STATISTICAL ANALYSIS PLAN

Trial Sponsor:	Taiho Oncology, Inc. (TOI) and Taiho Pharmaceutical Co. Ltd. (TPC)
Protocol Number:	TO-TAS-114-201
IND Number:	CCI [redacted]
EUDRACT Number:	2016-001806-40
Investigational Drug:	TAS-114/S-1
Indication:	Advanced or metastatic non-small cell lung cancer
Drug Number:	N/A
Dosage Form/Strength:	Tablets (TAS-114) / Capsules (S-1)

Protocol Title: A Randomized, Open-Label, Multi-Center, International Phase 2 Study of TAS-114 in Combination with S-1 in Patients with Advanced or Metastatic Non-Small Cell Lung Cancer

Last Revision Date:	29NOV2017
Final Sign-off Date:	29NOV2017
Archive Date:	

FIRST SIGN-OFF SIGNATURES

Study Biostatistician:

PPD

Study Biostatistician PPD

PPD

Signature PPD **Date**

Peer Review Biostatistician:

PPD

Sign PPD **Date**

Approved by:

PPD PPD

Taiho Oncology, Inc.

PPD PPD

Signature **Date**

Approved by:

PPD PPD

PPD

Taiho Oncology, Inc.

PPD PPD

Signature PPD **Date** PPD

PPD

CHANGE LOG FOR CHANGES MADE AFTER THE INITIAL APPROVAL

Revision Date**	Section(s) Modified	Brief Description of Revision(s) or Reason(s) for Revision	Modifications Reviewed and Approved by*
			Sponsor, Everest

* Provide person's initial and last name.
** Update the Last Revision Dates on the cover page and the document header.

TABLE OF CONTENTS

GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
5-FU	5-fluorouracil
AE	Adverse event
ALK	Anaplastic lymphoma kinase
AT	As-treated
BID	Twice daily
BSA	Body surface area
CI	Confidence interval
CPH	Cox proportional hazards
CR	Complete Response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DPD	Dihydropyrimidine dehydrogenase
DR	Duration of response
dUTPase	Deoxyuridine triphosphatase
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
HR	Hazard ratio
ICF	Informed consent form
ITT	Intent-to-treat
IU	International Units
IXRS	Interactive voice/web response system
MedDRA	Medical Dictionary For Regulatory Activities
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
OPRT	Orotate phosphoribosyltransferase

GLOSSARY OF ABBREVIATIONS

ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
CCI	[redacted]
PR	Partial response
QA	Quality assurance
QC	Quality control
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SI	International System (of Units)
TR	Tumor response
WHO	World Health Organization
WHO-DDE	World Health Organization - Drug Dictionary Enhanced
WHO-HD	World Health Organization - Herbal Dictionary

1. INTRODUCTION

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide (Siegel et al, 2016). Despite treatment with immunotherapy, platinum- and taxane-based chemotherapy, patients with refractory metastatic NSCLC have a median survival of approximately 8 to 10 months. Moreover, there has been little overall survival improvement from several new agents, including pemetrexed, erlotinib and bevacizumab beyond very small subpopulations. Therefore, the majority of NSCLC cases remain a disease with high burden and unmet medical need.

Chemotherapy regimens containing 5-FU drugs as the backbone are mainstays for the treatment of many cancers including breast, colorectal, and gastric cancer. Many combination chemotherapies employing 5-FU with chemical modulators have been investigated and have demonstrated efficacy against a variety of carcinomas to date (Longley et al, 2003). Oral fluoropyrimidines such as S-1, a fixed dose combination of tegafur, a prodrug of 5-FU, gimeracil, a dihydropyrimidine dehydrogenase (DPD) inhibitor that prevents degradation of 5-FU by the body and maintains 5-FU exposure, and oteracil potassium, an orotate phosphoribosyltransferase (OPRT) inhibitor that decreases the activity of 5-FU in normal gastrointestinal mucosa have been developed (Shirasaka et al, 2009). However, chemotherapies using 5-FU or S-1 can cause intrinsic and acquired resistance to the 5-FU drugs. Studies indicate that deoxyuridine triphosphatase (dUTPase) may be one of the causal factors for resistance to 5-FU-based chemotherapies (Wilson et al, 2012). Therefore, the development of new drugs that can be expected to achieve higher efficacy than the existing 5-FU drugs is urgently required.

TAS-114 is a modulator of 5-fluorouracil (5-FU), and can enhance antitumor activity of 5-FU. S-1 is an oral fluoropyrimidine that combines tegafur (5-fluoro-1-(tetrahydro-2-furyl) uracil, FT), a prodrug of 5-FU. Based on non-clinical pharmacology and toxicology models, the combination of TAS-114 with S-1 has demonstrated a potential to enhance the antitumor activity of S-1 with acceptable changes in its toxicity profile.

See Protocol Section 6 for details.

2. STUDY OBJECTIVES

2.1 Primary Objective

- To compare progression-free survival (PFS) of patients with advanced or metastatic NSCLC, when treated with TAS-114/S-1 combination versus S-1.

2.2 Secondary Objectives

- To investigate the overall survival (OS), overall response rate (ORR), disease control rate (DCR), and duration of response (DR).
- To investigate the safety and tolerability.

CCI [redacted]

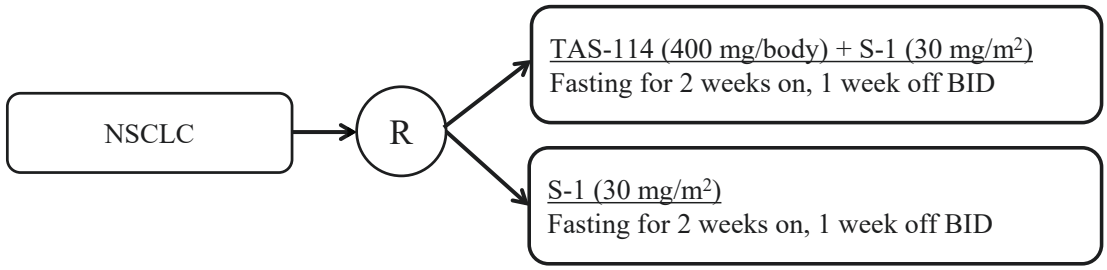
3. STUDY DESIGN

3.1 Study Design

This is a randomized, open-label, Phase 2 study of TAS-114 administered in combination with S-1, to investigate the efficacy, safety, and tolerability of the TAS-114/S-1 regimen in patients with advanced or metastatic NSCLC.

