
Kg	Kilogram
L	Liter
Lb	Pounds
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities Terminology
meq	Milliequivalent
mg	Milligrams
mL	Milliliter
mmHg	Millimeters of Mercury
mo	Months
N	Total Sample Size
Na	Sodium

ng	Nanogram
NIMH	National Institute of Mental Health
OC	Observed Cases
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over the Counter Medication
PCS	Potential Clinical Significance
PFS	Progression-Free Survival
PK	Pharmacokinetic
PP	Per-Protocol Population
PR	Partial Response
QoL	Quality of Life
QTc	QT duration corrected for heart rate
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
RBC	Red Blood Cell Count
ROW1	Rest of World 1 (Everything except Japan)
ROW2	Rest of World 2 (Everything except US, EU, Japan)
ROW3	Rest of World 3 (Everything except US)
S	Sex
s.d./SD	Standard Deviation
SD	Stable Disease
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SR	Sustained Release
TEAE	Treatment Emergent Adverse Event
TEAESI	Treatment Emergent Adverse Event of Special Interest
TG	Treatment Group
TS	Transdermal Delivery System-Placebo

ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WBC	White Blood Cell Count
WHO	World Health Organization
yr	Years

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol TO-TAS-102-302.

Protocol Revision Chronology:		
Protocol TO-TAS-102-302	30-JUN-2015	Original

This SAP was developed per standard operating procedure S-CS-001 and guidance document G-CS-001, G-CS-018, G-CS-020.

All decisions regarding final analysis, as defined in this SAP document, will be made prior to Database Freeze (unblinding) of the study data. Further information can be found in the DMC Charter or protocol.

3. STUDY OBJECTIVES AND ENDPOINTS

The present SAP is intended to support a marketing application of TAS-102.

3.1. Study Objectives

The objectives of this study are to evaluate the following endpoints in patients with refractory metastatic gastric cancer receiving TAS-102 plus BSC or placebo plus BSC:

3.1.1. Primary Objective

Overall survival (OS)

3.1.2. Key Secondary Objectives

Progression free survival (PFS) based on Investigator assessment of radiologic images
Safety and tolerability

3.1.3. Other Secondary Objectives

Overall response rate (ORR)

Disease control rate (DCR)

Time to deterioration of Eastern Cooperative Oncology Group (ECOG) performance status to score of 2 or higher

Quality of Life (QoL) (EORTC QLQ-C30, QLQ-STO22) []

3.2. Study Endpoints

3.2.1. Primary Efficacy Endpoint

Overall survival (OS) is the primary efficacy endpoint of this study and is defined as the time from the date of randomization to the death date (ITT population). In the absence of death confirmation or for patients alive as of the OS cut-off date, survival time will be censored at the date of last study follow-up, or the cutoff date, whichever is earlier. The cut-off date will be defined by the date of the 384th death. Patients having a documented survival status (alive or dead) after this date will be censored at the cut-off date.
With the OS cut-off date being event driven, for operational efficiency, the cut-off date for all other study endpoints will be fixed at close proximity of the OS cut-off date, when the milestone is nearing completion.
The clinical cut-off date for all endpoints other than OS was fixed as 31st of March 2018. Details of the rules for cut-off of the submission database are provided in the CCI

3.2.2. Key Secondary Efficacy Endpoints

Progression free survival (PFS) will serve as a key secondary efficacy endpoint of the study. PFS is defined as the time from the date of randomization until the date of the investigator-assessed radiological disease progression or death due to any cause. Patients who are alive with no disease progression as of the analysis cut-off date will be censored at the date of the last tumor assessment. Patients who receive non-study cancer treatment before disease progression, or patients with clinical but not radiologic evidence of progression will be censored at the date of the last radiologic evaluable tumor assessment before the non-study cancer treatment is initiated [redacted].

3.2.3. Other Secondary Efficacy Endpoints

The study will include 4 additional secondary efficacy endpoints.

3.2.3.1. Overall Response Rate

The assessment of ORR will be based on Investigator review of radiologic images and following RECIST criteria (version 1.1 2009). ORR is defined as the proportion of patients with objective evidence of CR or PR. The primary assessment of ORR will be in the ITT population, restricted to patients with measurable disease (at least 1 target lesion) at Baseline.

At the analysis stage, the best overall response will be assigned for each patient as the best response recorded from all responses recorded from the start of treatment through the treatment period (excludes assessments during follow-up). If applicable, responses recorded after radiologic disease progression or initiation of non-study antitumor therapy will be excluded. A patient's best response assignment of SD needs to be maintained for at least 6 weeks from the start of treatment.

3.2.3.2. Disease Control Rate

DCR is defined as the proportion of patients with objective evidence of CR, PR, or SD (stable disease). The assessment of DCR will parallel that of ORR.

3.2.3.3. Time to Deterioration of ECOG Performance Status

The time to deterioration of ECOG performance status is defined as the time from randomization to the first date on which an ECOG performance status score of 2 or higher is observed. Patients not reaching an ECOG of 2 or more will be censored at the last recorded ECOG assessment on study.

3.2.3.4. Quality of Life

The EORTC quality of life questionnaire (QLQ) is an integrated system for assessing the health related quality of life (QoL) of cancer patients participating in international clinical trials. The core questionnaire, the QLQ-C30, incorporates 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status scale, and a number of single items assessing additional symptoms commonly reported by cancer patients

(dyspnea, loss of appetite, insomnia, constipation and diarrhea) and perceived financial impact of the disease.

The gastric cancer module (QLQ-STO22) is meant for use among gastric cancer patients varying in disease stage and treatment modality.

4. STUDY DESIGN

4.1. Summary of Study Design

This is a multinational, double-blind, two-arm, parallel, randomized, Phase 3 study evaluating the efficacy and safety of TAS-102 plus BSC versus placebo plus BSC in patients with metastatic gastric cancer who have received at least 2 prior regimens for advanced disease. The study will be conducted under the sponsorship of Taiho Pharmaceutical Co., Ltd. for sites in Japan and Taiho Oncology, Inc. for sites in the rest of the world (ROW).

Eligible patients will be centrally randomized (2:1) to TAS-102 + BSC (experimental arm) or placebo + BSC (control arm) using a dynamic allocation method (biased coin) via an Interactive Voice/Web Response System (IXRS), stratified by:

- Region (ROW1 vs. Japan)
- ECOG PS (0 vs. 1)
- Prior treatment with ramucirumab (yes vs. no)

Study medication should be started within 3 calendar days after the date of randomization and continue until a discontinuation criterion is met or until completion of the primary endpoint analysis, whichever is sooner.

TAS-102 (35 mg/m^2/dose) or placebo 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 [1, 2, 3, 4, 5, 6, 7].

Computed tomography (CT) scans will be performed at baseline and every 8 weeks thereafter until disease progression. On-site tumor assessments will be performed by the Investigator/local radiologist. Tumor assessments will be analyzed using Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Version 1.1, 2009). If patient discontinuation is for reasons other than radiologic disease progression (i.e., with intolerable side effects), patients will be followed every 8 weeks for tumor response until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first).

Quality of life assessments (EORTC QLQ-C30 and QLQ-STO22) will be performed prior to start of dose administration in each cycle.

Flow chart of the Study is presented in the Figure 1.

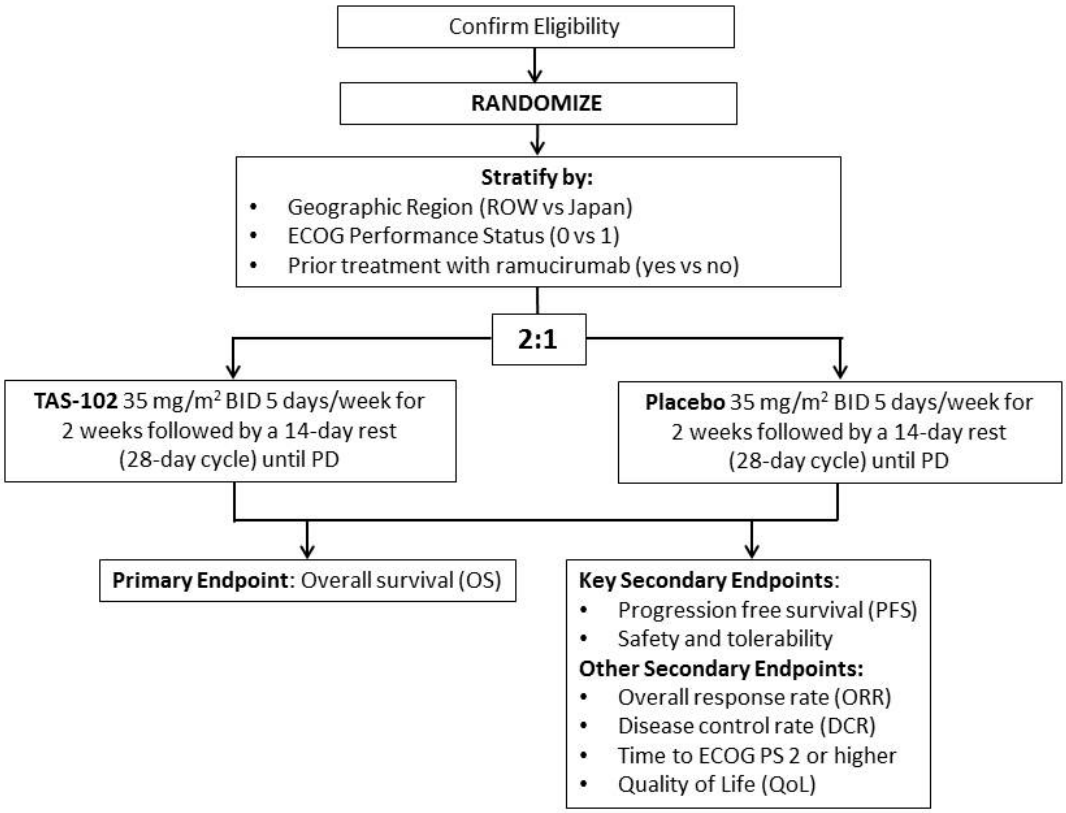

Figure 1. Flow chart of the Study.

