CLINICAL STUDY PROTOCOL

Study Title:	Open-Label, Global, Multicenter, Randomized, Phase 3 Study of Sacituzumab Govitecan Versus Docetaxel in Patients With Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) With Progression on or After Platinum-Based Chemotherapy and Anti-PD-1/PD-L1 Immunotherapy
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	156176
EU CT Number:	2021-003578-30
ClinicalTrials.gov Identifier:	NCT05089734
Indication:	Non-Small Cell Lung Cancer
Protocol ID:	GS-US-577-6153
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 11 August 2021 Amendment 1: 15 September 2021 Amendment 2: 22 December 2022

This study will be conducted under United States Food and Drug Administration investigational new drug application regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, the United Kingdom, and Switzerland are not included under the investigational new drug application and are considered non-investigational new drug application sites.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	antidrug antibody
ADC	antibody-drug conjugate
AE	adverse event
ALK	anaplastic lymphoma kinase
BRAF	proto-oncogene B-raf
CI	confidence interval
C_{max}	maximum observed concentration of drug
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CSR	clinical study report
CT	computed tomography
C_{trough}	concentration at the end of the dosing interval
DCR	disease control rate
DMC	data monitoring committee
DOR	duration of response
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EORTC QLQ-C30 v3	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Version 3
EOT	end of treatment
EQ-5D-3L	EQ-5D-3 level
EU	European Union
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose (18F)
FFPE	formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
Gilead	Gilead Sciences
HIV	human immunodeficiency virus
HR	hazard ratio
IARC	International Agency for Research on Cancer
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IRB	institutional review board

IRT	Interactive Response Technology
ITT	intent to treat
IUD	intrauterine device
IV	intravenous
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTNBC	metastatic triple-negative breast cancer
mUC	metastatic urothelial cancer
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
NSCLC-SAQ	non-small cell lung cancer Symptom Assessment Questionnaire
NTRK	neurotrophic tyrosine receptor kinase
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death protein 1
PD-L1	programmed death ligand 1
PET	positron emission tomography
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PR	partial response
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
QOL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	ROS proto-oncogene 1
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SG	sacituzumab govitecan
SSR	special situation report
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
Trop-2	trophoblast cell surface antigen-2
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal
US	United States

PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title: Open-Label, Global, Multicenter, Randomized, Phase 3 Study of Sacituzumab Govitecan Versus Docetaxel in Patients With Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) With Progression on or After Platinum-Based Chemotherapy and Anti-PD-1/PD-L1 Immunotherapy

IND Number: 156176
EU CT Number: 2021-003578-30
ClinicalTrials.gov Identifier: NCT05089734

Study Centers Planned: Approximately 250 centers globally.

Objectives and Endpoints:

Primary Objective	Primary Endpoint
• To compare the overall survival (OS) of sacituzumab govitecan (SG) versus docetaxel.	• OS is defined as the time from the date of randomization until death due to any cause in the Intent-to-Treat (ITT) Analysis Set.
Secondary Objectives	**Secondary Endpoints**
To compare the effect of SG versus docetaxel on the following:	
• Progression-free survival (PFS) as assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.	• PFS is defined as the time from the date of randomization until the date of objective disease progression or death (whichever comes first) as assessed by the investigator per RECIST Version 1.1.
• Objective response rate (ORR) as assessed by the investigator per RECIST Version 1.1.	• ORR is defined as the proportion of patients who achieve a complete response (CR) or partial response (PR) that is confirmed at least 4 weeks later as assessed by the investigator per RECIST Version 1.1.
• Duration of response (DOR) as assessed by the investigator per RECIST Version 1.1.	• DOR is defined as the time from the first documentation of CR or PR to the earlier of the first documentation of progressive disease (PD) or death from any cause (whichever comes first) as assessed by the investigator per RECIST Version 1.1.
• Disease control rate (DCR) as assessed by the investigator per RECIST Version 1.1.	• DCR is defined as the proportion of patients who achieve a CR, PR, or stable disease (SD) as assessed by the investigator per RECIST Version 1.1.
• Safety and tolerability.	• Incidence of treatment-emergent adverse events (TEAEs) and clinical laboratory abnormalities.
• Quality of life (QOL) using non–small cell lung cancer (NSCLC) Symptom Assessment Questionnaire (NSCLC-SAQ).	• Time to first deterioration in shortness of breath domain as measured by NSCLC-SAQ. • Time to first deterioration in NSCLC-SAQ total score.

Exploratory Objectives	Exploratory Endpoints
• To characterize the pharmacokinetics (PK) and immunogenicity of SG.	• Peak (C_{max}) and trough (C_{trough}) concentrations over time and antidrug antibodies (ADAs) over time.
• To assess disease-related symptoms and health related QOL using EQ-5D-3 level (EQ-5D-3L); NSCLC-SAQ; the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Version 3 (EORTC QLQ-C30 v3); Patient Global Impression of Severity (PGIS); and Patient Global Impression of Change (PGIC).	• Mean change from baseline of total score and all domains of NSCLC--SAQ not assessed as secondary endpoints. • Mean change from baseline of all domains of EORTC QLQ-C30 v3. • The proportion of patients with meaningful change in each QOL domain while on treatment. • Time to first improvement and time to first deterioration in each QOL domain not assessed as secondary endpoints.
• To assess and compare treatment-related symptoms using the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).	• Frequency, severity, or interference of treatment-related symptoms.
• To assess tumor expression of trophoblast cell surface antigen-2 (Trop-2) as a potential predictive biomarker of response to SG.	• Correlation of clinical response with baseline tumor Trop-2 expression.
• To explore blood and tumor biomarkers that may be associated with response to SG treatment.	• Correlation of clinical response with tumor, tumor microenvironment, and blood biomarkers at baseline and after SG treatment. • Clearance of circulating tumor DNA upon SG treatment.

Study Design: Study GS-US-577-6153 is an open-label, global, multicenter, randomized, Phase 3 study to compare the efficacy and safety of SG versus docetaxel in patients with advanced or metastatic NSCLC with progression on or after platinum-based chemotherapy and anti-programmed death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) immunotherapy received either in combination or sequentially. Patients with actionable genomic alterations will also be included if they have received prior treatment with an appropriate tyrosine kinase inhibitor (TKI).

Patient participation will include screening, randomization, treatment, and follow-up. Screening will last no longer than 28 days to confirm eligibility and establish disease characteristics prior to randomization and treatment.

Approximately 580 eligible patients will be randomly assigned in a 1:1 ratio to receive either SG (Investigational Arm A) or docetaxel (Control Arm B). Randomization will be stratified based on histology (squamous versus nonsquamous), response to last prior immune therapy received (best response PD/SD vs CR/PR on immune therapy), and if they have received prior therapy for actionable genomic alteration (yes vs no).

The primary endpoint of the study is OS. Secondary efficacy endpoints are PFS, ORR, DOR, and DCR as assessed by the investigator per RECIST Version 1.1; time to first deterioration in NSCLC-SAQ total score; and time to first deterioration in shortness of breath as measured by NSCLC-SAQ. Safety will be assessed by the reporting of adverse events (AEs), assessments of vital signs, laboratory results, and extent of exposure to study drug. Additional QOL assessments will be conducted. Pharmacokinetics, ADA, and various biomarkers will also be assessed.