The study will be conducted internationally in 2 regions: Asian (Japan) and Western (Europe and US). Patients will be randomized to TAS-114/S-1 arm versus S-1 control arm in a 1:1 ratio. The overall study design is described in Figure 1.

Figure 1 Study Schema



Stratification factors:

1. Geographical: Region 1: Asian (Japan); Region 2: Western (Europe and US)
2. Histological subtypes: non-squamous (including mixed); squamous

R = Randomization

3.2 Randomization

Randomization will take place once the consented patient has completed all the necessary baseline procedures and is deemed eligible for study entry. Treatment assignment will be done centrally using a dynamic allocation method (biased coin) via an interactive voice/web response system (IXRS) stratified by:

- Geographical region (Region 1: Asian [Japan]; Region 2: Western [Europe and US])
- Histological subtypes (nonsquamous cell carcinoma [including mixed] and squamous cell carcinoma)

3.3 Hypothesis Testing

The null and alternative hypotheses regarding PFS can be phrased in terms of the hazard ratio function, $\lambda_{Group\ A} / \lambda_{Group\ B}$, where $\lambda_{Group\ A}$ represents the hazard function of progression/death for patients in the Group A (TAS-114/S-1 arm) and $\lambda_{Group\ B}$ represents the hazard function of progression/death for patients in Group B (S-1 arm). A hazard ratio < 1 indicates that PFS is prolonged for patients in Group A compared with those patients in Group B. The null (H_0) and alternative (H_a) hypotheses, respectively, can be written as follows:

H_0: $\lambda_{Group\ A} / \lambda_{Group\ B} = 1$

H_a: $\lambda_{Group\ A} / \lambda_{Group\ B} < 1$.

The hazard ratio (HR) and the corresponding 95% confidence interval (CI) and p-value (based on a one-sided stratified log-rank test at the 0.05 significance level) will be estimated using a Cox proportional hazards model stratified by geographic region and histological subtypes.

If the results from the log-rank test lead to the rejection of H_0 in favor of H_a, it will be concluded that the TAS-114/S-1 arm is associated with longer PFS than patients in the S-1 control arm.

3.4 Interim Analysis

No formal interim analysis is planned with respect to stopping the trial early or for lack of efficacy purposes.

3.5 Sample Size

The planned sample size is approximately 124 advanced or metastatic NSCLC patients. The study is designed to differentiate 4.2 months median PFS of treatment with TAS-114/S-1 from 2.2 months median PFS of treatment with S-1 (hazard ratio of 0.524) with 80% statistical power and a 1-sided type 1 error of 0.05. Using a treatment allocation of 1:1 (TAS-114/S-1: S-1), a target of 60 events (PD or deaths) will be required for the primary analysis, which corresponds to 71 events based on investigator review under the assumption that the discrepancy in PD events between the independent central review and investigator review is 15%. A total sample size of 124 patients is planned from the assumption that accrual period is 10 months, the percentage of PFS events is 65%, and the percentage of patients lost to tumor follow-up caused by study discontinuation is 10%.

3.6 Study Procedures

The following study procedures will be performed during the study:

- Informed consent
- Medical history

- Physical examination
- Height, vital signs, and weight
- Performance status
- Electrocardiogram
- Clinical laboratory evaluations
- Pregnancy test
- [redacted]
- Prior and concomitant medications (therapies)
- Adverse event assessment
- Tumor assessments/scans
- 30-day safety follow-up

3.7 Schedule of Assessments

Table 1 Study Schedule of TAS-114 and S-1 Arm

	Baseline		On-Treatment						End of Treatment/Study		
	Baseline Day		Cycle 1 (Day of Cycle)			Subsequent Cycles (Day of Cycle)			End of Treatment[i)]	30-Day Safety Follow-up Visit[ii)]	Survival Follow-up
Visit ID/Procedure	**-28 to -1**	**-7 to 0[iii)]**	**1**	**8**	**15**	**1**	**15**	**End of Recovery**			
Visit Window	**0**	**0**	**-1 to 0**	**± 3**	**± 3**	**-1 to 0**	**± 3**	**± 7**	**± 3**	**-7**	
Sign ICF	X										
Inclusion/Exclusion	X		X								
Assign Patient Number	X[iv)]										
Medical History	X										
Baseline Signs and Symptoms	X	X	X								
Physical Exam[v)]	X	X	X[v)]	X	X	X[v)]			X	X	
Height	X										
Vital Signs/Weight[v)]	X	X				X[v)]			X	X	
Performance Status[v)]	X	X	X			X[v)]			X	X	
ECG	X								X	X	
Hematology[v)]	X	X		X	X	X[v)]	X[v)]		X	X	
Serum Chemistry[v)]	X	X		X	X	X[v)]	X[v)]		X	X	
Coagulation[v)]	X	X		X	X	X[v)]	X[v)]		X	X	
Urinalysis	X	X							X	X	
Pregnancy test [vi)]		X									
Concomitant Medications[vii)]	→	→	→	→	→	→	→	→	→	→	
AE/Toxicity Assessment[vii)]	→	→	→	→	→	→	→	→	→	→	
Tumor Assessment[viii)]	X							X[viii)]	X[viii)]		
TAS-114[ix)]			→	→	→	→	→				
S-1.[x)]			→	→	→	→	→				

CCI [redacted]

	Baseline		On-Treatment						End of Treatment/Study		
	Baseline Day		Cycle 1 (Day of Cycle)			Subsequent Cycles (Day of Cycle)			End of Treatment[i)]	30-Day Safety Follow-up Visit[ii)]	Survival Follow-up
Visit ID/Procedure	-28 to -1	-7 to 0[iii)]	1	8	15	1	15	End of Recovery			
Survival Status[xii)]	→										

Abbreviations: AE = adverse event; BID = twice daily; ECG = electrocardiogram; ICF = informed consent; CCI .

i) End of Treatment: If the decision to discontinue TAS-114/S-1 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 TAS-114 (because of disease progression or other reasons) is made more than 2 weeks after the last treatment visit, an End of Treatment visit is required. See Section 10.4.1 of the protocol.

ii) 30-Day Safety Follow-up Visit: If the patient starts new anticancer therapy within 30 days of the end of treatment, the 30-day Safety Follow-up visit should be performed before the start of new anticancer therapy within the 30-day window. See Section 11.13 of the protocol.

iii) Baseline Assessment (Day -7 to -1) will be obtained within 7 days before treatment on Day 1 of Cycle 1.

iv) Patient Number Assignment: A patient number will be assigned once a patient has entered study screening (ie, has signed the ICF).