4.2. Definition of Study Drugs

TAS-102 (Study Drug) is an oral combination of an antineoplastic thymidine-based nucleoside analogue (trifluridine [FTD]) and a thymidine phosphorylase inhibitor (tipiracil hydrochloride [TPI]). Following 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 thymidine phosphorylase (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.

4.3. Sample Size Considerations

4.3.1. Sample Size Justifications

The study is designed to detect with 90% power a hazard ratio for death of 0.70 (30% risk reduction) in the TAS-102 arm compared with the placebo arm with an overall 1-sided type 1 error of 0.025. A variable accrual period of 18 months and a 5%/year loss to survival follow-up rate has been assumed. Using a treatment allocation of 2:1 (TAS-102:placebo) of 500 patients, 384 deaths will be targeted for the final OS analysis.
Based on these design operating characteristics and assuming a median survival time of approximately 5 months in the control arm, the primary analysis target events milestone will be reached approximately 8 months after the last patient is randomized in the study. The median OS in the control arm was estimated based on the observed median OS of 3.8 months in the placebo arm of the 2nd line Phase 3 ramucirumab (REGARD) study, and the observed median OS of 4.3 months in the placebo arm of the 2nd & 3rd line Phase 3 everolimus (GRANITE) study [13]. The estimate was further increased to 5 months to account for the higher control median projected in the Japanese population.

4.4. Randomization

Patients will be centrally randomized in a 2:1 ratio to TAS-102 plus BSC or placebo plus BSC via an IXRS based on a dynamic allocation method (biased coin). Further details can be found in the IXRS specifications manual CCI via an IXRS based on a dynamic allocation method (biased coin)..

4.5. Clinical Assessments

This Section will describe the clinical assessments that will be performed during the Study course.

4.5.1. Vital Signs, Height and Weight

Patient's vital signs (blood pressure, heart rate, body temperature, and respiration rate), height and body weight will be collected at the time points presented in the Study Schedule (Table 2). All the vital signs will be taken in a position that is consistent for all time points for each patient.

4.5.2. Performance Status

Patient's performance status (ECOG) will be collected at the following time points (Table 2).

- Within 28 days prior to Day 1 of Cycle 1
- At time of randomization (within 3 calendar days prior to start of study treatment on Day 1 of Cycle 1)

- Beginning with Cycle 2, obtain within 24 hours prior to start of study treatment in every cycle
- End of Treatment Visit (if applicable)
- 30-day Safety Follow-up Visit

4.5.3. Laboratory Evaluations

Clinical laboratory assessments will include hematology, serum chemistry and urinalysis tests described below.

4.5.3.1. Hematology

Samples of the patient's blood will be collected for hematological assessments at the following time points (Table 2) and when clinically indicated:

- Within 7 days prior to Day 1 of Cycle 1 (Laboratory results obtained prior to signing ICF may be used if the results were obtained within 7 days prior to Day 1 of Cycle 1.)
- Day 15 of Cycle 1
- Beginning with Cycle 2, obtain within 24 hours prior to start of study treatment in every cycle
- End of Treatment Visit (if applicable)
- 30-day Safety Follow-up Visit

4.5.3.2. Serum Chemistry

Samples of the patient's blood will be collected for chemistry assessments at the following time points (Table 2) and when clinically indicated:

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

4.5.3.3. Urinalysis

Samples of the patient's urine will be collected for qualitative (dipstick) analysis within 7 days prior to Day 1 of Cycle 1 (Laboratory results obtained prior to signing ICF may be used if the results were obtained within 7 days prior to Day 1 of Cycle 1.) and when clinically indicated.

4.5.4. Pregnancy Testing

For patients who are female and of childbearing potential, perform pregnancy testing with serum or urine beta-human chorionic gonadotrophin （β -HCG) at the following time points and record the date, time, and test results in the patient's source document (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 and 30-day Safety Follow-up Visit

Female patients who are considered not to be of childbearing potential must have a history of being post-menopausal (no menses for 12 months without an alternative medical care), or hysterectomy that is clearly documented in the patient's source documents.
Data on pregnancy testing will be presented in listings only.

4.5.5. Quality of Life

Analysis of the quality of life will be performed using EORTC Quality of Life Questionnaire - Core Questionnaire (EORTC QLQ-C30) and Gastric-specific module (QLQ-STO22). The EORTC QLQ-C30 was developed as an integrated system for assessing the health related quality of life (QoL) of cancer patients participating in international clinical trials. It is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.
Patients will complete the EORTC QLQ-C30QLQ-STO22CCI at the following time points:

- Within 7 days prior to randomization
- Prior to dose administration on Day 1 of Cycles ≥2At the 30-day Safety Follow-up Visit if not performed within the previous 4 weeks

4.5.6. Tumor Measurements

Computed tomography tumor assessments/imaging studies of the chest and abdomen (and pelvis if clinically indicated) must be performed and obtained at each time point listed below for all patients:

- Within 28 days prior to Day 1 of Cycle 1. Scans obtained prior to patient ICF may be used if the date of the scan is within 28 days of randomization.
- Every 8 weeks during study treatment
- For patients who discontinue treatment for reasons other than radiologic disease progression, every effort should be made to perform a tumor assessment prior to the start of new anticancer therapy.
- For patients who discontinued treatment for reasons other than radiologic disease progression, every 8 weeks until the patient develops radiologic progression or the start of new anticancer treatment (whichever occurs first)

On-site tumor assessments will be performed by the Investigator/local radiologist according to RECIST criteria (version 1.1, 2009). 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 medication. Response definitions are provided in Section 11 .
If the Investigator determines that a patient develops clinical progression manifested by symptomatic deterioration but not supported by radiologic evidence of progression, the patient should stop treatment. Symptoms of clinical progression must be documented in the patient's source documents. Every effort should be made to document objective progression even after discontinuation of treatment.

If a patient is withdrawn due to radiologic disease progression, additional CT scans are not required at the end 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. Results of any unscheduled evaluations should be recorded in the patient's source documents.

4.5.7. Concomitant Medications

All therapies and medications, prescription and over-the-counter, from the time of signed ICF through the 30-day Safety Follow-Up Visit, will be collected and summarized in the tables. This will include any medication used to treat AEs or SAEs during the safety follow-up period.
At the 30-day Safety Follow-Up Visit, any new anticancer therapy and the date of initiation will be collected.
During the survival follow-up period, only anticancer therapies will be collected.

5. PLANNED ANALYSES

5.1. Interim Analyses

One interim analysis for efficacy and futility is planned for the study after approximately 1/2 of the total target events are observed (192 deaths). The Lan-DeMets alpha-spending approach will be used with O'Brien-Fleming stopping boundaries to guide the efficacy evaluation at the interim and final OS analysis. This approach will account for multiple testing and preserve the overall 1-sided study significance level of 0.025. A fixed HR boundary will be used to assess futility (non-binding). Additional details will be taken from the final analysis plan described in the present SAP (please refer to the Section 10 and to the Section 12 for additional details).

5.2. Final Analyses

Final analysis is planned for the study when the total target events are observed (384 deaths). The final analysis will follow instructions presented in this SAP.

6. STUDY DURATION AND VISIT SCHEDULE

The study was designed presuming accrual period of 18 months and a 5%/year loss to survival follow-up rate. Using a treatment allocation of 2:1 (TAS-102 : placebo) of 500 patients, 384 deaths will be targeted for the final OS analysis.

Based on these design operating characteristics and assuming a median survival time of approximately 5 months in the control arm, the primary analysis target events milestone will be reached approximately 8 months after the last patient is randomized in the study. The median OS in the control arm was estimated based on the observed median OS of 3.8 months in the placebo arm of the 2nd line Phase 3 ramucirumab (REGARD) study and the observed median OS of 4.3 months in the placebo arm of the 2nd & 3rd line Phase 3 everolimus (GRANITE) study [13]. The estimate was further increased to 5 months to account for the higher control median projected in the Japanese population.