Patients will receive study drug until PD, death, unacceptable toxicity, or another treatment discontinuation criterion is met. Follow-up will begin at the time of the completion of the end of treatment visit, which will occur 30 days (± 7) after the last dose of study drug. All patients will be followed for survival until 1 of the discontinuation criteria from the study is met.

An independent data monitoring committee will be convened at regular intervals to assess the progress of this study, review safety data, and conduct the interim efficacy analysis.

Following completion of global enrollment, additional patients may be enrolled at sites in mainland China in the China Extension Cohort, to ensure adequate number of Chinese participants are enrolled to meet local regulatory requirements. Those participants enrolled in China after global enrollment is complete will not be a part of the primary analysis for global study. The details on China extension cohort is provided in China-specific amendment.

Number of Patients Planned:

Global Study: Approximately 580 eligible patients will be enrolled.

Target Population: Patients with advanced or metastatic NSCLC with progression on or after platinum-based chemotherapy and anti-PD-1/PD-L1 immunotherapy.

Duration of Treatment: Patients will receive study drug until PD, death, unacceptable toxicity, or another treatment discontinuation criterion is met.

Treatment with either SG or docetaxel beyond the initial investigator-assessed PD per RECIST Version 1.1 is permitted if there is evidence of clinical benefit per the investigator and the patient is tolerating study drug. The following clinical criteria should be met for patients to continue to receive treatment beyond the investigator-assessed progression:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in performance status
- Absence of symptomatic rapid disease progression requiring urgent medical intervention (eg, symptomatic pleural effusion, spinal cord compression)

Sponsor consultation is required before patients initiate the treatment beyond progression. If this occurs, the patient will remain in the study and continue to be monitored according to the study procedures table. All patients will be followed for survival until 1 of the discontinuation criteria from the study is met

Diagnosis and Main Eligibility Criteria: Female or male patients, 18 years of age or older, must be able to give signed, written informed consent and comply with protocol requirements. Patients must have pathologically documented Stage 4 NSCLC. Patients must have progressed after platinum-based chemotherapy in combination with anti-PD-1/PD-L1 antibody OR platinum-based chemotherapy and anti-PD-1/PD-L1 antibody (in either order) sequentially. No additional treatments are allowed in the recurrent/metastatic setting for patients with no actionable genomic alterations. Patients with epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), or any other known actionable genomic alterations must have also received treatment with at least 1 locally approved and available TKI appropriate to the genomic alteration. Patients must have documented radiographic disease progression while on or after receiving the most recent treatment regimen for advanced or metastatic NSCLC.

Study Procedures/Frequency: The study procedures table and study schema are presented in Table 1 and Figure 1, respectively.

Test Product, Dose, and Mode of Administration: Sacituzumab govitecan is administered at 10 mg/kg via intravenous (IV) infusion on Days 1 and 8 of a 21-day cycle.

Reference Therapy, Dose, and Mode of Administration: Docetaxel is administered at 75 mg/m^2 via IV infusion on Day 1 of a 21-day cycle.

Statistical Methods:

Analysis Sets

The ITT Analysis Set will include all randomized patients according to the treatment arm to which the patient is randomized, unless otherwise specified. This is the primary analysis set for all efficacy analyses.

The Safety Analysis Set will include all patients who received at least 1 dose of any study drug, with treatment assignments designated according to the actual treatment received. This is the primary analysis set for all safety analyses.

The PK analysis will be conducted on Pharmacokinetic Analysis Set, defined as all randomized patients who received at least 1 dose of SG per the protocol and have at least 1 measurable posttreatment serum concentration of SG.

The immunogenicity analysis will be conducted on Immunogenicity Analysis Set, defined as all randomized patients who received at least 1 dose of SG and have at least 1 evaluable posttreatment anti-SG antibody test result.

The biomarker analysis will be conducted on the Biomarker Analysis Set, defined as all patients who received any study drug and have at least 1 evaluable posttreatment biomarker measurement available.

Quality of life assessments will be analyzed for patients in the ITT Analysis Set.

Primary Efficacy Analysis

The primary analysis of OS for comparing SG versus docetaxel will be performed in the ITT Analysis Set using the log-rank test stratified by randomization stratification factors. The hazard ratio (HR) and its 95% CI estimated using a Cox proportional hazard regression model stratified by randomization stratification factors will also be presented. Overall survival will be summarized by treatment arm using Kaplan-Meier estimates, which will include median and the proportion of patients alive at benchmark time points such as 12 and 18 months. Kaplan-Meier plots will be provided.

Secondary Efficacy Analyses

At the time of the OS interim analysis, PFS, ORR, and other secondary endpoints will be mature for the final analysis, which will be approximately 23 months after the first patient is randomized.

The secondary endpoint PFS assessed by the investigator per RECIST Version 1.1 will be performed using the same methods as described for the primary OS analysis. Patients who have not progressed or died at the time of analysis will be censored according to the censoring rules similar to those described in the United States Food and Drug Administration Guidance for Industry Clinical Trial Endpoints for the Approval of NSCLC Drugs and Biologics. The detailed PFS censoring rules will be described in the statistical analysis plan.

The ORR will be based on RECIST Version 1.1 using investigator-assessed response data. The ORR will be analyzed and compared between the treatment arms using the Cochran Mantel-Haenszel test stratified by the stratification factors used for randomization. The 2-sided 95% CIs for each treatment will be calculated using the Clopper-Pearson exact method.

Kaplan-Meier estimates of median DOR and its 95% CI will be calculated for responders (CR or PR) in each treatment arm.

Disease control rate will be analyzed using the same methods as described for ORR.

The NSCLC-SAQ instrument will generate scores for 5 domains and a total score for each assessment visit. The analysis of time to first symptom deterioration in NSCLC-SAQ total score and time to first deterioration in NSCLC-SAQ shortness of breath domain will be conducted between the 2 treatment groups using the log-rank test stratified by randomization stratification factors in the ITT Analysis Set.

Safety Analysis

Safety data will be summarized by treatment arm using descriptive statistics for TEAEs, clinical laboratory tests, vital signs, and concomitant medications. Information regarding study drug administration, study drug compliance, and other safety variables will also be summarized descriptively by treatment arm.

Pharmacokinetic Analysis

Serum samples for PK analysis will be collected for patients who receive SG. Plasma concentrations and PK parameters (ie, C_{max}, C_{trough}) will be listed and summarized for SG, total SN-38, free SN-38, and total antibody using descriptive statistics.

Immunogenicity Analysis

Serum samples for ADA analysis will be collected for patients who receive SG. The impact of immunogenicity, if detected, will be evaluated in relation to PK and clinical responses, safety/tolerability, and efficacy.

Biomarker Analysis

Baseline Trop-2 analysis will be performed and correlated with clinical outcomes. The baseline level, absolute level, and change from baseline level over time will be summarized using descriptive statistics for each biomarker at the sample collection time point by treatment arm, as appropriate. Exploratory analyses may be performed to evaluate the association of each biomarker or combination of biomarkers with clinical outcomes.