v) The physical exam, vital signs determination, weight, performance status, laboratory evaluations (hematology, serum chemistry, and coagulation) will be obtained within 1 day before study drug administration on Day 1 of each cycle. After Cycle 4, the Day 15 laboratory evaluations are not required unless clinically indicated by the investigator. After Cycle 6, the laboratory evaluations can be accepted within 2 days before study drug administration on Day 1 of each cycle, if there are no drug-related AEs greater than Grade 2 observed in the latest cycle.

vi) Pregnancy Test: Pregnancy test is required at Baseline (within 7 days prior to Day 1 of Cycle 1) and at End of Treatment and 30-day Safety Follow-up visit. More frequent pregnancy assessments may be performed as required by local law.

vii) Concomitant medications and AE/toxicity assessments will be collected from the time of signing of the ICF through 30 days after administration of the last dose of study drug.

viii) Tumor assessments/scans will be performed at baseline, at the end of every 6 weeks (± 7 days) beginning at Cycle 2 throughout all the treatment cycles, and at the time of discontinuation. See Section 11.12 of the protocol, Tumor Assessments/Scans for details. Computerized tomography (CT) scans obtained before signing the ICF may be used as the baseline tumor scan if it is within 28 days of the first study drug administration. If the patient has discontinued treatment for reasons other than radiologic disease progression, a CT scan should be performed every 6 weeks (± 1 week) until the patient starts new anticancer therapy visit. Following Cycle 6, CT assessments may be adjusted to every 9 weeks.

ix) TAS-114 administration: orally BID together with S-1 on Days 1 through 14 of each cycle. See Section 9.1.2.1 of the protocol for TAS-114 Dose Levels.

x) S-1 administration: orally BID together with TAS-114 on Days 1 through 14 of each cycle.

CCI [redacted]

xii) Survival Follow-up: Obtain survival status (alive/dead) at scheduled 8-week intervals until death. Survival status should be collected for up to approximately 12 months after the first dose of treatment with TAS-114/S-1 of the last patient enrolled or until the target number of events is reached, whichever occurs first, even if consent for study participation has been withdrawn.

Table 2 Study Schedule of S-1 Arm

	Baseline		On-Treatment						End of Treatment/Study		
	Baseline Days		Cycle 1 (Day of Cycle)			Subsequent Cycles (Day of Cycle)			End of Treatment[i] for S-1	30-Day Safety Follow-up Visit[ii]	Survival Follow-up
Visit ID/Procedure	**-28 to -1**	**-7 to 0[iii]**	**1**	**8**	**15**	**1**	**15**	**End of Recovery**			
Visit Window	**0**	**0**	**-1 to 0**	**± 3**	**± 3**	**-1 to 0**	**± 3**	**± 3**	**± 3**	**-7**	
Sign ICF	X										
Inclusion/Exclusion	X		X								
Assign Patient Number	X[iv]										
Medical History	X										
Baseline Signs and Symptoms	X	X	X								
Physical Exam[v]	X	X	X[v]	X	X	X[v]			X	X	
Height	X										
Vital Signs/Weight[v]	X	X				X[v]			X	X	
Performance Status[v]	X	X	X			X[v]			X	X	
ECG	X								X	X	
Hematology[v]	X	X		X	X	X[v]	X[v]		X	X	
Serum Chemistry[v]	X	X		X	X	X[v]	X[v]		X	X	
Coagulation[v]	X	X		X	X	X[v]	X[v]		X	X	
Urinalysis	X	X							X	X	
Pregnancy test[vi]		X									
Concomitant Medications[vii]	→										
AE/Toxicity Assessment[vii]	→										
Tumor Assessment[viii]	X							X[viii]	X[viii]		
S-1 Treatment[ix]			→			→					
CCI [redacted]											
Survival Status[xi]	→										

Abbreviations: AE = adverse event; BID = twice daily; ECG = electrocardiogram; ICF = informed consent; CCI [redacted].

i) End of Treatment: If the decision to discontinue S-1 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 S-1 (because of disease progression or other reasons) is made more than 2 weeks after the last treatment visit, an End of Treatment visit is required. See Section 10.4.1 of the protocol.

ii) 30-Day Safety Follow-up Visit: If the patient starts new anticancer therapy within 30 days of the end of treatment, the 30-day Safety Follow-up visit should be performed before the start of new anticancer therapy within the 30-day window. See Section 11.13 of the protocol.

iii) Baseline Assessment (Day -7 to -1) will be obtained within 7 days before treatment on Day 1 of Cycle 1.

iv) Patient Number Assignment: A patient number will be assigned once a patient has entered study screening (ie, has signed the ICF).

v) The physical exam, vital signs determination, weight, performance status, laboratory evaluations (hematology, serum chemistry, and coagulation) will be obtained within 1 day before study drug administration on Day 1 of each cycle starting at Cycle 2. After Cycle 4, the Day 15 laboratory evaluations are not required unless clinically indicated by the investigator. After Cycle 6, the laboratory evaluations can be accepted within 2 days before study drug administration on Day 1 of each cycle, if there are no drug-related AEs greater than Grade 2 observed in the latest cycle.

vi) Pregnancy Test: Pregnancy test is required at Baseline (within 7 days prior to Day 1 of Cycle 1) and at End of Treatment and 30-day Safety Follow-up visit. More frequent pregnancy assessments may be performed as required by local law.

vii) Concomitant medications and AE/toxicity assessments will be collected from the time of signing of the ICF through 30 days after administration of the last dose of study medication.

viii) Tumor assessments/scans will be performed at baseline, at the end of every 6 weeks (± 7 days) beginning at Cycle 1 Day 1 throughout all the treatment cycles, and at the time of discontinuation. See Section 11.12 of the protocol, Tumor Assessments/Scans for details. Computerized tomography (CT) scans obtained before signing the ICF may be used as the baseline tumor scan if it is within 28 days of the first study drug administration. If the patient has discontinued treatment for reasons other than radiologic disease progression, a CT scan should be performed within 2 weeks of the End of Treatment visit. Following Cycle 6, CT assessments may be adjusted to every 9 weeks.

ix) S-1 administration: orally BID on Days 1 through 14 of each cycle.

CCI [redacted]

) Survival Follow-up: Obtain survival status (alive/dead) at scheduled 8-week intervals until death. Survival status should be collected for up to approximately 12 months after the first dose of treatment with S-1 of the last patient enrolled or until the target number of events is reached, whichever occurs first, even if consent for study participation has been withdrawn.