After the end of treatment, all patients will be followed for survival every 4 weeks until death or until the target number of events (deaths) is met. If the primary endpoint of the study is met and efficacy as well as safety support a favorable benefit/risk ratio for TAS-102, patients currently or previously treated with placebo who continue to meet study eligibility criteria will be offered the option to crossover to open-label TAS-102. Patients receiving TAS-102 will also be switched to open-label TAS-102 at that time. Patients who receive open-label TAS-102 treatment after conclusion of survival follow-up will be followed for safety and tumor response according to the site standard of care.

The study schedule of events and assessments can be found in Table 2 .

Table 2: Schedule of the Study.

Visit ID / Procedure	Baseline Period		On-Treatment Period								End of Treatment/ End of Study Period		
	Baseline Day		CYCLE 1 Day of Cycle[14]				SUBSEQUENT CYCLES Day of Cycle[14]						
	-28 to -1	-7 to -1	1	12	15	End of Recovery	1	12	15	End of Recovery	End of Treat-ment[16]	30-Day Safety Follow-up Visit	Survival Follow-up
Sign ICF	X[1]												
Enrollment	X[2]												
Randomization			X[3]										
Medical History	X												
Histological Confirmation	X												
HER2 status (if available)	X												
Physical Examination[4]		X					X[15]				X	X	
Baseline Signs & Symptoms		X											
Height		X											
Vital Signs[5] & Weight		X					X[15]				X	X	
ECOG Performance Status[6]	X		X				X[15]				X	X	
Hematology[7]		X			X		X[15]				X	X	
Serum Chemistry[7]		X			X		X[15]				X	X	
Urinalysis[7]		X											
Pregnancy Test[8]		X									X	X	
Tumor Measurements[9]	X									X[9]	X[9]		X[9]
Quality of Life Assessment[18]		X[18]					X[18]					X[18]	
Concomitant Medications[10]	X	→	→	→	→	→	→	→	→	→	→	→[10]	X[11]
AE/SAE Assessment[12]			X	→	→	→	→	→	→	→	→	X	
TAS-102 or Placebo Treatment[13]			X (D 1-5)	X (D 8-12)			X (D 1-5)	X (D 8-12)					
Survival Status			→	→	→	→	→	→	→	→	→	→	X[17]

[1] Sign ICF: Written informed consent should be obtained prior to the performance of any study procedure.
[2] Enrollment: Enroll patient by entering baseline data into the electronic case report form (eCRF) in order to receive a unique 6-digit patient number.
[3] Randomization: Central randomization via IXRS following confirmation of baseline eligibility criteria. Patients should receive the first dose of study medication within 3 calendar days of randomization.
[4] Physical Exam: Beginning with Cycle 2, and for all subsequent cycles, perform within 24 hours prior to Day 1 study drug administration.
[5] Vital Signs: Heart rate, blood pressure, body temperature, respiratory rate; beginning with Cycle 2, and for all subsequent cycles; collect within 24 hours prior to Day 1 study drug administration.

[6] ECOG Performance Status: Collect within 24 hours prior to Day 1 study drug administration for all cycles.

[7] Hematology, Serum Chemistry, Urinalysis: Hematology and serum chemistry assessments will be performed at Baseline (within 7 days prior to Day 1 of Cycle 1; on Day 15 of Cycle 1; and within 24 hours prior to Day 1 study drug administration of Cycles ≥2. Urinalysis is required at Baseline and thereafter as clinically indicated. Laboratory results obtained prior to signing ICF may be used if the results were obtained within 7 days prior to Day 1 of Cycle 1.
[8] Pregnancy Test: Pregnancy test is required at Baseline (within 7 days prior to Day 1 of Cycle 1) and at either the End of Treatment or 30-day Safety Followup visit. More frequent pregnancy assessments may be performed as required by local law.
[9] Tumor Measurements: Obtain a contrast-enhanced computed tomography (CT) scan of the chest and abdomen (and pelvis, if clinically indicated) within 28 days prior to Day 1 of Cycle 1 and every 8 weeks thereafter during study treatment. If a patient discontinues treatment due to 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 prior to 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 8 weeks 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 RECIST criteria (v. 1.1, 2009). CT scans obtained prior to signing ICF may be used if the date of the scan is within 28 days prior to Day 1 of Cycle 1.
[10] Concomitant Medications: Collect from time of signed Informed Consent Form (ICF) through the end of therapy, including any medications used to treat AEs or SAEs; at the 30-day safety follow-up period, collect date of initiation of any new anticancer therapy.
[11] Concomitant Medications: Collect anticancer therapies only during survival follow-up.
[12] AE/SAE Assessment: Monitor patients for any untoward medical events from the first dose of study drug through the 30-day safety follow-up period or until initiation of new anticancer treatment, whichever comes first. Adverse events reported from time of signed ICF to first dose of study drug should be recorded as Medical History.
[13] Study Drug Treatment: TAS-102 or placebo will be administered twice daily (BID) on Days 1 through 5 and 8 through 12 of each cycle.
[14] Assessment Windows: A window of +/-3 days is allowable for study procedures (+/-7 days allowable for CT scans), as long as the proper order is maintained.
[15] Subsequent Cycles ≥2: Obtain within 24 hours prior to Day 1 study drug administration. Prior to starting subsequent cycles, verify that patients with toxicities have met resumption criteria prior to administering study drug.
[16] End of Treatment: Assessments will be performed at time of withdrawal of study medication (TAS-102 or Placebo). If the decision to discontinue study medication 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 medication (due to 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.
[17] Survival Status: Obtain survival status (alive/dead) at scheduled 4-week time intervals until death. Survival status should be collected until the target number of events (deaths) is met.
[18] Quality of Life: Patients should complete the EORTC – QLQ-C30 and QLQ-STO22 questionnaires within 7 days prior to randomization, prior to dose administration on Day 1 of Cycles ≥2, and at the 30-day safety follow-up if not performed within the prior 4 weeks..

7. ANALYSIS POPULATIONS

7.1. Intent-To-Treat (ITT) Population

The "Intent-to-Treat (ITT) Population" comprises all randomized patients, regardless of whether or not study drug was administered. This population will serve as the primary population for the analysis of the efficacy data. All analyses using this population will be based on the treatment assigned by IXRS.

7.2. As-Treated (AT) Population (Safety Population)

The "As-Treated (AT) Population" is defined as all subjects who receive at least one dose of study medication. This population will be used in the assessment and reporting of safety data. The "As-Treated Population" is equivalent to "Safety Population". This population will be used for safety analyses. All analyses using this population will be based on the treatment actually received.

7.3. Tumor Response(TR) Population

The "Tumor Response (TR) Population" will include all patients in the ITT population that meet both of the two following criteria:

1. Subject has measurable disease (at least one target lesion) at baseline;
2. Subject has at least one post-baseline evaluation or early disease progression/cancer-related death occurred before first evaluation on treatment (post-baseline) took place.

All analyses using this population will be based on the treatment assigned by IXRS.

8. DERIVED AND TRANSFORMED DATA

8.1. Age (relatively to Informed Consent Date)

Subject's age in years (whole number, no decimals) will be calculated using date of informed consent (IC) as the reference point. An appropriate SAS expression recommended by SAS Institute for calculation of a correct age of a person will be applied to calculate the age. The expression is supposed to take into account leap years and other peculiarities of the Gregorian calendar. The formula reads as follows:

Age (year) = INT(INTCK("MONTH", date of informed consent – date of birth)/12)

IF MONTH(date of birth) = MONTH(date of informed consent)

THEN Age = Age - (DAY(date of birth) > DAY(date of informed consent));

where INT( ) function (SAS) returns the integer part of the result, INTCK("MONTH", DATE2 – DATE1) function (SAS) returns a number of months between DATE1 and DATE2, MONTH( ) and DAY( ) – standard SAS functions returning month and day of the month of the argument, correspondingly.

8.2. Study Day

If the date of interest occurs on or after the first dose/randomization date then study day will be calculated as (date of interest – date of first dose/randomization) + 1. If the date of interest occurs prior to the first dose/randomization date then study day will be calculated as (date of interest – date of first dose/randomization). If the date of the first dose is different from the date of randomization (protocol allows 3 day window between randomization and start of the treatment), the date of the first dose will be used in the aforementioned calculations. There will be no study day 0.

8.3. Baseline

Baseline assessment is defined as the last valid/non-missing measurement obtained prior to administration of the first dose of study medication. If the time of the medication and/or time of the assessment is not available, baseline is defined as last valid measurement obtained prior to or on the date of administration of the first dose of study medication

If the multiple results are available that were obtained at the same date and there is no reasonable way to uncover their chronological order, the average value will be used as a baseline (for continuous variables).

All recorded valid data will be considered for analysis of baseline values (including test performed at unscheduled visits).

8.4. Change from Baseline

Change from baseline is calculated as (post-baseline result – baseline result).
Percent change from baseline is calculated as (change from baseline/baseline result * 100).
If either the baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline is set to missing as well.

8.5. Day 1

The date of first administration of study medication (first dosing) is defined as Day 1 of treatment (D1). The date of first administration of study medication (first dosing) within the Cycle N is defined as Day 1 of the Cycle N (CND1).