Sample Size Calculation

Global Study

Approximately 580 eligible patients will be randomly assigned in a 1:1 ratio to receive either SG or docetaxel over a planned nonuniform accrual period of 19 months.

The sample size is estimated based on the primary endpoint of OS. The assumed OS treatment effect under the alternative hypothesis is an average HR of 0.70 for SG versus docetaxel, which is characterized by a median OS of 11 months on docetaxel treatment and a median OS of 15.7 months on SG treatment assuming OS is exponentially distributed. A total of 336 death events are required to detect a statistically significant difference at overall 1-sided alpha of 2.5% with 90% power based on a log-rank test. It is estimated that approximately 580 patients will provide 336 death events after approximately 29 months of survival follow-up after the first patient is randomized. EAST® 6.5 was used to calculate the sample size.

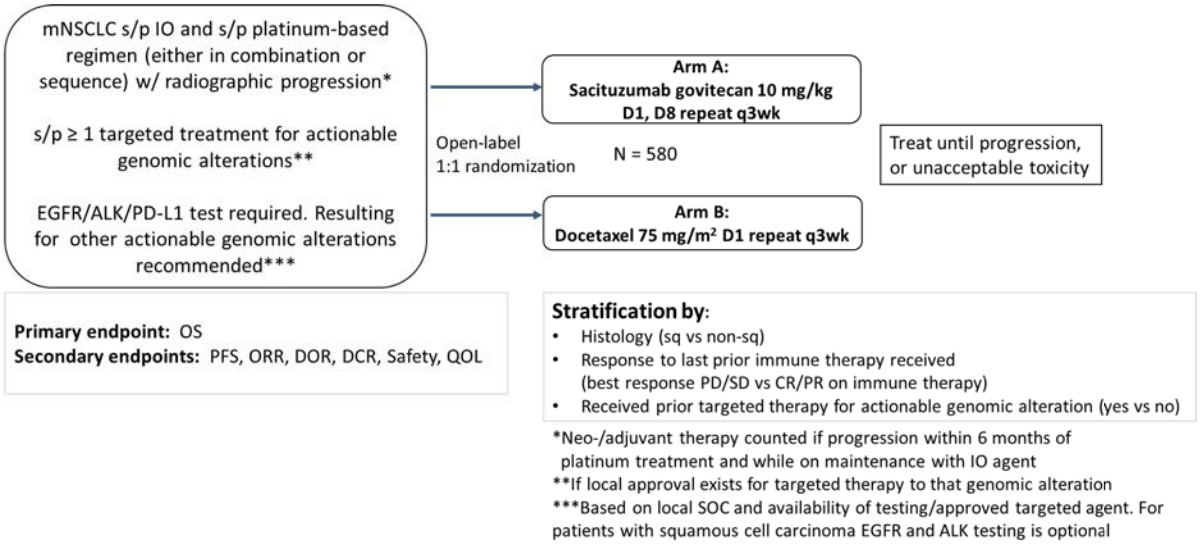
China Extension Study

Following completion of the global enrollment, additional participants may be enrolled at sites in mainland China in the China Extension cohort, to ensure adequate number of Chinese participants are enrolled to meet local regulatory requirements. Those participants enrolled in China after global enrollment is complete will not be a part of the primary analysis for global study. The details on China extension cohort is provided in China-specific amendment.

This study will be conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SCHEMA

Figure 1. GS-US-577-6153 Study Schema



ALK = anaplastic lymphoma kinase; CR = complete response; D = day; DOR = duration of response; DCR = disease control rate; EGFR = epidermal growth factor receptor; IO = immuno-oncology; mNSCLC = metastatic non-small cell lung cancer; non-sq = non-squamous; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-L1 = programmed death ligand 1, PFS = progression-free survival; PR = partial response; PRO = patient-reported outcomes; q3wk = every 3 weeks; SD = stable disease; SOC = standard of care; s/p = status post; sq = squamous; vs = versus

STUDY PROCEDURES TABLE

Table 1. GS-US-577-6153: Study Procedures Table

Phase	Pretreatment	Treatment				Posttreatment		
Period	Screening	(21-Day Cycles)				End of Treatment[a]	Follow-up	
		Cycle 1		Cycle 2 Through Last Cycle				
Day	Days −28 to −1	Day 1	Day 8	Day 1	Day 8	30 Days (± 7) After Last Dose	Every 12 Weeks From EOT Visit (± 7)	Notes
Written informed consent	X							
Demography	X							
Medical/surgical history	X							Including prior anticancer, anticancer surgery, and radiation therapy
Vital signs[b]	X	X	X	X	X	X		Blood pressure, pulse, respiratory rate, and body temperature; Section 6.3.3
ECOG	X	X		X		X		
Complete physical examination	X							
Clinically-targeted physical examination		X		X		X		
Height	X							

Phase	Pretreatment	Treatment				Posttreatment		
Period	Screening	(21-Day Cycles)				End of Treatment[a]	Follow-up	
		Cycle 1		Cycle 2 Through Last Cycle				
Day	Days −28 to −1	Day 1	Day 8	Day 1	Day 8	30 Days (± 7) After Last Dose	Every 12 Weeks From EOT Visit (± 7)	Notes
Weight	X	X		X		X		
ECG[c]	X	X						
QOL questionnaires[d]		X		X		X		
Hematology	X	X	X	X	X	X		See Section 6.3.5
Chemistry	X	X	X	X	X	X		See Section 6.3.5
Creatinine clearance	X							
PT/INR, PTT[e]	X							
LDH and uric acid[f]	X							
Hepatitis and HIV testing	X							See Table 4
Blood sample for UGT1A1 genotyping	X							
Urinalysis	X							See Table 4
FSH	X							Conduct as needed per Appendix 3 for determination of childbearing potential

Phase	Pretreatment	Treatment				Posttreatment		
Period	Screening	(21-Day Cycles)				End of Treatment[a]	Follow-up	
		Cycle 1		Cycle 2 Through Last Cycle				
Day	Days −28 to −1	Day 1	Day 8	Day 1	Day 8	30 Days (± 7) After Last Dose	Every 12 Weeks From EOT Visit (± 7)	Notes
Serum pregnancy test[g]	X							For female patients of childbearing potential
Urine pregnancy test[h]		X		X		X	X	
PK[i]		X	X	See footnote		X		
Immunogenicity[j]		X			See footnote	X		
Blood samples for biomarkers	X			X[k]				
Optional genomic research (biomarker)		X[l]						
Tumor tissue for EGFR, ALK, or PD-L1 testing if status unknown[m]	X							
Tumor tissue for Trop-2 and other biomarkers (archival or newly acquired)[n]	X							
SG administration		X	X	X	X			
Docetaxel administration		X		X				
CT or MRI tumor assessments[o]	X	Throughout study						

Phase	Pretreatment	Treatment				Posttreatment		
Period	Screening	(21-Day Cycles)				End of Treatment[a]	Follow-up	
		Cycle 1		Cycle 2 Through Last Cycle				
Day	Days −28 to −1	Day 1	Day 8	Day 1	Day 8	30 Days (± 7) After Last Dose	Every 12 Weeks From EOT Visit (± 7)	Notes
Bone scan, whole body bone MRI, or 18F-FDG PET scan[p]	X	As clinically indicated						If known or suspected bone metastasis
Adverse events	X	Throughout study					X[q]	
Prior and concomitant medications	X	Throughout study						
Subsequent anticancer therapy							X	
Survival information							X	