4. DATA AND ANALYTICAL QUALITY ASSURANCE

The overall quality assurance procedures for the study data, statistical programming and analyses are described in the Everest's Standard Operating Procedures. Detailed data management procedures are documented in the Data Management Plan, Data Validation Check Specifications, and Data Review Plan. Detailed statistical and programming quality control and quality assurance procedures are documented in the Statistical Analysis and Programming QC/QA Plan.

The study endpoints and analytic approaches are both prospectively defined and documented in the protocol and in this SAP. The SAP will be finalized prior to the database lock.

5. ANALYSIS POPULATIONS

The analysis populations defined in this SAP differ slightly from the populations defined in the protocol in order to adhere to the FDA guidance (ICH E9).

5.1 Intent-to-Treat (ITT) Population

The ITT population is defined as all patients randomized in the study, regardless of whether they actually received any study treatment (TAS-114 or S-1) or not. All analyses using this population will be based on the treatment assigned by IXRS.

5.2 Tumor Response (TR) Evaluable Population

The TR evaluable population includes all patients in the ITT population with measurable disease (at least one target lesion) at baseline and with at least one tumor evaluation (Patients who have disease progression or have a cancer related death prior to their 1st tumor evaluation will also be considered evaluable.) All analyses using this population will be based on the treatment assigned by IXRS.

5.3 As-Treated (AT) Population

The AT population is defined as all patients who received at least 1 dose of TAS-114 or S-1. All analyses using this population will be based on the treatment actually received. This population will be used for safety analyses.

CCI

[redacted]

6. SPECIFICATION OF ENDPOINTS AND VARIABLES

6.1 Demographic and Baseline Characteristics

Demographics, baseline characteristics, cancer history, medical history/active symptoms and prior cancer treatments will be collected at the baseline Day -28 visit; medical history/active symptoms will be confirmed (and updated as needed) at the baseline Day -7 visit and Cycle 1 day 1 visit:

- Demographic variables include age, sex, female reproductive status, race, ethnicity and geographic region. The age will be calculated as the integer part of (date of consent-date of birth)/365.25 for sites that collect date of birth. The age entered on the CRF will be used for sites that do not collect the date of birth.

- Baseline characteristics include height, weight, and ECOG performance status.

- Cancer history includes time from the initial diagnosis to first study drug dose, location of primary tumor, tumor grade, histology subtype, presence of metastases (yes vs. no), EGFR mutation (yes, no vs. unknown), ALK translocation (yes, no vs. unknown), ROS1 rearrangements (yes, no vs. unknown), and other gene abnormality (yes, no vs. unknown). Time from the initial diagnosis to first study drug dose (months) will be calculated as (first treatment dose date -date of original diagnosis) / 30.4375. Time from the metastatic diagnosis to first study drug dose (months) will be calculated will be calculated as (first treatment dose date- date of metastatic diagnosis) / 30.4375. If the day of the initial or metastatic diagnosis is missing, then the missing day will be imputed by the first day of the month for calculation purposes. If the day and month of the initial or metastatic diagnosis are both missing, then the missing day and month will be imputed by January 1st.

- Medical history and active symptoms include diagnosis or symptoms entered on the Medical History and Active Symptoms form. Verbatim descriptions of diagnosis or symptoms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 19.0).

- Prior cancer treatments include medication/surgery entered on the Prior Radiotherapy form, the Prior Surgery form, the Prior Systemic Drug Therapies for Cancer form).

- Prior medication on Concomitant Medications and Therapies form. Prior medication is defined as any medication with start date on or before the first day of study drug (TAS-114 or S-1), or checked to be prior to first study drug administration date, or medication with start date missing.

  Verbatim descriptions of prior medications will be mapped to the World Health Organization (WHO) Drug Dictionary Enhanced (WHO-DDE) and Herbal Dictionary (WHO-HD) (version Q1 2016).

6.2 Efficacy

6.2.1 Primary Efficacy Variables

Progression-free survival (PFS) is defined as the time (in months) from the day of randomization to the start of radiologic disease progression or death (any cause), whichever occurs first: (earlier of: date of first radiologic PD or date of death [all cause] – date of randomization +1)/30.4375.

Progressive disease (PD) events assessed by the central independent review (blinded radiological review) will be used for primary efficacy analysis. Central tumor imaging assessments will be performed using RECIST guidelines (Version 1.1, 2009).

Patients who do not have disease progression or have not died will be censored at the last known time that the patient was progression free (e.g. date of last evaluable tumor assessment) before receiving any new anti-cancer treatment. Patients without disease assessment post-baseline will be censored at the time of the randomization.

Refer to **Table 3** for censoring rules for progression-free survival.

Table 3 – Censoring Rules for Progression-Free Survival

Situation	End Date	Censored
Documented radiological PD	Date of the first tumor assessment that determined PD	No
Death during the study before PD	Date of death	No
Treatment discontinuation for other than radiologic PD or death with no post-baseline tumor assessments	Date of randomization	Yes
Treatment discontinuation for other than radiologic PD or death with post-baseline tumor assessments	Date of last adequate tumor assessment prior to initiation of non-study anti-cancer treatment	Yes
Patients still followed without radiologic PD as of cut-off date	Date of last adequate tumor assessment prior to cut-off date	Yes
Non-study anti-cancer treatment initiated before radiologic PD	Date of last adequate tumor assessment prior to initiation of non-study anti-cancer treatment	Yes
Death or radiologic PD after a missed (or not available/not evaluable) tumor assessment	Date of last adequate tumor assessment prior to **missed** tumor assessment A response assessment is considered "missed" if more than 13 weeks (91 days) has elapsed since the last image-based response assessment. If a patient develops progressive disease or dies after this interval, the tumor response assessment will be excluded from the analysis and censored at the last evaluable assessment. However, if a response assigned as CR, PR, or SD is obtained after more than 13 weeks, then the tumor response assessment will not be excluded from the analysis as long as no other censoring events have occurred. Note: If patient dies within the 13 weeks from the last non-PD tumor assessment, death will be counted as a PFS event	Yes

	unless the non-study anti-cancer treatment is initiated.	
Only non-evaluable (NE) tumor assessments after CR, PR, or SD	Date of last adequate tumor assessment prior to NE tumor assessments	Yes
No baseline tumor assessment	Date of randomization	Yes
General Considerations: Tumor response assessment dates will be assigned based on the date the image was performed, not the date the image was assessed.		

Note: Tumor response assessments will be considered "adequate" for analysis if they are assigned as CR, PR, SD, or PD and are not censored (e.g., obtained within 13 weeks since the last assessment and prior to initiation of non-study anti-cancer treatment: systemic anti-cancer therapy, radiotherapy or cancer surgery).