8.6. End of Study

The final data cut off will be defined by the date of the 384th death. All patients dying on the calendar date of the 384th death will be included in the analysis should more than one patient die on the calendar date of the 384th death. Subjects that will be alive on the calendar date of the 384th death will be considered as ongoing study.

8.7. Visit Windows

Windows mentioned in the protocol of the present study are used for operational purposes only and they will not be utilized for any analysis.

For the purpose of analysis lab tests, vital examinations, ECOG performance status, tumor assessments, etc. will be assigned to an appropriate cycle according to the start date of this cycle and the start date of the next one. In general, Cycle N will be defined as all days starting with Day 2 of the Cycle N until the Day 1 (including) of the Cycle (N+1). Detailed instructions how an assignment should be performed will be presented in the CCI [redacted] ("Data Handling Guidance").

For the purpose of presentation of AE and/or CM in the listings an assignment to the appropriate cycle will be performed. In general, Cycle N will be defined as all days starting with Day 1 of the Cycle N till the day (including) before Day 1 of the Cycle (N+1). For the last cycle a standard 30 days window after the last dose will be applied. Detailed instructions how an assignment should be performed will be presented in the CCI [redacted] ("Data Handling Guidance").

8.8. Multiple Assessments

When valid multiple assessments within the same cycle (refer to) are available their presentation will depend on the specific output. Detailed instruction for analysis will be presented in and in the "Data Handling Guidance").

8.9. Time Adjusted Incident Rate (per 100 Subject Year)

The incidence rate (per 100 patient year) of a given event/TEAE is defined as the number of patients experiencing the event/TEAE during time at risk divided by the total time of patients at risk to contribute an event to the analysis multiplied by 100 (per 100 patient year).

Here Time at risk [patient years] = (date of first onset of event/TEAE - study drug start date + 1)/365.25. If the event/TEAE of interest did not occur for a patient, time at risk will be censored at the end of the event/TEAE period, which is defined in Section 11.1.2

8.10. Days to "Recovery" (Grade 3 or Grade 4 abnormalities)

The number of days to "recovery" for the Grade 3 or Grade 4 abnormalities (that worsen from baseline or had missing baseline) in clinical lab tests for a subject is defined as the number of days from the moment when this abnormality is recorded for the first time until the time (subsequent event) when CTCAE grade for this test is reduced to a value 2 or 1. If the test continues to demonstrate the same (or higher) CTCAE grade (i.e., Grade 3 or Grade 4) continuing to the end of the study or the subject's death (whichever occurs earlier), the duration is censored at either the end of the study or the subject's death as appropriate.

8.11. Creatinine Clearance/Level

The creatinine level/clearance will be calculated using well-accepted Cockcroft-Gault equation. The formula allows the creatinine clearance to be estimated from the serum creatinine in a patient with a stable serum creatinine. The expression read as follows:

For males: $$CrCl[mL/min] = \frac{(140 - age[years]) * weight[kg])}{serum\ creatinine\ [\mu mol/L]} \times 1.228$$

For females: $$CrCl[mL/min] = \frac{(140 - age[years]) * weight[kg])}{serum\ creatinine\ [\mu mol/L]} \times 1.044$$

8.12. Renal Function

The creatinine level/clearance will be used to identify the renal function. For the purpose of the present SAP the following subdivision will be used (round the calculated result for the creatinine clearance to the nearest whole number before application of the table below):

Renal Function	Creatinine Clearance (CrCl)
Normal	**≥90 mL/min**
Mild Impairment	**60-89 mL/min**
Moderate Impairment	**30-59 mL/min**
Severe Impairment	**≤29 mL/min**

8.13. Handling of Missing Data

8.13.1. Missing Efficacy Endpoints

No imputation of the missing data will be performed, unless otherwise specified, for example, censoring rules, as applicable.

8.13.2. Missing Start and Stop Dates for Prior and Concomitant Medication

Incomplete concomitant medication start and/or stop dates will be imputed as follows. If either the start of medication date is completely missing or the month and/or year of the start date is missing, the start date will be set to the first dose date. If only the day is missing, the day will be set to the first day of the month except if the start month is the same as the first dose month. If the latter is true, the start day will be set to the first dose day. No imputations will be applied to the stop date. Imputed dates will be flagged in the individual supportive subject data listings.

8.13.3. Missing Start and Stop Dates for Adverse Events

No imputation for stop dates of TEAEs will be performed.

Missing and/or partial start dates of TEAEs will be imputed using the algorithms presented in the
.

8.13.4. Missing Birth Date

Incomplete birthday date will be imputed as follows. If only the day is missing (i.e., both year and month are known and valid), the day will be set to the first day of the month. Otherwise, if both the day and month are missing (i.e., year only is known and valid), the day will be set to the first day of the first month (January 1st). Imputed dates of birth will be flagged in the individual supportive subject data listings.

8.13.5. Missing Exposure End Date

Incomplete or missing exposure end date (last cycle) will be imputed assuming that subject took the full 12 days course of the study drug. If the subject discontinued treatment or died during this period (12 days since the start of the cycle) than the date used for imputation will be the date of treatment discontinuation or death. If the subject discontinued treatment and died during this period than the date used for imputation will be the earliest of these two dates (treatment discontinuation and death).

8.13.6. Partial or Missing Date of Start of Antitumor Therapy

The instructions presented in this subsection will be applied when it will be required to check if post-baseline antitumor therapy (specifically: systemic therapies, radiotherapy and cancer surgeries) was initiated prior to a response assessment.

1. Incomplete/partial date start of antitumor therapy will be imputed only if day only is missing. In this the last day of the month will be used for imputation.
2. Incomplete/partial date start of antitumor therapy will not be imputed only if month or year or both month and year are missing. In this case the patient will be considered as having received no post-baseline anti-tumor therapy.

8.14. Countries in EU

For the purpose of the present study the following countries will be defined as belonging to EU:

1. Belgium, Czech Republic, France, Germany, Ireland, Italy, Poland, Portugal, Romania, Spain, United Kingdom.
2. Belarus, Israel, Russian Federation, Turkey

9. GENERAL ANALYSIS

9.1. Subjects Disposition

A complete accounting of subject participation in the study will be presented according to requirements provided by ICH Guideline for Industry, 1996 (Structure and Content of Clinical Study Reports [CSR]) [15]. The purpose of this table is to track subjects from informed written consent through their exit from the study and to account for subject evaluation in major analyses of efficacy and safety, including reasons for early study termination or withdrawal.

9.2. Protocol Deviations

A set of "protocol deviations"/"major protocol deviations" is defined as a means to measure adherence to key aspects of the protocol. Summary of all major Protocol Deviations (at study entrance and during the study period) by type of deviation will be provided.

A summary of all protocol deviations (at study entrance and during the study period) by type of deviation will be provided.

A patient will be considered as having a protocol CSR reportable deviation if she/he meets at least one of the criteria presented below. These subjects will be identified based on reviews of the data prior to final unblinding of the treatment codes.

9.2.1. CSR Reportable Protocol Deviation

A CSR reportable Protocol Deviation is related to inclusion/exclusion criteria, conduct of the trial, patient management or patient assessments that impact the safety of the subjects or jeopardize the quality of the study data.

During the conduct of protocol TAS-102-302 the following categories will be used for CSR reportable Protocol Deviations:

RD1 - A subject that did not meet entry criteria

RD2 - A subject that developed withdrawal criteria but was not withdrawn

RD3 - A subject that received the wrong treatment or incorrect dose

RD4 - A subject that received an excluded medication

RD5 - Critical ICF, GCP and other Protocol Deviations

A CSR non-reportable Protocol Deviation may be important to address and document as part of site management and oversight, but is not considered reportable in the CSR.

The following categories will be used to capture non-reportable PDs.

NRD1 - SAE reporting

NRD2 - Informed consent

NRD3 - Study procedures

NRD4 - Investigational product (other than incorrect dose or wrong treatment)

Refer also to the study *Protocol Deviation Plan*, for details.

9.2.2. Major CSR Reportable Protocol Deviation

In addition, among all CSR Reportable Protocol Deviations, a set of "major protocol deviations" is defined as a means to measure adherence to key aspects of the protocol using pre-specified CCI analyses.

Study Entrance:

MRD1 - No histological confirmation of gastric adenocarcinoma including adenocarcinoma of the gastroesophageal (GE) junction

MRD2 - No metastatic disease

MRD3 - No measurable or nonmeasurable disease as defined by RECIST 1.1 criteria

MRD4 - Received fewer than 2 prior regimens (at least 1 cycle per regimen) of standard chemotherapy for advanced gastric or GE junction cancer or was not refractory to or was able to tolerate their last prior therapy. The regimens are supposed to meet the following criteria:

a. Prior regimens must have included a fluoropyrimidine, platinum, and either a taxane- and/or irinotecan-containing regimen; patients whose tumors are HER2-neu-positive (HER2+) must have received prior anti-HER2+ therapy if available.

b. Patients must have progressed based on imaging during or within 3 months of the last administration of their last prior regimen.

c. Patients who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will also be eligible to enter the study.

d. Patients who have received postoperative adjuvant chemotherapy and radiotherapy, and had recurrence during or within 6 months of completion of the adjuvant chemotherapy are allowed to count the adjuvant therapy as one prior regimen for advanced disease. Patients who have received pre- and post-operative adjuvant chemotherapy, and had recurrence during or within 6 months of completion of the adjuvant chemotherapy are allowed to count the adjuvant therapy as one prior regimen only if the same regimen was administered both pre- and post-operatively.