ADA = antidrug antibody; ALK = anaplastic lymphoma kinase; C = cycle; CR = complete response; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; EORTC QLQ-C30 v3 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Version 3; EOT = end of treatment; EQ-5D-3L = EQ-5D-3 level; FDG = fluorodeoxyglucose (18F); FFPE = formalin-fixed, paraffin-embedded; FSH = follicle-stimulating hormone; INR = international normalized ratio; IV = intravenous; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; NSCLC-SAQ = Non–small Cell Lung Cancer Symptom Assessment Questionnaire; PD = progressive disease; PD-1 = programmed death protein 1; PD-L1 = programmed death ligand 1; PET = positron emission tomography; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic; PR = partial response; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PT = prothrombin time; PTT = partial thromboplastin time; QOL = quality of life; SAE = serious adverse event; SG = sacituzumab govitecan; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

Treatment visit windows are permitted either 1 day before or within 2 days after scheduled visits and ± 7 days for imaging.

a An EOT visit will occur 30 days (± 7) after the last dose of study drug.

b Vitals to be assessed at screening and at predose during treatment.

c Twelve (12)-lead ECG will be obtained at screening and prior to infusion on C1D1. Abnormal findings should be evaluated as clinically indicated, including repeated ECGs. ECGs may be performed at other time points during the study if clinically indicated. See Section 6.3.4 for further information.

d EQ-5D-3L, NSCLC-SAQ, EORTC QLQ-C30 v3, PGIS, PGIC, and PRO-CTCAE will be assessed on Day 1 prior to dosing of every cycle for the duration that patients are receiving SG or docetaxel treatment until and at the EOT visit. The QOL assessments will be conducted before other study procedures occur, including study drug administration.

e PT/INR and PTT testing will be conducted at screening and as clinically indicated. See Section 6.3.5 for further information.
f LDH and uric acid testing will be conducted at screening and as clinically indicated. See Section 6.3.5 for further information.
g Serum pregnancy test will be conducted at screening as discussed in Appendix 3.
h During posttreatment, pregnancy testing will continue every 28 days after the last dose of study drug up to 6 months after the last dose of study drug per the duration of required contraception as discussed in Appendix 3. Testing during the posttreatment period may be performed at home and the result self-reported by the patient. See Section 7.4.2.3 for pregnancy reporting. If a urine pregnancy test is positive or equivocal, a confirmatory serum pregnancy test will be required.
i Serum samples for PK analysis will be collected for patients who receive SG. Collection times for PK samples are at predose and after the end of infusion on C1D1 and C1D8 and on Day 8 of Cycles 2, 6, and 10. Thereafter, PK samples will be collected at predose on Day 8 every 8 cycles (eg, C18D8, C26D8, etc) and at the EOT visit. The collection window is within 30 minutes prior to the start of infusion for predose samples and within 10 minutes after the end of infusion for postdose samples.
j Serum samples for immunogenicity (ADA) analysis will be collected for patients who receive SG. Collection times for ADA samples are at predose on C1D1 and on Day 8 of Cycles 2, 6, and 10. Thereafter, samples will be collected at predose on Day 8 every 8 cycles (eg, C18D8, C26D8, etc) and at the EOT visit. The collection window for ADA sample is within 30 minutes prior to the start of infusion for predose samples.
k Sample to be collected at screening and at predose on Day 1 of Cycles 2 and 3.
l If the optional genomic sample is not collected at C1D1, it may be collected at any other study visit.
m Local tumor tissue testing will be conducted according to the study procedures table if EGFR, ALK, or PD-L1 status is unknown. If local testing is unavailable, tumor tissue testing can be performed by the central laboratory. For patients with squamous cell carcinoma, EGFR and ALK testing is optional.
n Archival tumor tissue (FFPE block) that was obtained preferably within 12 months prior to initial dosing (C1D1) or newly acquired tumor tissues from an evaluable core or excisional biopsy collected from patients within signing of the informed consent to prior to initial dosing (C1D1) may be submitted to the central laboratory. Tissue samples older than 12 months are acceptable. If tumor blocks are not available, it is recommended to submit freshly-cut unstained slides, sections of 4-5-micron thickness, serially cut from a single FFPE block and mounted on positively charged slides. Refer to the Laboratory Manual for further details. All efforts should be made to submit tumor tissue to the central laboratory. Consult with the sponsor if a sample is unavailable and the patient is unwilling to undergo a biopsy procedure.
o CT or MRI scans with IV contrast (unless contrast use is medically contraindicated) of chest, abdomen, pelvis, and any other involved disease sites (brain MRI required if clinically indicated, as determined by the investigator during screening, on-treatment, follow-up, and confirmation of response; brain MRI required if positive at screening, as determined by the investigator during on-treatment and follow-up. Once received at post-screening time point, examination will be required at all subsequent time points) are required in all patients at screening and every 6 weeks for first 12 months, and then every 9 weeks from the date of randomization until the occurrence of radiologic PD per RECIST Version 1.1 criteria requiring discontinuation of treatment. For each patient, the same imaging technique should be used throughout the study. Clinical progression leading to patient discontinuation should be documented by CT or MRI scan of target lesions if clinically feasible. Patients who discontinue treatment due to toxicity or for any reason other than objective progression will continue to obtain radiologic response assessments according to the protocol-required schedule until radiologic PD or initiation of subsequent anticancer therapy. For patients with evidence of CR and PR, a confirmatory scan must be obtained a minimum of 4 to 6 weeks after initial documentation of response. Additional CT or MRI scans may be performed at the discretion of the investigator to assess disease status as medically indicated. These results should be recorded. All radiology images and reports for screening, response, and progression will be provided to the central imaging vendor and held for potential further review.
p If a patient has known or suspected bone metastasis, a bone scan (99m-technetium polyphosphonate scintigraphy, whole body bone MRI, or 18F-NaF/FDG PET) to assess bone metastases will be performed within 6 weeks before C1D1 (historical scans are acceptable). Bone scan, whole body bone MRI, or 18F-FDG-PET scan required if clinically indicated, as determined by the investigator. For patients with evidence of complete response (CR) and partial response (PR), a confirmatory scan must be obtained a minimum of 4 to 6 weeks after initial documentation of response. In patients whose body CT/MRI scans indicate that CR has been achieved, a bone scan or 18F-NaF/FDG PET will be required at confirmation of CR to exclude the presence of new bone metastases or if clinically indicated, and will occur within 1 week, but not more than 2 weeks following a CR, as assessed by the investigator. For each patient, the same imaging technique used at screening should be used throughout the study to ensure comparability. Lesions detected on bone scans must be followed with cross-sectional imaging. All radiology images and reports for screening, response, and progression will be provided to the central imaging vendor and held for potential further review.
q Only SAEs should be reported (see Section 7.3.3).