Tumor response assessments obtained after initiation of non-study anti-cancer treatment will not be included in the efficacy analyses, but will be flagged in the data listings. Tumor response assessments obtained the same day as initiation of non-study anti-cancer treatment will not be excluded.

6.2.2 Secondary Efficacy Variables

6.2.2.1 Overall Survival

Overall survival (OS) in months is defined as the time from the day of randomization to death from any cause: (date of death – date of randomization +1)/30.4375. Patients who were alive at the end of study will be censored at the last date the patient is known to be alive. Patients without post-baseline information will be censored at the time of randomization.

6.2.2.2 Overall Response Rate and Disease Control Rate

Overall response rate (ORR) is defined as the proportion of patients with objective evidence of complete response (CR) or partial response (PR). The evaluation of ORR will be based on central independent review of the images (local CT image assessment and collect CT scans for central independent review).

CCI [redacted]

At the analysis stage, the best overall response will be assigned for each patient as the best response recorded after initiation of study treatment. If applicable, responses recorded after disease progression or initiation of new anti-cancer treatment will be excluded.

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

6.2.2.3 Duration of Response

Duration of response is derived for those patients with objective evidence of PR or CR. DR (in months) is defined as the time from the first documentation of response (CR or PR) to the first documentation of objective tumor progression or death due to any cause: (date of first progression or death – date of first CR or PR +1)/30.4375.

Patients who are alive and progression free as of the analysis cut-off date will be censored at their last evaluable tumor response assessment before initiation of any new anti-cancer cancer treatment. Refer to **Table 4** for censoring rules for duration of response.

Table 4 – Censoring Rules for Duration of Response

Situation	End Date	Censored
Documented radiological PD	Date of the first tumor assessment that determined PD	No
Death during the study before PD	Date of death	No
Patients still followed without radiologic PD as of cut-off date	Date of last adequate tumor assessment prior to cut-off date	Yes
Non-study anti-cancer treatment initiated before radiologic PD	Date of last adequate tumor assessment prior to initiation of non-study anti-cancer treatment	Yes
Death or radiologic PD after a missed (or not available/not evaluable) tumor assessment	Date of last adequate tumor assessment prior to missed tumor assessment A response assessment is considered missed if more than 13 weeks (91 days) has elapsed since the last image-based response assessment. If a patient develops progressive disease or dies after this interval, the tumor response assessment will be excluded from the analysis and censored at the last evaluable assessment. However, if an adequate image-based response assigned as CR, PR, or SD is obtained after more than 13 weeks, then the tumor response assessment will not be excluded from the analysis as long as no other censoring events have occurred.	Yes
Only non-evaluable (NE) tumor assessments after CR or PR	Date of last adequate tumor assessment prior to NE tumor assessments	Yes
General Considerations: Tumor response assessment dates will be assigned based on the date the image was performed, not the date the image was assessed.		

Note: Tumor response assessments will be considered "adequate" for analysis if they are assigned as CR, PR, SD, or PD and are not censored (e.g., obtained prior to initiation of non-study anti-cancer treatment).

Tumor response assessments obtained after initiation of non-study anti-cancer treatment (systemic anti-cancer therapy, radiotherapy or cancer surgery) will not be included in the efficacy analyses, but will be flagged in the data listings. Tumor response assessments obtained the same day as initiation of non-study anti-cancer treatment will not be excluded.

[redacted]

6.3 Safety

Safety parameters that will be measured in the study are:

1. Adverse events
2. Laboratory measurements
3. Vital signs
4. ECG
5. Physical examination
6. ECOG performance status
7. Pregnancy test
8. Concomitant medications and therapies
9. Other diagnostics and procedures

6.3.1 Study Day and Visit Window Definitions

The study windows listed in **Table 3** (based on visit dates) will be used to analyze physical examination, vital signs, height, weight, laboratory, ECOG and ECG measurements.

Table 3 Safety Study Windows

Visit	Safety Parameters	Target Day	Window
Baseline	Physical Examination, Vital Signs, Height, Weight, ECOG, Laboratory Measurements, ECG	Day -28 to Day 1	Day -28 to 1
Day 1 of Cycle 2 to 6	All	Day 1 of Cycle	Day -1 to 1 of Cycle
Day 1 of Cycle 7 and up	Laboratory Measurements	Day 1 of Cycle	Day -2 to 1 of Cycle
	Physical Examination, Vital Sign, Height, Weight, ECOG, ECG	Day 1 of Cycle	Day -1 to 1 of Cycle
Day 8 of all Cycles	All	Day 8 of Cycle	Day 2 to 11 of Cycle
Day 15 of Cycle 2 to 6	All	Day 15 of Cycle	Day 12 of Cycle to Day -2 of next Cycle
Day 15 of Cycle 7 and up	Laboratory Measurements	Day 15 of Cycle	Day 12 of Cycle to Day -3 of next Cycle
	Physical Examination, Vital Sign, Height, Weight, ECOG, ECG	Day 15 of Cycle	Day 12 of Cycle to Day -2 of next Cycle
End of Treatment	All	NA	No window will be used
30-Day Safety Follow-up	All	30 Days after Last Dose of Study Medication	Last Dose of Study Medication + 21 to Last Dose of Study Medication + 39 (i.e. +/- 9 days)

For post-baseline scheduled visits, the CRF visit will be used as analysis visit (i.e. no window will be used). Both scheduled and unscheduled assessments are included in the safety analyses. If more than one assessment is measured within the same visit window, the value closest to the target study day will be used for the analysis. If multiple values are the same number of days away from the target study day, then the latter value will be used. For Visit where time window is not applicable, the latest value would be used.

6.3.2 Extent of Exposure to Study Medication

The total dose received, number of treatment cycles received, and dose intensity will be derived using data from the TAS-114 and S-1 Administration form, and Study Drug Accountability form.

The **total dose received** for each study drug is the sum of dose received at each cycle, and the number of cycle received is the number of cycles with at least one dose taken during a cycle.

The **treatment duration** for each study drug (in weeks) is calculated from the date of first dose to the date of last dose + 7 or the start of new anti-cancer treatment, whichever is earlier, and then divided by 7.

Dose intensity is defined as the total dose actually received divided by the planned dose (i.e., total dose that would be given if no doses were missed and/or no dose reductions were made for the duration of time the patient received any component of study treatment) multiplied by 100%.