MRD5 - Prior anticancer therapy within 3 weeks prior to study drug administration

MRD6 - Subject has previously received TAS-102

Study period:

MRD7 - Patient received incorrect treatment (i.e. randomized to one arm but received the other arm)

MRD8 - Other concurrent chemotherapy or radiotherappy administered while receiving study medication

The number of patients with CSR Reportable deviations of one or more criteria and the number of patients with major CSR reportable protocol deviations will be listed and tabulated for all patients (including screen failures) and ITT population.

9.3. Demographic and Baseline Characteristics

The demographic and baseline characteristics will be summarized. The list of characteristics that will be summarized include but are not limited to the following:

- Gender
- Age (years) (#)
- Age group 1 (<65 years, ≥65 years)
- Age group 2 (3 groups: (<65 years, 65≤ - <75, 75≤ years)
- Race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Collectable, Other)
- Race Group (White, Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Collectable, Unknown)
- Region 1 (Japan, Rest of the World 1)
- Region 2 (US, EU, Japan)
- Region 3 (US, Rest of the World 3)
- ECOG status at baseline (0, 1)
- Height (cm) (#)
- Weight (kg) (#)
- BSA (m^2) (#)
- BSA (m^2) by Region 2 (#)
- Renal function at baseline (Normal/Mild/Moderate based on Cockcroft-Gault formula)

(#) indicates a continuous variable to be summarized.

9.4. Subject Inclusion and Exclusion Criteria

Information regarding subject's inclusion and exclusion criteria will be listed on an individual subject basis.

Patients who were randomized but have not met all inclusion and/or exclusion criteria will be identified and summarized by treatment arm and inclusion/exclusion criteria that were not met.

9.5. Medical History

Significant medical history will be summarized for the AT population. The patients are summarized using counts and percentages. All medical histories will be coded using MedDRA version 16.1 (or greater) and summaries will use the system organ class and preferred term codes, as appropriate.

9.5.1. Cancer Medical History

- Primary Cancer Type (gastric, gastroesophageal (GE) junction, both)
- Tumor Grade (WellDifferentiated, Moderately Differentiated, Poorly Differentiated, Unknown or Missing)
- Histology subtype (intestinal, diffused, mixed, unknown or N/A)
- Location of Primary Tumor
- Previous gastrectomy (Yes, No)
- Time from Initial Diagnosis to Randomization (months)
- Time from Confirmed Metastasis to Randomization (months)
- Number of prior regimens (<2, 2, 3, 4≤)
- Prior Treatment with Fluoropyrimidine (Yes, No)
- Prior Treatment with Platinum (Yes, No)
- Prior Treatment with Irinotecan (Yes, No)
- Prior Treatment with Taxane (Yes, No)
- Prior Treatment with Ramucirumab (Yes, No)
- Measurable disease (Yes, No)
- Number of metastatic sites (1-2, ≥3)
- Presence of liver metastases (Yes, No)
- Presence of lung metastases (Yes, No)
- Presence of peritoneal metastases (Yes, No)
- HER2 status

9.5.2. Non-Cancer Medical History

Non-cancer-related medical history will be presented as it is described in the beginning of the Section 9.5.

9.6. Prior, Concomitant, and Survival Follow-up Medications and Therapies

9.6.1. Prior Anti-Cancer Therapies

Prior anti-cancer therapies will be summarized for the AT population and will include the following:

- Number of prior regimens (<2, 2, 3, 4≤)
- Prior therapies (fluoropyrimidine, platinum, taxane, irinotecan, ramicurumab, immunotherapy (PD1/PDL1) containing regimens, HER2i).
- Prior Treatment with Ramucirumab (Yes, No)
- Prior Treatment with Irinotecan (Yes, No)
- Prior Treatment with Taxane (Yes, No)
- Prior Treatment with Fluoropyrimidine (Yes, No)
- Prior Treatment with Platinum (Yes, No)
- Prior Treatment with HER2i
- Prior Treatment with Immunotherapy (PD1/PDL1) (Yes, No)
- Prior surgery (Yes, No)
- Previous gastrectomy (Yes, No)
- Prior Radiotherapy (Yes, No)

9.6.2. Prior and Concomitant Medications

Prior and concomitant medications will be summarized for the AT population. The patients are summarized using counts and percentages. All concomitant medications and therapies will be coded using WhoDDE (September 2015) and summaries will use the system organ class and preferred term codes, as appropriate.

All medications, prescription and over-the-counter, from the time of signed ICF through the 30-day Safety Follow-Up Visit, will be collected and summarized in the tables. This will include any medication used to treat AEs or SAEs during the safety follow-up period. Summarization will be performed separately for prior and concomitant medications (two different tables).

9.6.3. Non-study Systemic Anti-cancer Treatment during Survival Follow-up Period

Patients receiving non-study systemic anti-cancer treatments initiated during the follow-up period will be summarized in a table by treatment arm. The table will display the number and type of new non-study systemic anti-cancer treatments. The time to start of the new anti-cancer treatment will be presented as a listing and is defined as the start date of the new anti-cancer therapy minus the date of last dose of study medication + 1. If the start date of the new anti-cancer treatment is missing, the time to start of anti-cancer therapy will be missing for that patient.

9.7. Exposure to Study Medication

Exposure will be summarized and tabulated for the AT population. Study drug administration for number of cycles initiated will be summarized by cycle and overall for each treatment group. Dose level by cycle will be summarized for each treatment group. Patients with at least one dose reduction and first cycle with target dose reduction will be summarized for each treatment group. The number of delays in cycle initiation ≥ 8 days and the 1st delay ≥ 8 days will be summarized by cycle and overall for each treatment group. The number of delays in cycle initiation of ≥ 4 days will also be presented. Duration of cycles (excluding last cycle) will be summarized by cycle and overall for each treatment group. The number of patients that received ≥ 90% of cycle 1 target dose, received ≥ 80% of cycle 1 target dose will be summarized for cycle 1, cycles > 1 and entire study for each treatment group. Patients receiving more than 100% of the cycle 1 target dose or the current cycle dose will be summarized in interval categories of 20% (e.g. >100% to 120%, >120% to 140%, etc.) The total dose administered (mg/m^2), dose intensity ($mg/m^2/wk$), relative dose intensity (ratio to planned) will be summarized.

9.8. Duration of Survival Follow-up

A summary table showing the duration of follow-up will be presented by treatment arm for the ITT and AT population. The follow-up period for the purpose of this analysis is defined as the time starting on the date randomized until the last day of contact, or the day of withdrawal from study or the day of death, whichever occurs last (note, this definition of the survival follow – up period is different from one used in the Study Protocol). It will be summarized using the reverse Kaplan-Meier method (deaths are censored, censored subjects constitute events at the censored time) [22].

10. EFFICACY ANALYSES

This Section contains instructions how the efficacy analysis of the collected data will be performed and presented. As a general rule (unless otherwise is stated) efficacy analysis will use values of stratification factors collected on IXRS.

Assignment of the tumor assessments to the appropriate cycle will be performed according to the instructions displayed in CCI [redacted] Additionally, if multiple tumor assessments are reported at an analysis time window (refer to Section 8.7 CCI [redacted]), then the logic described in Section 8.8 and specific data handling rules presented in CCI [redacted] will be applied.

10.1. Statement of the Null and Alternate Hypotheses

The null and alternate hypotheses are read as follows:

1. H_o: active treatment does not have a differential effect on the primary assessment of mortality risk (OS HR). The null hypothesis presumes that no statistically significant difference in overall survival (OS) between two groups of subjects (investigational drug and placebo-controlled) is observed in the study.
2. H_A: active treatment does have a differential effect on the primary assessment of mortality risk (OS HR). The alternate hypothesis presumes that there is a statistically significant difference in overall survival (OS) between two groups of subjects (investigational drug and placebo-controlled).

CCI [redacted]

10.3. Multiple Comparisons and Multiplicity

To account for the multiplicity of the primary efficacy endpoint comparisons (one interim and one final analysis), the Lan-DeMets alpha-spending approach will be used with O'Brien-Fleming stopping boundaries to guide the efficacy evaluation at the interim and final OS analysis (see Section 12 for details).

All secondary endpoints comparisons will be made at the 2-sided 0.05 significance level. Since PFS is the only key secondary endpoint for regulatory registration purposes, no further multiplicity adjustments will be made. Assuming that OS demonstrates significance, the same criteria will be used for the analysis of PFS.