1. INTRODUCTION

1.1. Background

Lung cancer is the leading cause of cancer-related mortality worldwide. It was estimated that in 2020, there were over 2 million new cases of lung cancer and approximately 1.8 million deaths worldwide {International Agency for Research on Cancer (IARC) 2020}. In the United States (US) in 2021, it is estimated that there will be over 235,000 new cases of lung cancer and over 131,000 deaths {American Cancer Society 2021}. Approximately 80% to 85% of all lung cancers are non-small cell lung cancer (NSCLC) {Ettinger 2019} and more than half of these are still identified at an advanced stage {Siegel 2019}.

Several genomic alterations have been identified in NSCLC that have an impact on therapy selection and molecular testing is part of the standard of care in the evaluation of NSCLC. Among these, epidermal growth factor receptor (EGFR) gene mutations (10% to 50% of NSCLC) and anaplastic lymphoma kinase (ALK) gene rearrangements (5%) are most common and are associated with response to EGFR and ALK tyrosine kinase inhibitors (TKIs), which are widely approved and in clinical use as first-line agents in these subtypes. Other genomic alterations such as ROS proto-oncogene 1 (ROS1), gene rearrangements, proto-oncogene B-raf (BRAF) point mutations MET exon 14 skipping, RET, and neurotrophic tyrosine receptor kinase (NTRK) mutations occur more rarely but have approved therapies targeting such alterations. Unfortunately, only a minority of new cases of NSCLC harbor actionable genomic alterations although the list is growing.

Recent advances with immune checkpoint inhibitor therapy have dramatically improved the prognosis of advanced lung cancer and these immune checkpoint inhibitor therapies, as monotherapy (programmed death protein1 [PD-1] $\geq$ 50%) or in combination with platinum-doublet chemotherapy (regardless of programmed death ligand 1 [PD-L1] expression), are mainly used in the frontline metastatic setting based on results of KN-024, KN-042, KN189, and KN407 and similar studies for patients who do not have actionable genomic alterations. Platinum doublet chemotherapy with or without PD-L1 inhibitor remains the standard treatment for patients with actionable genomic alterations when they have failed treatment with targeted agents or such treatment is not available. After failure of immune checkpoint inhibitor therapy and platinum-based chemotherapy, there are limited treatment options for most patients. According to National Comprehensive Cancer Network guidelines, the use of single-agent chemotherapy (including taxanes) is the standard of care for patients with recurrent or metastatic NSCLC after failure of platinum-based therapy and/or immune checkpoint therapy regardless of presence of genomic alterations and PD-L1 status {Ettinger 2019}. The main options for single-agent chemotherapy in this setting generally include docetaxel (with or without ramucirumab) and pemetrexed (for nonsquamous tumors if not previously used). In a study of docetaxel versus best supportive care in relapsed NSCLC, the median progression-free survival (PFS) was approximately 3 months with a median overall survival (OS) of approximately 6 to 8 months {Shepherd 2000}. These numbers have been borne out in more contemporaneous studies with docetaxel following failure of platinum-based regimens in NSCLC {Horn 2017,

Mazieres 2021}. Although docetaxel is considered standard of care in patients failing platinum-based regimens and checkpoint inhibitors, novel agents remain a significant unmet medical need in subsequent treatment of advanced NSCLC.

1.2. Sacituzumab Govitecan

1.2.1. General Information

Sacituzumab govitecan (SG) is an antibody-drug conjugate (ADC) composed of the following 3 components:

1) The humanized monoclonal antibody, hRS7 IgG1κ, which binds to trophoblast cell surface antigen-2 (Trop-2), a transmembrane calcium signal transducer that is overexpressed in many epithelial cancers, including triple-negative breast cancer

2) The camptothecin-derived agent SN-38, a topoisomerase I inhibitor

3) A hydrolyzable linker, with the company designation as CL2A that links the humanized monoclonal antibody to SN-38

Binding of Trop-2 by the parental RS7 antibody has been shown to result in internalization and processing of the antibody by the targeted cells {Shih 1994, Stein }. Because of its hydrolyzable linker, SG will release its SN-38 payload both intra- and extracellularly in the tumor microenvironment {Goldenberg 2015, Govindan 2013}. Sacituzumab govitecan delivers significantly greater amounts of SN-38 to a Trop-2-expressing tumor than conventional irinotecan chemotherapy {Sharkey 2015}. The extracellular release of SN-38 from SG also allows for bystander killing of Trop-2 negative tumor cells {Lopez 2020, Perrone 2020, Zeybek 2020}. Thus, SG can deliver cytotoxic chemotherapy to tumors, including adjacent cancer cells, in concentrations that are higher than those with standard chemotherapy and may reduce toxic effects in normal tissues that do not express the target.

For further information on SG, refer to the current investigator's brochure (IB).

1.2.2. Nonclinical Pharmacology and Toxicology

In the nonclinical program, SG demonstrated antitumor activity and significant inhibition of tumor growth in various epithelial cancer xenograft models compared to controls; SG also demonstrated low cytotoxicity in multiple cell lines representative of different epithelial tumors (half-maximal inhibitory concentration values ranged from 1.95 nM to 23.14 nM). Nonclinical studies confirmed that the majority of SN-38 administered as SG remains bound to the ADC in the serum and is not circulating as the free cytotoxic payload.

No evidence of hematological toxicity and no abnormal histology findings were observed in nonclinical acute toxicity studies in Swiss-Webster Mice with SG at doses of up to 750 mg/kg/dose (ie, cumulative doses of up to 1500 mg/kg). In nonclinical toxicology studies with Cynomolgus monkeys, SG administered 50 mg/kg/dose (human equivalent

dose = 16 mg/kg/dose) for 4 treatment cycles (Days 1 and 8 of a 21-day cycle) was considered a no observed adverse effect level and 120 mg/kg/dose administered 3 days apart (1 treatment cycle) was associated with mortality. In monkeys, target organs included the gastrointestinal tract (necrosis, erosions, inflammation, fibrosis, hemorrhage, and edema), bone marrow (reduced cellularity) with concomitant reductions in red blood cells, white blood cells, and platelets; female reproductive tract; lymphoid organs (lymphoid depletion); kidney (periarteritis); and skin (hair loss, pigmentation).

SN-38 is a camptothecin and hence might be carcinogenic and is a known developmental toxicant {CAMPTOSAR 2014}.

For additional information on the SG nonclinical program, refer to the current IB.

1.2.3. Clinical Studies of Sacituzumab Govitecan

Based on the results of Studies IMMU-132-05 and IMMU-132-06, SG has been approved in the US for the treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received 2 or more prior therapies, at least 1 of them for metastatic disease and has received accelerated approval in the US for the treatment of adult patients with metastatic urothelial cancer (mUC) who have previously received a platinum-containing chemotherapy and either PD-1 or PD-L1 inhibitor.

As of January 2021, clinical data are available for 3 clinical studies (2 completed and 1 ongoing) in which 795 patients were treated with SG:

- IMMU-132-01, a Phase 1/2, open-label, basket study in patients with metastatic epithelial cancers that were either relapsed or refractory after at least 1 standard therapeutic regimen for their tumor type (N = 495). Fifty-four patients with NSCLC were enrolled; 8 at a starting dose of 8 mg/kg and 46 at a starting dose of 10 mg/kg on Days 1 and 8 of 21-day cycles.