The planned dose for each drug at each cycle is as follows:

- TAS-114: 400 mg x 2 (BID) x 14 Days
- S-1: 30 mg/m^2 x BSA x 2 (BID) x 14 Days
  where BSA (m^2) = ([Body Weight (kg)] $^{0.425}$ x [Height (cm)] $^{0.725}$) x 0.007184.

The total planned dose is the sum of planned doses over all cycles.

The number of dose reductions, dose modifications, dose interruptions, and cycle delays will also be calculated.

6.3.3 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 19.0) and the severity of the toxicities will be graded according to the NCI CTCAE (Version 4.03).

Only treatment emergent adverse events will be included in summary tabulations. Treatment-emergent adverse events will be defined as adverse events with onset dates on or after the first dose of study medication and within 30 days after the last dose of study medication. Adverse events will be summarized by system organ class (SOC) and preferred term (PT), and worst severity grade.

<u>Adverse Events Counting Rules</u>

1. A patient with more than one different adverse event in a particular system organ class (SOC) will be counted only once in the total of patients experiencing adverse events in that particular SOC.

2. A patient having experienced the same event (AE preferred term) more than once during the study will be counted only once in the number of patients with that event.

3. If an event changes in intensity or in seriousness during the study, it will be counted only once with the worst grade and seriousness respectively.

4. If the causal relationship to the study drug is assessed differently, it will be counted only once by considering the "Worst" documented degree of relationship.

Missing Grade

An AE with missing severity grade will not be imputed but will be considered as '>=3' in the table presenting Grade 3 and above.

Missing Relationship to Study Drug

An AE with a missing relationship to study drug will be deemed as reasonably possible. Imputed values will not be listed in data listings.

Adverse Events with Incomplete Dates

The following algorithm should be used to estimate adverse event start dates for which only partial information is known:

- Missing day and month
  - If the year is same as the year of first day on drug, then the day and month of the start date of drug will be assigned to the missing fields.
  - If the year is prior to the year of first day on drug, then December 31 will be assigned to the missing fields.
  - If the year is after the year of first day on drug, then January 1 will be assigned to the missing fields.

- Missing month only
  - Treat day as missing and replace both month and day according to the above procedure.

- Missing day only
  - If the month and year are same as the year and month of first day on drug, then the start date of drug will be assigned to the missing day.
  - If the month and year are before the year and month of first day on drug, then the last day of the month will be assigned to the missing day.
  - If the month and year are after the year and month of first day on drug, then the first day of the month will be assigned to the missing day.

If the AE stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed using the stop date.

Adverse events with partially missing stop dates will be imputed a stop date as follows:
- *year is missing* - date left missing.

- *month is missing* - impute 'December'.
- *day is missing* - impute 'last day of that month'.

6.3.4 Deaths

All deaths will be captured on the Death/Autopsy Form.

6.3.5 Laboratory Data

Laboratory assessments include:

- Hematology: red blood cell (RBC) count, hemoglobin, hematocrit, platelets, white blood cell (WBC) count with differential, neutrophils (both segmented and band neutrophils), lymphocytes, monocytes, eosinophils, basophils.

- Serum chemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALK), albumin, total bilirubin (direct bilirubin, indirect bilirubin), creatinine, sodium, potassium, calcium, chloride, blood urea nitrogen (BUN) or urea, phosphorus, bicarbonate, glucose, creatine kinase (CK)/creatine phosphokinase [CPK] (creatine kinase MB, creatine kinase MM) .

- Coagulation: international normalized ratio (INR), activated partial thromboplastin time (aPTT)

- Urinalysis: urinary protein (qualitative), urinary glucose (qualitative), and urine specific gravity density.

All laboratory data will be stored in the database with the units in which they are originally reported. Laboratory data in summary tables and subject data listings will be presented in the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before further processing or data analysis.

Baseline value is the subject's last observation prior to the initiation of study drug (including Cycle 1 Day 1).

Laboratory tests will be graded using NCI-CTCAE v4.03 toxicity grading (see Appendix 1).

Time to maximum/worst grade 3 or 4 value (in days) is defined as the time from the date of first study treatment to the earliest date of maximum or minimum (nadir) laboratory parameter value with Grade 3 or above: (date of maximum/worst grade 3 or above – date of first study treatment + 1). If toxicity grade is defined for abnormal high/increase in NCI-CTCAE grading criteria, maximum is used. Otherwise, minimum (nadir) is used.

If there is no grade 3 or 4 laboratory value, the time to worst grade 3 or 4 value analysis will be censored at their last available laboratory assessment before the initiation of any new anti-cancer treatment, if applicable.

Time to resolution (in days) is defined as the time from the date of the worst grade 3 or 4 value to the earliest date of the laboratory parameter value return to baseline grade or below with an improvement of at

least one grade for the same type of abnormality (high/low): (date of return to baseline grade or below – date of worst grade 3 or above +1).

In case the laboratory value does not return to baseline grade or below, the time to resolution analysis will be censored at their last available laboratory assessment before the initiation of any new anti-cancer treatment, if applicable.

6.3.6 Vital Signs

Vitals signs include systolic/diastolic blood pressure, heart rate, respiratory rate, temperature, and weight.

Baseline value is the subject's last observation prior to the initiation of study drug (including Cycle 1 Day 1).

6.3.7 Electrocardiogram (ECG)

The electrocardiogram assessment includes the QT Interval (msec), QTc Interval (msec), RR Interval (msec) and the general result (interpretation).

6.3.8 Physical Examination

A physical examination will be performed at baseline and at each cycle, but no result from the physical examination will be entered in the database. The significant findings from the physical examination will be reported in the Medical History (prior to study drug administration) or the Adverse Event (after study drug administration) forms.

6.3.9 Pregnancy Test

A pregnancy test will be performed at baseline and at the End of Treatment and 30-day Safety Follow-up visit for females with childbearing potential.

6.3.10 Concomitant Medications and Therapies

Concomitant medications will be collected for all visits.

Verbatim descriptions of concomitant medications and therapies will be mapped to the World Health Organization (WHO) Drug Dictionary Enhanced (WHO-DDE) and Herbal Dictionary (WHO-HD) (version Q1 2016).

Concomitant medication/treatment is any medication/treatment with start date on or after the initial dosing of TAS-114 or S-1, whichever occurs first. Medication/treatment that started before the first dose and continued during the study treatment will also be counted as concomitant medication/treatment.

Concomitant Medications Counting Rules:

A patient with more than one different medications in a particular medication class will be counted only once in the total of patients taking that particular medication class.

A patient having the same medication more than once during the study will be counted only once in the number of patients with that medication.