10.4. Analysis of the Primary Efficacy Endpoint

10.4.1. Primary Efficacy Analysis

OS in the ITT population will be compared between the 2 treatment groups (ITT population) using the stratified log-rank test (based on PROC LIFETEST, CCI [redacted]. One- and 2-sided p-values will be presented. The study will be declared to have met its primary objective if the 1-sided p-value is be less than 0.0215 (please refer to Section 12 for more details). The estimate of the hazard ratio (HR) and corresponding 95% CI will be provided using a Cox proportional hazards (CPH) model including treatment and the 3 stratifications factors in the model. Survival for each arm will be summarized using Kaplan Meier curves and further characterized in terms of the median and survival probability at 3, 6, 9 and 12 months, along with the corresponding 2-sided 95% CI for the estimates. The stratification factors will be populated as per the IXRS assignment.

Confidence intervals for median survival are based upon the methods of Brookmeyer and Crowley [16]. Confidence intervals for survivorship estimates are calculated using the log-log transformation [17] where the estimated variance of $\log(-\log(\hat{S}(t))$ is:

$$\tau^2(t) = \sigma^2[\hat{S}(t)] / [\hat{S}(t)\log(\hat{S}(t))]^2 .$$

The 100 x (1-α)% confidence interval for $S(t)$ is given by:

$$[\hat{S}(t)]^{\exp(z_{\alpha/2}\tau(t))} \leq S(t) \leq [\hat{S}(t)]^{\exp(-z_{\alpha/2}\tau(t))}$$

CCI

[redacted]

10.4.2.1. Tests

The unstratified log-rank test and a CPH model (only treatment effect included in the model).

10.4.2.2. Potential Prognostic/Predictive Factors

Multivariate analysis using the CPH model, including the 3 stratification factors (as per IXRS) and potential prognostic/predictive factors: age group 1 (<65, ≥65 years), race group (White, Asian, Other), gender, number of prior regimens (≤2, 3+), prior therapy (taxane yes or no, irinotecan yes or no), previous gastrectomy, gastroesophageal (GE) junction involvement, presence of peritoneal metastases, presence of liver metastases, presence of lung metastases, number of metastatic sites (1-2, 3+), time from confirmed metastases to randomization , measurable disease (yes, no), histology subtype (diffuse, intestinal), and HER2 status at the baseline.

10.4.2.2.1. Selection Process

Factors included in the model (please refer to Section 10.4.2.2) will be assessed for co-linearity and a stepwise selection process will be applied to identify a final subset of prognostic/predictive factors in the model. Once the subset has been established (retaining factors significant at the 10% level), treatment will be added to the final model to assess its effect in the presence of the identified covariates.

CCI

[redacted]

CCI [redacted]

10.4.3. Key Secondary Efficacy Analysis

PFS will be analyzed with the methodology specified in Section 10.4.1, Section 10.4.2.1 Section 10.4.2.2.1, and Section 10.4.2.2.2. Comparisons will be made at the 2-sided 0.05 significance level. In line with FDA guidance (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics) CCI [redacted] The list of other planned examinations reads as follows:

- Analysis that includes clinical progression as a PFS event in addition to the presence of radiological evidence of progression.
- Analysis including clinical progression as a PFS event that also counts initiation of non-study antitumor therapy as an event date rather than as date used to sensor subsequent response assessment.
- Analysis that includes all deaths and response assessments (without censoring missed visits) and counts as an event any one of the following list: radiological evidence of progression, clinical progression, initiation of non-study antitumor therapy, and death through the date of cut-off for survival.
- Analysis of time to first, second and third radiological tumor assessments from the date of randomization (Kaplan-Meier curves of times will be depicted and the corresponding supporting tables will be created; log-rank test will be applied for examination and comparison of the two groups).
- Analysis described above will also be run excluding high accrual (>25 patients) CCI [redacted]

10.4.4. Other Secondary Efficacy Analysis

All other secondary endpoints comparisons will be made at the 2-sided 0.05 significance level.

10.4.4.1. ORR

Overall response rate (ORR) is defined as the proportion of patients with objective evidence of CR or PR. The treatment comparison for ORR will be based on the TR population using Fisher's exact test in the subset of patients in the Intent-to-treat population with measurable disease at baseline (TR population). Treatment estimates and differences will be presented along with the associated 2-sided 95% CIs constructed using the Clopper-Pearson approximation to the exact binomial proportion [17] for individual estimates within group; and the normal approximation for the difference between groups.

10.4.4.2. DCR

Disease control rate (DCR) will be analyzed using the same methodology as that for ORR.

10.4.4.3. Time to Deterioration of ECOG Performance Status

Time to deterioration of ECOG performance status to a score of 2 or higher will be analyzed using methodology described in Section 10.4.1. Patients not reaching an ECOG of 2 or more (3, 4 or 5) will be censored at the last recorded ECOG assessment. CCI [redacted]

Assignment of the ECOG Performance Status results to the appropriate cycle will be executed according to the instructions displayed in CCI [redacted] Additionally, if multiple ECOG status outcomes are reported at an analysis time window (refer to Section 8.7 CCI [redacted]), then the logic described in Section 8.8 and specific data handling rules presented in CCI [redacted] will be applied.

10.4.4.4. Quality of Life

Analysis of the EORTC QLQ-30 and QLQ-STO22 questionnaire should follow the instructions described in the manual created by the developers of the questionnaire. The manual SCManualQLQ-C30 can be found on the EORTC site http://www.eortc.be/qol/files. Note that the document contains SAS programs for correct calculation of scoring.

The QLQ-30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. The QLQ-STO22 is composed of 5 multi-item scales and 4 single-item measures.

Assignment of the QoL test to the appropriate cycle will be performed according to the instructions displayed in CCI [redacted]. Additionally, if multiple QoL tests are reported at an analysis time window (refer to Section 8.7 CCI [redacted]), then the logic described in Section 8.8 and specific data handling rules presented in CCI [redacted] will be applied.

10.4.4.4.1. Compliance

Questionnaire compliance rates (for all measures - both multi-item scales and single-item ones), will be assessed at each measurement time point (baseline, prior to cycle 2, 3, 4, etc.) and presented as a separate table.

10.4.4.4.2. Missing Values

If at least half of the items in multi-item scale is not missing, the standard instructions described in aforementioned manual will be applied for calculation of the scale scores and any item with missing value will be ignored when the calculations is performed. If less than half of the items in multi-item scale is not missing than the scale score will be set to missing. If the item is missing in the single-item measure, than the score of this measure will be set to missing.

10.4.4.4.3. Internal Consistency and Reliability

Internal reliability and consistency of the multi-item scales (five in QLQ-30 and five in QLQ-STO22) will be assessed using Cronbach's alpha approaches and the results will be presented in the separate table.

10.4.4.4.4. Analysis – Descriptive Statistics

Descriptive statistics (for all measures - both multi-item scales and single-item ones) for the summary scores, will be provided for each assessed time point. The statistics will include number of subjects, number of non-missing/missing scales, mean, standard deviation, median, minimum

and maximum. The results will be summarized for the actual and change from baseline values for all available scales and study visit time points.

10.4.4.4.5. Deterioration vs Stable Proportion

For each EORTC QLQ-C30 and QLQ-STO22 score, deterioration in QoL will be defined as a decrease in the score from baseline level of at least five points, the threshold proposed by Osoba et al. [21] as a small but meaningful change in QoL. For each EORTC QLQ-30 and QLQ-STO22 measure, the proportion of patients with deteriorating and (stable or improving) scores at weeks 4, 8 and 12 will be compared using Fisher's exact test. The results will be summarized as a separate table.

10.4.4.4.6. Time to Deterioration – Main Analysis

Time to first deterioration in QoL (refer to Section 10.4.4.4.5 for definition) will be evaluated for each arm using Kaplan-Meier estimates and compared using the log-rank test (and Cox proportional hazards models adjusting for the baseline value of the EORTC QLQ-C30 and QLQ-STO22 score, country and primary tumour type). Patients with no deterioration in EORTC QLQ-C30 and QLQ-STO22 scores will be censored at the end of study, cut-off date or death date.

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11. SAFETY ANALYSES

This Section contains instructions how the analysis of the safety aspects of the collected data will be performed and presented. As a general rule (unless otherwise is stated) efficacy analysis will use values of stratification factors collected on CRF pages.

11.1. Adverse Events

11.1.1. Definition of Adverse Event

An ***adverse event*** (AE) is defined as any untoward medical occurrence in a clinical investigation of a patient that may or may not have casual relationship with treatment (21 CFR 312.32(a)). An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the clinical study, independent of the relationship to the investigational product.

Any AE that started after signing of informed consent and before treatment start date will be presented in the Medical History section of the summary tables.

Any adverse event starting more than 30 days after the last dose of study medication will be excluded from the summary analyses, unless the event caused patient discontinuation from the study.

11.1.2. Definition of Treatment Emergent Adverse Event

Treatment-emergent adverse events (TEAE) will be defined as those events, which meet one of the two criteria:

- started on or after treatment start date (first dose of study medication ⇔ Cycle1, Day 1) through 30 days after treatment end date (last dose of study medication)
- started before treatment start date and became worse (more severe) after treatment start date (first dose of study medication ⇔ Cycle1, Day 1) through 30 days after treatment end date (last dose of study medication)

Only treatment-emergent adverse events will be summarized, non-treatment emergent AE will be listed only.