- IMMU-132-05, a Phase 3 study of SG compared with single-agent chemotherapy in patients with unresectable locally advanced or mTNBC who had received at least 2 prior therapies (N = 582 including 258 with SG and 224 with single-agent chemotherapy); included a pharmacokinetic (PK)-electrocardiogram (ECG) substudy of 29 patients from the SG-treated group to assess the effects of SG on cardiac repolarization (QTc interval) and other ECG parameters.

- IMMU-132-06, an ongoing Phase 2 study in patients with locally advanced or mUC (N = 135) that included: 1) a cohort of patients who progressed after prior platinum-based and PD-1/PD-L1 inhibitor therapy (N = 113) and 2) a cohort of patients who were platinum ineligible and received PD-1/PD-L1 inhibitor therapy in the first line metastatic setting (N = 22).

Summaries of PK, clinical efficacy, and clinical safety are provided in the following sections. For additional information on the SG clinical program, refer to the current IB.

1.2.3.1. Summary of Clinical Safety

Unresectable Locally Advanced/Metastatic Triple-Negative Breast Cancer and Locally Advanced/Metastatic Urothelial Cancer

The safety profile for SG was similar in the treatment of mTNBC and mUC. The most common adverse events (AEs) were nausea, diarrhea, neutropenia, fatigue, alopecia, anemia, vomiting, and constipation. The most clinically relevant Grade 3 or Grade 4 AEs with SG were neutropenia and diarrhea. The most frequent AEs that led to treatment modification were neutropenia and diarrhea. The frequent AEs leading to permanent discontinuation of study drug were fatigue, diarrhea, pneumonia, and neutropenia.

Neutropenia occurred in the first cycle of treatment and resolved within approximately 1 week of onset. Most cases of neutropenia were not febrile, were nonserious, and could be managed with granulocyte-colony stimulating factor administration and/or dose reduction after Cycle 1.

Diarrhea with SG occurred within the first treatment cycle (median time of 12 days to first event) and resolved within approximately 1 week of onset. Most of the cases of diarrhea were nonsevere, nonserious, and did not lead to either a treatment interruption or dose reduction.

Higher incidences of neutropenia, febrile neutropenia, and anemia were seen in patients who were homozygous for the uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1)*28 allele compared with patients who were heterozygous for the UGT1A1*28 allele and patients who were homozygous for the wild-type allele.

No evidence for QTc prolongation was seen with SG in the PK-ECG substudy in the mTNBC study.

For further information on SG, refer to the current IB.

Non-Small Cell Lung Cancer

In Study IMMU-132-01 (data cutoff of 01 March 2019), the most common AEs (≥ 25% of patients) reported in NSCLC patients (N = 54) were nausea (83.3%), diarrhea (66.7%), fatigue (51.9%), alopecia (48.1%), vomiting (44.4%), constipation (42.6%), decreased appetite (38.9%), anemia (35.2%), and neutropenia (29.6%). The frequencies of these most common AEs were similar between the patients with NSCLC group and the overall population across multiple tumor types and starting doses (N = 495; 402 patients received 10 mg/kg of SG, 81 received 8 mg/kg of SG, and 12 received ≥ 12 mg/kg of SG) with the exception of nausea and neutropenia (the incidence of nausea was > 10% higher in patients with NSCLC versus the overall population and neutropenia was ≥ 10% higher in the overall population versus patients with NSCLC). These AEs are consistent with the known safety profile of SG.

For patients with NSCLC, Grade 3 or higher AEs were reported in 79.6% of patients, serious AEs (SAEs) in 42.6%, AEs leading to study drug discontinuation in 3.7%, and AEs leading to dose interruption in 42.6%. The incidence of these was similar to or lower than the overall population.

No events of pneumonitis or interstitial lung disease were reported in patients with NSCLC.

1.2.3.2. Summary of Clinical Efficacy

Non-Small Cell Lung Cancer

Sacituzumab govitecan has been evaluated in patients with metastatic NSCLC in 2 clinical studies: IMMU-132-01 (completed; 54 patients enrolled) and IMMU-132-11 (ongoing; preliminary results are not available yet).

In IMMU-132-01, objective response rate (ORR) based on local response assessment was 16.7% for the NSCLC population; all responses were partial responses (PRs). The majority of patients had at least a 30% reduction in the size of the target lesion.

Median duration of response (DOR) by local assessment was 6.0 months (range: 2.5 to 21.0). The Kaplan-Meier estimate of the percentage of patients with a response of 6 months was 44.4% (95% CI: 13.6, 71.9).

Unresectable Locally Advanced/Metastatic Triple-Negative Breast Cancer

In Study IMMU-132-05, a statistically significant and clinically meaningful benefit for SG over single-agent chemotherapy was seen for PFS (hazard ratio [HR], 0.41; $P < 0.0001$) and OS (HR: 0.48; $P < 0.0001$). Significant benefits with SG for PFS and OS were seen irrespective of BRCA status and in all other prespecified subgroups, including by age and other previous treatments for mTNBC, including prior treatment with PD-1/PD-L1. The ORR was also significantly improved with SG versus single-agent chemotherapy in Study IMMU-132-05 (35% vs 5%).

In Study IMMU-132-01, ORR and median DOR for patients with mTNBC were 33.3% and 7.7 months, respectively. Median PFS and median OS were 5.6 and 13.0 months, respectively.

Locally Advanced/Metastatic Urothelial Cancer

In patients who progressed after prior platinum-based and PD-1/PD-L1 inhibitor therapy, ORR was 27% in Studies IMMU-132-01 and IMMU-132-06 with an associated median DOR of 20 months (mUC subgroup N = 15; median follow-up duration of approximately 12 months) and 7.2 months (median follow-up duration of 9.1 months), respectively. The clinical benefit rates for Studies IMMU-132-01 and IMMU-132-06 were 44.4% and 37.2%, respectively.

1.3. Information About Docetaxel

1.3.1. Description of Docetaxel

Docetaxel is an anticancer cytotoxic agent classified as an antimicrotubule inhibitor. Docetaxel is indicated for the treatment of multiple solid tumors, including advanced NSCLC, as a single agent {Taxotere® 1995, Taxotere® 1996}.

1.4. Rationale for This Study

There remains a high unmet need for novel agents in the treatment of advanced NSCLC particularly in patients who have failed treatment with immune checkpoint inhibitors and platinum-based chemotherapy due to poor outcomes with current treatment in this patient population. Even though much progress has been made in development of targeted treatments for specific genomic alterations, eventually most patients have progressive disease (PD) on these treatments after which they are treated with platinum chemotherapy and immune checkpoint inhibitors. For patients whose cancers have failed the aforementioned treatments, very few treatment options exist, and they represent a patient population of high unmet medical need. Sacituzumab govitecan has demonstrated encouraging activity and a manageable safety profile in advanced NSCLC and thus warrants further evaluation. A Phase 3, randomized, multicenter study is the most reliable design, with randomization and a global footprint providing minimization of potential bias. Docetaxel, the comparator agent for this study, is the appropriate standard of care in this setting and has been evaluated in numerous studies in patients with NSCLC, so that both its efficacy and safety profiles are well established. Overall survival as the primary endpoint remains the most robust and unbiased endpoint in cancer clinical studies, and the endpoint most important to both patients and clinicians. The current study design will therefore provide a reliable assessment of SG in the treatment of NSCLC in patients with PD after a platinum-based regimen and a checkpoint inhibitor.