Medications with Incomplete Dates:

For concomitant medications with missing or partially missing start dates, they will be imputed, if necessary, using the same algorithm described for adverse event onset dates (see Section 6.3.3). If the stop date is missing or partially missing, the imputation rule is applied in the following order:

1) *year is missing* - the medication will be considered to have been received at all periods after that period determined by the start date. Date left missing.

2) *month is missing* - impute 'December'.

3) *day is missing* - impute 'last day of that month'.

6.3.11 Other Diagnostics and Procedures

Other diagnostics and procedures are collected though the entire study.

6.3.12 New Anti-Cancer Treatments

New anti-cancer treatments are collected after the patients discontinue the study treatment on the Post-Treatment form.

Medications with Incomplete Dates:

When checking to see if anti-cancer treatments is initiated prior to a response assessment in cases where the start date of the anti-cancer therapy is only partially provided, use the last day of the month if the day is missing. If the month or year is missing do not impute a date and do not count the patient as having received anti-tumor therapy.

7. STATISTICAL ANALYSIS

7.1 General Data Handling Rules and Definitions

All data collected on case report forms will be provided in listings, except data collected only for confirmation of study entry criteria and for study administrative purposes. If any randomized patient is found to not have valid documented informed consent, that patient's data will be excluded from the report, except as necessary to document the error.

All analyses will be conducted using SAS version 9.4.

Except where specified, all continuous variables will be summarized with descriptive statistics (number of non-missing values, mean, standard deviation, median, Q1 and Q3, minimum and maximum) and all categorical variables will be summarized with frequency counts and percentages, by treatment group.

Missing data will be maintained as missing unless specified otherwise. For variables where missing data is imputed, the analysis dataset (ie. ADaM) will contain one variable with the imputed value and the original variable with missing maintained as missing.

7.2 Patient Disposition

The number of patients in each study population and the reasons for exclusion will be summarized. In addition, patients' status with regard to study treatment and follow-up will also be summarized, along with the reasons for study treatment discontinuation. The number of patients in each study population and reason for study treatment discontinuation will also be summarized by geographical region.

7.3 Protocol Deviations

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-114-201 the following categories will be used for CSR reportable Protocol Deviations:

- A subject that did not meet entry criteria
- A subject that developed withdrawal criteria but was not withdrawn
- A subject that received the wrong treatment or incorrect dose
- A subject that received an excluded medication
- 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.

- SAE reporting
- Informed consent
- Study procedures
- Investigational product (other than incorrect dose or wrong treatment)

Refer to *Protocol Deviation Plan*, Section 2 for details.

The key protocol violations include, but are not limited to:

- No measurable disease (assessed by investigator or central independent review)
- Did not receive at least 2 prior therapies for advanced or metastatic disease condition, including platinum doublet and pemetrexed, docetaxel, or immunotherapy
- No documentation of histologically diagnosed or cytologically proven advanced or metastatic NSCLC patients, either Stage IIIB/Stage IV disease (according to Version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or recurrent disease following radiation therapy or surgical resection

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

7.4 Demographic and Baseline Characteristics

Demographics variables, baseline characteristics, cancer history, medical history/active symptoms and prior cancer treatment will be summarized by treatment group for the ITT population. Cancer history, prior systemic drug therapies, and standard prior systemic therapies (platinum doublet and pemetrexed, docetaxel, immunotherapy) will also be summaried by geographical region.

All the data fields will also be presented in patient data listings.

7.5 Efficacy Analyses

The following sections outline the planned analyses of the primary and secondary objectives of the study TO-TAS-114-201.

Comparison of time-to-event endpoints (PFS, OR and DR) will be based on the Cox proportional hazard model, stratified or unstratified, as specified, where the hazard ratio (HR), corresponding 90% and 95% confidence interval, and p-values will be estimated. Details of the hypothesis testing for the PFS analysis are described in Section 3.3. Survival curves and the estimated median time-to-event will be provided by the Kaplan-Meier method (Kaplan and Meier, 1958).

Overall response rate (ORR) and disease control rate (DCR) will also be compared between treatment groups using Fisher's exact test.

Refer to Appendix 2 for the SAS code used for the efficacy analyses.

7.5.1 Primary Efficacy

The progression-free survival analysis will be based on the ITT population.

PFS in the efficacy population will be compared between the TAS-114/S-1 and S-1 control treatment groups using the stratified log-rank test with a one-sided significance level of 5%. CCI [redacted]

CCI [redacted]

Median time to PFS for each group being compared will be estimated using the Kaplan-Meier method, along with the corresponding 95% CI. Confidence intervals for median progression-free survival will be based upon the methods of Brookmeyer and Crowley. The 25th and 75th percentiles will also be calculated. Kaplan Meier estimates of progression-free at 2, 4, 6 and 8 months and their confidence intervals (calculated with the log-log transformation methodology of Kalbfleisch and Prentice) will be tabulated. The Kaplan-Meier plots will be displayed.

The primary analysis for PFS will be conducted after 60 events have been observed based on independent assessment or after all patients have been followed for at least 3 months, whichever is later.

CCI

CCI

CCI

CCI [redacted]

CCI [redacted]

7.5.2 Secondary Efficacy

7.5.2.1 Overall Survival

The overall survival (OS) analysis will be based on the ITT population.

The estimate of the hazard ratio and corresponding 95% CI will be provided using a univariate CPH model (only treatment effect in the model). Median time to OS for each group being compared will be estimated using the Kaplan-Meier method, along with the corresponding 95% CI. Confidence intervals for the median will be based upon the methods of Brookmeyer and Crowley. The 25th and 75th percentiles will also be calculated. Kaplan Meier estimates at 3, 6, 9 and 12 months and their confidence intervals (calculated with the log-log transformation methodology of Kalbfleisch and Prentice) will be tabulated. The survival curves will be estimated using the Kaplan-Meier method. The unstratified log-rank test will be done for the comparison of treatment effect.

The stratified log-rank test will also be performed for the comparison of treatment effect using the same stratification factors used for PFS.

The same multivariable analysis as for PFS will be performed for OS.

OS will also be presented by geographical region.

7.5.2.2 Overall Response Rate and Disease Control Rate

The overall response rate and disease control rate analyses will be based on the Tumor Response (TR) evaluable population.

ORR and DCR in the efficacy population will be compared between the 2 treatment groups using Fisher's exact test. The estimates and differences will be presented along with the associated exact 95% CIs for each treatment group.

Best response will be summarized into four RECIST categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The summary will also include a category for unevaluable patients if applicable.

CCI [redacted]

ORR and DCR will also be presented by geographical region.