11.1.3. Definition of Serious Adverse Event

SAE, as per FDA regulations defined in 21 CFR 312.32(a), is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant /incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may or may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

If either the Sponsor or Investigator believes that the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting (21 CFR 312.32(a) and 312.32(c)(1)).

11.1.4. Definition of Treatment Emergent Adverse Event of Special Interest

The TEAEs of special interest (TEAESI) will be selected based on the list of appropriate MedDRA terms provided by the Sponsor. The TEAESI will include the following items: Gastrointestinal (nausea, vomiting and diarrhea), Hematologic Impairment-Related adverse events. The full list will be provided before the study is unblinded. The lists of terms (PTs) will be located in Appendices ().

11.2. Summaries of Adverse Event

All adverse event verbatim text will be coded and classified by system organ class (SOC) and preferred term (PT) using the MedDRA (Version 20.1). AE summary tables will use the following algorithms for counting subject events within the summary tables:

- Preferred term rows: Each subject is counted once within each unique preferred term at the maximum grade. Subjects experiencing the same AE preferred term several times with different grades would only be counted once with the maximum grade.
- System organ class rows: Each subject is counted only once in the maximum grade at each system organ class level, although they may have several different preferred term events within the same SOC.
- Any event row: Each subject with an event is counted only once at the maximum grade although they may have several events. For drug related AE table, each subject with an event is counted only once at the most related although they may have several events.

Unless specified otherwise, the summaries of adverse events will be based on the safety population.

TEAEs will be presented in alphabetical order of System Organ Class and within each System Organ Class, in decreasing order of the total number of combined TAS-102 patients who experienced each TEAE at the preferred term level.

11.2.1. Overview and Summaries of Adverse Events

AE incidence will be calculated by the worst CTCAE grade at every level of summarization (SOC or PT), i.e., if a patient has multiple occurrences of the same AE with different toxicity grades during a period, the patient will be accounted for in AE frequency tabulation in the worst grade. An overall summary table (overview) of all adverse events will be presented, summarizing:

- Total number of TEAE
- Total number of Serious TEAE
- Total number of TEAESI
- Total number and percentage of subjects with at least one TEAE
- Total number and percentage of subjects with at least one Serious TEAE
- Total number and percentage of subjects with at least one related TEAE
- Total number and percentage of subjects with at least one related Serious TEAE
- Total number and percentage of subjects with at least one severe (Grades 3 - 5) TEAE
- Total number and percentage of subjects with at least one TEAE leading to dose modification
- Total number and percentage of subjects with at least one TEAE leading to dose reduction
- Total number and percentage of subjects with at least one TEAE leading to discontinuation of the study treatment
- Total number and percentage of subjects with at least one TEAE leading to death
- Total number and percentage of subjects with at least one TEAESI

The primary AE summary will also be all TEAE by SOC and PT regard to the relationship to study medication (AT population CCI).

In addition to the overview table, a number of the summaries will be created. The primary AE summary will tabulate all TEAE by SOC and PT (AT population CCI - Section 4.1). Other summaries will present various aspects of collected AE. Calculations in the tables will follow the basic principles of counting described in the beginning of Section 11.2. The following summaries will be created:

- TEAE (all and grades 3-5) summarized by SOC and PT, by treatment group (AT population CCI)
- TEAEs (all and grades 3-5) related to study drug summarized by SOC and PT, by treatment group (AT population CCI)
- TEAE summarized by SOC and PT, by CTCAE grades, by treatment group (AT population)
- TEAE (all and grades 3-5) summarized by PT in descending order, by treatment group (AT population)
- TEAE (all and grades 3-5) related to study drug summarized by PT in descending order, by treatment group (AT population)
- TEAE (all and grades 3-5) leading to dose modification summarized by SOC and PT, by treatment group (AT population)

- TEAE (all and grades 3-5) leading to dose reduction summarized by SOC and PT, by treatment group (AT population)
- TEAE (all and grades 3-5) leading to treatment discontinuation summarized by SOC and PT, by treatment group (AT population)
- TEAE (all and grades 3-5) leading to death summarized by SOC and PT, by treatment group (AT population)
- TEAE of Special Interest (all and grades 3-5) summarized by SOC and PT, by treatment group (AT population CCI)
- Incidence rate (per 100 patient years) of all TEAESIs (summarizing the incidence rate (per patient year) for each SOC and PT as per description in Section 8.9.)
- Serious TEAE (all and grades 3-5) summarized by SOC and PT, by treatment group (AT population CCI)
- Serious TEAE (all and grades 3-5) related to study drug summarized by SOC and PT, by treatment group (AT population CCI)
- Serious non-treatment emergent AE (all and grades 3-5) summarized by SOC and PT, by treatment group (AT population)
- Selected adverse events and lab abnormalities of special interest (the exact list will be determined prior to study unblinding) will be presented in the graphical form ("forest plot" format). Figure will include the relative risk and associated 95% asymptotic confidence intervals

11.2.3. Missing and Partial AE Onset Dates

The start/onset dates for AEs are important for the:

1. Treatment emergent algorithm.
2. Designation of unique AE occurrences.

Completely missing or partially missing AE onset dates will be queried and every reasonable effort will be made to resolve the issue and to obtain accurate AE information from site, investigator or any other trustful source. Once all attempts of this kind has failed, the missing or partially missing AE onset date will be imputed.

The following algorithm should be used to impute adverse event start dates for which only partial information is available.

1. If onset date is completely missing or the year of the end date is missing:
    a. Set onset date to the date of the first treatment if the end date of the AE (if available) remains sensible after imputation (i.e., imputed start date precedes end date).
    b. Set onset date to the 1st of January of the same year as the end date is if the end date of the AE (if available) presumes that the AE ended before the first treatment of the study.
2. If (year is present and month and day are missing) or (year and day are present and month is missing):
    a. If year = year of the first dose, then set month and day to month and day of first dose.
    b. If year ≠ year of the first dose, then set month and day to January 1st.
3. If month and year are present and day is missing:
    a. If year and month = year and month of first dose, then set month and day to month and day of first dose.
    b. If year and month ≠ year and month of first dose, then impute the first day of the available month.

Imputed dates will be flagged in the individual supportive subject listings.

11.3. Pregnancy

On study pregnancy, if any, will be reported in a data listing.

11.4. Overdose

All occurrences of overdosing (accidental or intentional; regardless of whether it is associated with an AE) will be reported in a data listing.

11.5. Concomitant Medications and Anticancer Therapies

All medications will be coded using the World Health Organization Drug dictionary (WHO-DD) version SEPT2015. The therapeutic class will correspond to the second level of Anatomical Therapeutic Chemical (ATC) code corresponding to the first 3 figures.

Concomitant medications, prescribed and over the counter, that the subject takes or continues to take after the date of signed Informed Consent Form will be summarized in the table. The data will be presented by treatment group and for all treated subjects. The same subject counting procedures will also apply (e.g., major class frequencies will represent subjects only once even though the same subject can be counted for multiple minor sub-classes and generic names).

The supportive individual subject data listing will be organized displaying trade and generic drug names, start and stop dates, days relative to the start of therapy, dose, frequency, route, and indication(s).

Medications will be coded using the WHO Drug Reference List Version 2015: Q1 or higher. Prior and concomitant medications will be tabulated separately according to ATC Level III and preferred name. Chemotherapies will be further summarized according to the "regimen" (combination of individual chemotherapy medications administered in a regimen irrespective of dose, route of administration or dosing schedule). The number and percent of patients receiving granulocyte colony stimulating factor (G-CSF) will be tabulated by cycle.

11.6. Clinical Laboratory Data

All laboratory values will be converted to SI units and classified as normal, low, or high based on normal ranges (converted to SI units if needed) supplied by the laboratory performed the test. Laboratory categories will be expressed in terms of the L (below LLN), N (between LLN and ULN) and H (above ULN) classifications for numerical measurements and normal, abnormal for characteristic measurements. Additionally, abnormal laboratory values will be presented according to the NCI CTCAE v4.3 laboratory toxicity grades. All laboratory data will be coded with CTCAE grade, where CTCAE grading is available. Local laboratory ranges will be used for grading. In the event a range is not available a standard set of lab ranges as detailed in CCI [redacted] will be utilized and flagged in the database.

Tables of descriptive statistics for hematology, biochemistry and urinalysis will be presented. Summary statistics (descriptive statistics) for quantitative laboratory parameters will include number of subjects, mean, standard deviation, median, minimum and maximum. Continuous parameters will be summarized for the actual and change from baseline values for all available parameters and study visit time points. Categorical results will be represented by shift tables (by visit) for the tests where NCI CTCAE grading is not available.