1.5. Rationale for Dose Selection of Sacituzumab Govitecan

In Study IMMU-132-01 in patients with diverse metastatic solid cancers including mTNBC and NSCLC, dose escalation was performed according to a standard 3 + 3 design and based on planned initial dose levels of 8, 12, and 18 mg/kg. An SG dose of 12 mg/kg was formally identified as the maximum tolerated dose (MTD) but was associated with dose delays and reductions in several patients. In order to determine a maximum acceptable dose, additional patients were treated at the 8 mg/kg dose level and an intermediate dose cohort of 10 mg/kg was added. The 8 mg/kg and 10 mg/kg dose levels were shown to be better tolerated in the first cycle than the formally determined MTD of 12 mg/kg, allowing repeated cycles with a better safety profile. There were no major differences in safety (worsening of AE incidences or severity) between the 8 mg/kg and the 10 mg/kg dose levels, and there was a trend for better efficacy in patients with mTNBC with the 10 mg/kg dose {Ocean 2017}. Based on these results, the 10 mg/kg dose of SG was selected as the maximum acceptable dose.

1.6. Rationale for Open-Label Study Design

The treatment schedules for SG and docetaxel are different. Sacituzumab govitecan is administered on Days 1 and 8 of a 21-day cycle while docetaxel is administered only on Day 1 of a 21-day cycle. Moreover, docetaxel requires premedication with corticosteroids 3 days prior to treatment administration, which may be difficult to implement and place undue burden on patients if given in a blinded fashion.

1.7. Risk/Benefit Assessment for the Study

The outlook for patients with NSCLC who have developed progressive neoplastic disease despite treatment with a platinum-based regimen and a checkpoint inhibitor is dire, with median survival times measured in months. In addition, both progressive neoplastic disease in the lung as well as metastatic disease in patients with advanced NSCLC produce severe morbidity and a markedly diminished quality of life (QOL). Given the demonstrated response and clinical benefit rates for SG and the ongoing need for novel therapies in the treatment of advanced lung cancer, the risk/benefit equation favors the continued development of SG in the population of patients with NSCLC who have progressive neoplastic disease despite treatment with a platinum-based regimen and a checkpoint inhibitor.

An infectious disease pandemic may pose additional risks to study drug availability, the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 2 for further details on the risks and risk mitigation strategy.

1.7.1. Clinical Data for Docetaxel

Docetaxel is approved for use as monotherapy in multiple solid tumors including NSCLC, head and neck squamous cell carcinoma, breast cancer, hormone refractory prostate cancer, and gastric adenocarcinoma. Docetaxel is also widely used as standard of care in multiple solid tumors, including mUC and mNSCLC, who fail frontline chemotherapy and/or immune checkpoint therapy {Taxotere® 1995, Taxotere® 1996}.

The most common AEs across all docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia {Taxotere® 1995, Taxotere® 1996}. Docetaxel is contraindicated in patients with neutrophil counts less than 1500 cells/mm^3 and in patients with hypersensitivity to docetaxel or polysorbate 80 {Taxotere® 1995, Taxotere® 1996}. Docetaxel carries a black box warning for toxic deaths, hepatotoxicity, neutropenia, hypersensitivity reactions, and fluid retention. In addition, cutaneous reactions, severe skin toxicity, neurologic reactions (including paresthesia, dysesthesia, and pain), asthenia, and potential fetal harm have been observed with docetaxel.

Docetaxel has been evaluated in several randomized clinical studies in patients with NSCLC following failure of platinum-based regimens, with early studies comparing docetaxel to other chemotherapy agents and more recent studies comparing docetaxel to checkpoint inhibitors.

In a study comparing docetaxel to best supportive care, docetaxel produced an ORR of 7.1% and a median OS of 7 months; 1-year survival was 37% {Shepherd 2000}. In the TAX 320 study comparing docetaxel to either vinorelbine or ifosfamide, docetaxel produced an ORR of 6.7% with PFS of 26 weeks; 1-year survival was 32% {Fossella 2000}. In a study comparing docetaxel to pemetrexed, docetaxel was associated with an ORR of 8.8% and median OS of 7.9 months {Hanna 2004}.

More contemporaneous studies of docetaxel versus checkpoint inhibitors have shown similar results. A pooled analysis of the CheckMate 017 and CheckMate 057 studies of nivolumab versus docetaxel in platinum failures, the 1-year PFS for docetaxel was 9% (in nonsquamous NSCLC) and 14% in squamous NSCLC {Horn 2017}. In the OAK and POPLAR studies comparing atezolizumab and docetaxel, docetaxel had median OS values of 9.7 and 9.8 months, respectively. In the Keynote 010 study comparing pembrolizumab to docetaxel, docetaxel was associated with a median OS of 8.2 months, a median PFS of 4.1 months, and an ORR of 8% {Mazieres 2021}.

In summary, docetaxel is used as a standard of care option for second and later lines of therapy for multiple solid tumor types after frontline chemotherapy and/or immune checkpoint therapy and has been evaluated extensively in patients with NSCLC.

1.8. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoint
• To compare the OS of SG versus docetaxel.	• OS is defined as the time from the date of randomization until death due to any cause in the Intent-to-Treat (ITT) Analysis Set.
Secondary Objectives	**Secondary Endpoints**
To compare the effect of SG versus docetaxel on the following:	
• PFS as assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.	• PFS is defined as the time from the date of randomization until the date of objective disease progression or death (whichever comes first) as assessed by the investigator per RECIST Version 1.1.
• ORR as assessed by the investigator per RECIST Version 1.1.	• ORR is defined as the proportion of patients who achieve a complete response (CR) or PR that is confirmed at least 4 weeks later as assessed by the investigator per RECIST Version 1.1.
• DOR as assessed by the investigator per RECIST Version 1.1.	• DOR is defined as the time from the first documentation of CR or PR to the earlier of the first documentation of PD or death from any cause (whichever comes first) as assessed by the investigator per RECIST Version 1.1.
• Disease control rate (DCR) as assessed by the investigator per RECIST Version 1.1.	• DCR is defined as the proportion of patients who achieve a CR, PR, or stable disease (SD) as assessed by the investigator per RECIST Version 1.1.
• Safety and tolerability.	• Incidence of treatment-emergent adverse events (TEAEs) and clinical laboratory abnormalities.
• QOL using NSCLC Symptom Assessment Questionnaire (NSCLC-SAQ).	• Time to first deterioration in shortness of breath domain as measured by NSCLC-SAQ. • Time to first deterioration in NSCLC-SAQ total score.