7.5.2.3 Duration of Response

The duration of response analysis will be based on the TR evaluable population, only for patients that have a CR or PR response. Duration of response will be analyzed in the same manner as OS.

CCI [redacted]

7.5.2.4 Tumor Response Assessments - Investigator versus Central Independent Review

The tumor response assessments based on the investigator's review will be compared to the tumor response assessments based on the central independent review (blinded radiological review):

- Discordance in best response will be tabulated
- Summary statistics for the number of days between investigator date of progression and central independent review date of progression will be displayed

CCI [redacted]

7.1 Safety Analyses

All safety data will be summarized by treatment groups in tables and presented in patient data listings. The analysis population for all safety analyses will be the as-treated population. Patients are assigned to treatment groups for safety analyses based on the study treatment they actually received.

7.1.1 Exposure of Study Treatment

The TAS-114/S-1 or S-1 control administration profile will be summarized with mean, standard deviation, median, minimum, and maximum for the total dose received, number of treatment cycles received, and dose intensity. Dose reduction, dose modifications, dose interruptions, subsequent cycle delays, dose discontinuation of TAS-114/S-1 or S-1 control, and their corresponding reasons will also be tabulated by treatment group.

7.1.2 Duration of Follow-Up

A summary table showing the duration of follow-up will be presented by treatment arm for the ITT population. The follow-up period 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. The duration of

follow-up will be analyzed using the reversed Kaplan-Meier method, where deaths will be censored on the date of death.

7.1.3 Adverse Events

All AEs from the time a patient starts receiving study treatment through the period of patient follow-up (30 days after the last dose of study drug or until the start of new anti-cancer therapy, whichever is earlier) will be summarized (incidence) by the system organ class, preferred term, toxicity/severity grade, and causal relationship to TAS-114/S-1 or S-1 control.

The following adverse events summaries will be reported:

- Overall summary of safety including AEs, fatal AEs, treatment-related AEs, serious AEs, treatment-related serious AEs, AEs of grade 3 and above, AE leading to study drug interruption, AEs leading to study drug dose reduction, AEs leading to study drug administration
- Incidence rates of AEs
- Incidence rates of AEs related to study drug
- Incidence rates of serious AEs
- Incidence rates of serious treatment-related AEs
- Incidence rates of AEs by NCI-CTCAE v4.03 grade
- Incidence rates of AEs leading to study drug interruption by NCI-CTCAE v4.03 grade
- Incidence rates of AEs leading to study drug dose reduction by NCI-CTCAE v4.03 grade
- Incidence rates of AEs leading to study drug discontinuation by NCI-CTCAE v4.03 grade
- Incidence rates of non-serious AEs
- Incidence rates of AEs of special interest (based on the grouped AE terms in Appendix 4)

Adverse events will also be summarized by geographical region.

7.1.4 Deaths

Summaries of number of deaths and cause of death will be produced by treatment group.

7.1.5 Laboratory Data

Hematology, serum chemistry, and coagulation results will be summarized by toxicity grade (using NCI-CTCAE v4.03 toxicity grading – see Appendix 1 at baseline and post-baseline measurements that worsened by at least one grade. 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 Appendix 3 will be utilized and flagged in the database.

The worst change from baseline in toxicity grade for selected laboratory parameters will also be presented in shift tables: in each treatment arm, the patient's baseline grade will be cross-tabulated by the patient's maximum post-baseline grade during the treatment.

Time to maximum/worst grade 3 or 4 value and time to resolution will be summarized for all quantitative laboratory parameters if toxicity grade is defined in NCI-CTCAE v4.03. The Hematology parameters will include Hemoglobin, Hematocrit, RBC, WBC, ANC, Thrombocytopenia, and Platelets, and the Chemistry

parameters will include AST, ALT, Total Bilirubin, and Alkaline Phosphatase. Count of the events and the censored, minimum and maximum of the event time will be presented by treatment group. Meanwhile, median time to worst grade 3 or 4 value and time to resolution for each group being compared will be estimated using the Kaplan-Meier method, along with the corresponding 95% CI.

The qualitative urinalysis results will be summarized by visit and treatment groups. A shift table for qualitative urinalysis results from baseline to worst past-baseline will also be presented.

7.1.6 Vital Signs

Vitals signs (systolic/diastolic blood pressure, heart rate, respiratory rate, temperature, and weight) and their changes from baseline will be summarized by visit.

7.1.7 Concomitant Medications and Therapies

Concomitant medications will be summarized by treatment groups and sorted alphabetically by Anatomical-Therapeutic-Chemical classification (ATC) class and preferred drug name.

7.1.8 Other Diagnostics and Procedures

Other diagnostics and procedures will be summarized by treatment groups.

7.1.9 New Anti-Cancer Treatments

New anti-cancer treatments will be summarized by treatment groups. The number and percentage of patients receiving any chemotherapy, radiotherapy, surgery, immunotherapy, and other treatments will be summarized descriptively for the ITT population. The number of regimens received by each patient will also be summarized.

7.1.10 Other Safety Assessments

Results from the electrocardiogram and the ECOG performance status will be summarized by visit.

CCI

[redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

8. CHANGES FROM METHODS PLANNED IN THE PROTOCOL

Time to treatment failure is added as a post hoc analysis.

Any changes to methods planned in this statistical analysis plan will be documented in a revision to this statistical plan prior to database lock, or identified in the clinical study report.

9. STATISTICAL SOFTWARE

SAS Version 9.4 in the UNIX environment will be used for all statistical analyses.

10. REFERENCES

1. Brookmeyer and Crowley, A Confidence Interval for the Median Survival Time, Biometrics 38, 29-41, March 1982.

2. Kaplan, E. L. Meier, P. (1958). Nonparametric estimation from incomplete observations. J. Amer. Statist. Assn. 53 (282): 457–481. JSTOR 2281868.

3. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. Nat Rev Cancer. 2003; 3(5):330-338.

4. Shirasaka T. Development history and concept of an oral anticancer agent S-1 (TS-1): its clinical usefulness and future vistas. Jpn J Clin Oncol. 2009; 39(1):2-15.

5. Siegel RL, Miller KD, Jemal A. Global Cancer Statistics CA Cancer J Clin 2016; 66:7–30.

6. Wilson, PM, LaBonte MJ, Lenz HJ, Mack PC, Ladner RD. Inhibition of dUTPase induces synthetic lethality with thymidylate synthase-targeted therapies in non-small cell lung cancer. Mol Cancer Ther. 2012. 11(3):616-28.

7. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, FDA guidance, May 2007.