Changes in the NCI CTCAE grade from baseline to the worst grade recorded post-baseline will be tabulated in the form of shift tables. Applicable bi-directional laboratory tests will be represented as one artificial one-directional tests, where hypo- part (below the LLN) will be assigned with negative signs and hyper- part (above the ULN) will continue to keep positive values. Therefore, valid grades for this artificial test will cover span from -4 to +4, where Grade 0 will correspond to

the values lying within the normal range. The definition of hypo- and hyper-toxicity grades follows the definition provided by the NCI CTCAE v4.3 definition document. Laboratory tables with CTCAE grading will only be produced for laboratory parameters for which CTCAE grading is available. An overall shift summary will also be provided comparing baseline to worst post-dose toxicity observed across all visits.

The number and percentage of patients with laboratory abnormalities of Grade 3 or Grade 4 that worsened from baseline by ≥ 1 grade or are missing at baseline will be summarized. For patients with more than 1 value recorded in a cycle/group of cycles, the abnormality with the highest grade will be selected for tabulation.

Time to event/worst grading will be assessed for selected clinical tests (hemoglobin, neutrophils, platelets) were CTCAE grading is available. The time to event/worst grading is defined as time from the date of the first dose of study medication to the date of the first occurrence of worth post-baseline CTCAE grade. If multiple events of the same worst grading occur, the earliest occurrence will be used. If no abnormal post-baseline values were recorded, the time to event/worst grading will be censored.
Presentation of the time to event/worst grading will be based on the Kaplan-Meier product-limit method is applied to estimate the mean, standard deviation, median, 25% percentile, and 75% percentile of the time to event/worst grading.

All observed (including unscheduled) laboratory parameters will be listed. The supportive listings for hematology, serum chemistry, and urinalysis will include the subject number, subject age and sex; laboratory test, lab test units, lab test result, and the lower and upper limits of normal (provided by the local laboratory where the test was performed); sample collection date, time of collection, and relative day; type of visit. The listing will be sorted by laboratory parameter, subject number, and by time points within laboratory parameter and subject number. Abnormal results will be flagged based on the categories mentioned above.

Specific rules how to handle clinical laboratory data can be found in the .

11.6.1. Hematology

The following test will be summarized and tabulated, all other hematology tests will be listed only:

Red blood cells count (RBC)	White Blood Cells (WBC)	
Hemoglobin	Neutrophils (absolute value)	Neutrophils (%)
Hematocrit	Lymphocytes (absolute value)	Lymphocytes (%)
Platelets	Monocytes (absolute value)	Monocytes (%)
	Eosinophils (absolute value)	Eosinophils (%)
	Basophils (absolute value)	Basophils (%)

The "most extreme value" recorded, and the corresponding number of days to the most extreme value recorded, will be summarized descriptively for Grade 3 or 4 abnormalities. This will be limited to the following selected "parameters of interest": hemoglobin, neutrophils and platelets for the "most extreme" is defined as the value of smallest magnitude. Additional parameters may be added to this analysis as appropriate.

The median number of days to 'recovery' (Section 8.10) in patients with Grade 3 or 4 abnormalities that worsened from baseline will be obtained from Kaplan-Meier estimates.

Shift tables showing changes in the NCI CTCAE grade from baseline to the worst grade recorded post-baseline are tabulated. Parameters with NCI CTCAE criteria defined bi-directionally have low value abnormalities represented by a negative sign so that they may be differentiated from high value abnormalities. If the NCI CTCAE criteria are uni-directional the negative sign is not used even if the criteria are defined to flag low value abnormalities.

The rate per 100 patient years (see Section 8.9 for the appropriate details) of Grade 3 or 4 abnormalities in hemoglobin (low), neutrophils, and platelets, along with the corresponding 95% Poisson CIs, will be summarized.

11.6.2. Serum Chemistry

The following test will be summarized and tabulated, all other serum chemistry tests will be listed only:

ALT (SGPT)	Creatinine	Chloride
AST (SGOT)	Blood urea nitrogen (BUN)	Calcium
Alkaline phosphatase	Sodium	Albumin
Bilirubin	Potassium	Glucose

In case of elevation in total bilirubin, fractionation (direct/indirect) should be performed and listed.

11.6.3. Urinalysis

Urinalysis will include tests for protein, glucose, urobilinogen, RBC, and WBC. If a new abnormality is identified during the Study, quantitative urinalysis should be performed.

CCI [redacted]

11.7. Vital Signs

Vital signs (VS) will include: systolic/diastolic blood pressure, body temperature, heart rate, respiratory rate and weight. To integrate VS evaluations with different collection times, they will be summarized by analysis visit cycles as specified at Section 4.1.2.

The presentation of VS results will focus on the change from baseline to post-dose on treatment evaluations. All patients who had a baseline and at least one post-dose on-treatment VS assessment will be included in the presentation of the VS data. If multiple results are reported at an analysis time window (refer to Section 8.7 and CCI), then the logic described in Section 8.8 and specific data handling rules presented in CCI will be applied. Tables of descriptive statistics for vital signs will present both actual values and change from baseline values. Summary statistics will include number of subjects, mean, standard deviation, median, minimum and maximum.

11.8. ECG

ECG data were not collected.

11.9. Physical Examination

According to the recent updates in CDISC "Guide for implementation" the results of physical examination (abnormalities only) are collected as part of adverse events or medical history (based on the appropriate dates and time). Therefore, results of the physical examination will be not summarized as separate tables.

12. INTERIM ANALYSES

One interim analysis for efficacy and futility is planned for the study after approximately 1/2 of the total target events are observed (192 deaths). The Lan-DeMets alpha-spending approach will be used with O'Brien-Fleming stopping boundaries to guide the efficacy evaluation at the interim and final OS analysis. This approach will account for multiple testing and preserve the overall 1-sided study significance level of 0.025. A fixed HR boundary will be used to assess futility (non-binding). Stop due to futility will be recommended if observed HR will be $\geqslant$ 0.95 when conditional power is less than 2%. Stopping the study for efficacy will be recommended if calculated 1-sided p-value is less than 0.0015. The corresponding HR for such significant results is less than approximately 0.63, associated with a median OS improvement from 5 to 7.9 months. The exact boundaries will be derived based on the actual number of events used for the interim analysis.
For the final analysis of the primary efficacy endpoint the result will be considered as significant if 1-sided p-value will be less than 0.0245. The corresponding HR for such significant result is less than approximately 0.808 associated with a median OS improvement from 5 to 8 months).
Additional details are provided in the DMC charter.

The interim analysis was performed based on 220 events (deaths) reported as of August 31, 2017. The associated efficacy boundary suggested to the DMC was 1-sided p-value of 0.0031. CCI [redacted]
Considering the alpha-spending that took place for the interim analysis the associated efficacy boundary for the final analysis (assuming 384 events as planned) is 1-sided p-value of 0.0215.

13. DATA MONITORING COMMITTEE

A DMC is established for this study to provide additional, independent oversight that can enhance safety of study participants and the study conduct. The DMC comprises of clinicians and a statistician, all independent from the Sponsor and investigative sites and selected as to avoid conflict of interest.

The primary objectives of this DMC are to provide independent safety monitoring comparing safety between the study groups and to provide a recommendation based on the planned interim analysis.

A DMC charter has been written to establish well-defined standard operating procedures including meeting proceedings and structure, data assessments, documentation and record keeping, process for DMC recommendations, and regulatory reporting as applicable. The charter is written as a separate stand alone document and contains procedures ensuring the minimization of bias, such as maintaining confidentiality of any interim data.

14. CHANGES IN/ CLARIFICATIONS TO THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

Since the version 1.05 of the SAP (06JULUL2016) was approved, the following clarifications/changes were made in the text of the SAP:

- Reference date for age calculation was changed from randomization date to the date of informed consent (Section 8.1).
- Definitions for Cycle windows (Section 8.7) and handling of Multiple Assessments (Section 8.8) were further detailed and documented in SAP CCI ("Data Handling Guidance").
- Time Adjusted Incidence Rate calculations were revised from 1 year to 100 years (Section 8.9).
- Creatinine Clearance levels for the severe renal function impairment group were added to the definition (Section 8.11).
- Imputation rules for partial birth dates, missing end of exposure dates, and start of antitumor therapy dates were added (Section 8.13)
- Definitions of CSR Reportable Protocol Deviations were added to the existing Major Protocol Deviations (Section 9.2).
- Part of the demographic and baseline characteristics summaries was relocated under cancer medical history (Section 9.3 and Section 9.5.1).
- Details of how the prior cancer medical history are summarized were updated (Section 9.5.1).
- Details of how the prior anti-cancer therapies are summarized were updated (Section 9.6.1).
- Medical history will be summarized for AT, instead of the ITT population (Section 9.5).

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- SAS code for the primary efficacy analysis was documented CCI

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CCI

- List of TEAE summaries was updated (Section 11.2.1).
- The efficacy boundary (p-value) for the final analysis was derived, based on the actual event count used for the interim analysis (Section 12).
- A Data Handling Guidance appendix was added CCI that further details data handling rules for safety endpoints.
- PFS Censoring rules were updated CCI
- Standard lab ranges were updated to include the normal range for Indirect Bilirubin CCI .
- Date for the clinical cut-off was established and rules for submission database were added CCI

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