Exploratory Objectives	Exploratory Endpoints
• To characterize the PK and immunogenicity of SG.	• Peak (C_{max}) and trough (C_{trough}) concentrations over time and antidrug antibodies (ADAs) over time.
• To assess disease-related symptoms and health-related QOL using EQ-5D-3 level (EQ-5D-3L); NSCLC-SAQ; the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Version 3 (EORTC QLQ-C30 v3); Patient Global Impression of Severity (PGIS); and Patient Global Impression of Change (PGIC).	• Mean change from baseline of total score and all domains of NSCLC-SAQ not assessed as secondary endpoints. • Mean change from baseline of all domains of EORTC QLQ-C30 v3. • The proportion of patients with meaningful change in each QOL domain while on treatment. • Time to first improvement and time to first deterioration in each QOL domain not assessed as secondary endpoints.
• To assess and compare treatment-related symptoms using Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).	• Frequency, severity, or interference of treatment-related symptoms.
• To assess tumor expression of Trop-2 as a potential predictive biomarker of response to SG. • To explore blood and tumor biomarkers that may be associated with response to SG treatment.	• Correlation of clinical response with baseline tumor Trop-2 expression. • Correlation of clinical response with tumor, tumor microenvironment, and blood biomarkers at baseline and after SG treatment. • Clearance of circulating tumor DNA upon SG treatment.

3. STUDY DESIGN

3.1. Study Design Overview

Study GS-US-577-6153 is an open-label, global, multicenter, randomized, Phase 3 study to compare the efficacy and safety of SG versus docetaxel in patients with advanced or metastatic NSCLC with progression on or after platinum-based chemotherapy and anti-PD-1/PD-L1 immunotherapy received either in combination or sequentially. Patients with actionable genomic alterations will also be included if they have received prior treatment with an appropriate TKI (see Appendix 8).

This study will be conducted in approximately 250 centers globally. Patient participation will include screening, randomization, treatment, and follow-up. Screening will last no longer than 28 days to confirm eligibility and establish disease characteristics prior to randomization and treatment. The study procedures table and study schema are presented in Table 1 and Figure 1, respectively.

Approximately 580 eligible patients will be randomly assigned in a 1:1 ratio to receive either SG (Investigational Arm A) or docetaxel (Control Arm B). Randomization will be stratified based on histology (squamous vs nonsquamous), response to last prior immune therapy received (best response PD/SD vs CR/PR on immune therapy), and if they have received prior therapy for actionable genomic alteration (yes vs no).

The primary endpoint of the study is OS. Secondary efficacy endpoints are PFS, ORR, DOR, and DCR as assessed by the investigator per RECIST Version 1.1; time to first deterioration in NSCLC-SAQ total score; and time to first deterioration in shortness of breath as measured by NSCLC-SAQ. Safety will be assessed by the reporting of AEs, assessments of vital signs, laboratory results, and extent of exposure to study drug. Additional QOL assessments will be conducted. Pharmacokinetics, ADA, and various biomarkers will also be assessed.

Sacituzumab govitecan will be administered at 10 mg/kg via IV infusion on Days 1 and 8 of a 21-day cycle. Docetaxel will be administered at 75 mg/m^2 via IV infusion on Day 1 of a 21-day cycle. Patients will receive study drug until PD, death, unacceptable toxicity, or another treatment discontinuation criterion is met. Follow-up will begin at the time of the completion of the end of treatment (EOT) visit, which will occur 30 days (± 7) after the last dose of study drug. All patients will be followed for survival until 1 of the discontinuation criteria from the study is met.

An independent data monitoring committee (DMC) will be convened at regular intervals to assess the progress of this study, review safety data, and conduct the interim efficacy analysis.

Extension Study in China

After the enrollment period of the global study is completed, subjects from China will continue to be enrolled in the extension study, to collect additional efficacy and safety data in patients from mainland China in order to support future local registration in China. The extension study will be identical to the global study (eg, inclusion and exclusion criteria, study endpoints, primary and secondary objectives, study procedures), with the exception of an additional supplemental statistical analysis plan (SAP) for Chinese patients.

3.2. Study Treatments

This is a randomized, open-label study. Eligible patients will be randomly assigned (1:1) to receive either:

- Sacituzumab govitecan 10 mg/kg via IV infusion on Days 1 and 8 of a 21-day cycle (ie, 2 weekly doses plus 1 week without treatment)
- Docetaxel 75 mg/m^2 via IV infusion on Day 1 of a 21-day cycle (ie, once every 3 weeks)

The details of study drugs administered in this study are described in Section 5. Details regarding the formulation, packaging, and labeling of SG and docetaxel are provided in Sections 5.2 and 5.7, respectively.

3.3. Duration of Treatment

Patients will receive study drug until PD, death, unacceptable toxicity, or another treatment discontinuation criterion is met (see Section 3.4 for further details about discontinuation criteria).

Treatment with either SG or docetaxel beyond the initial investigator-assessed PD per RECIST Version 1.1 (Appendix 6) is permitted if there is evidence of clinical benefit per the investigator and the patient is tolerating study drug. The following clinical criteria should be met for patients to continue to receive treatment beyond the investigator-assessed progression.

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in performance status
- Absence of symptomatic rapid disease progression requiring urgent medical intervention (eg, symptomatic pleural effusion, spinal cord compression)

Sponsor consultation is required before patients initiate any treatment beyond progression. If this occurs, the patient will remain in the study and continue to be monitored according to the study procedures table (Table 1). All patients will be followed for survival until 1 of the discontinuation criteria from the study is met (Section 3.4.2).

3.4. Discontinuation Criteria

3.4.1. Discontinuation From Study Treatment

Study drug may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the patient's best interest. Discontinuation criteria for toxicities, dose delays, or failure to resolve a toxicity are detailed in Section 5.5 and Section 5.10.
- Initiation of alternative anticancer therapy, including any investigational agent
- Disease progression with no evidence of clinical benefit (see Section 6.3.7)
- Patient request to discontinue for any reason.
- Patient noncompliance.
- Pregnancy during the study (see Appendix 3).
- Discontinuation of the study at the request of Gilead Sciences (hereafter referred to as Gilead) or an institutional review board (IRB) or independent ethics committee (IEC)
- Lost to follow-up
- Investigator or treating physician decision in the absence of any of the above

Study drug discontinuation should not result in patient discontinuation from the study and the patient should continue to be followed up in the study for PD and survival as per Section 3.4.4. Reasons for discontinuation from the study are outlined in Section 3.4.2.

3.4.2. Discontinuation From the Study

Patients will discontinue the study under any of the following instances:

- Death
- Patient withdrawal of consent from the study
- Lost to follow-up (Section 3.4.3)
- Termination of the study at the request of Gilead or an IRB/IEC

3.4.3. Lost to Follow-up

Should the patient fail to return to the study site for a scheduled protocol-specific visit, sites will need to make at least 4 attempts by a combination of phone calls, text messages, email messages, etc to contact the patient to reschedule the study visit as well as confirm survival status. Sites must document all attempts to contact the patient. If a patient does not respond within 1 month after the fourth contact, the patient will be considered lost to follow-up. For patients who are considered lost to follow-up from the study prior to completion of all protocol-required visits for study assessments or survival follow-up as described in the study procedures table (Table 1), the investigator may search publicly available records (where permitted by local laws and regulations) to ascertain survival status unless the patient withdraws consent for such follow-up. This ensures reduced risk of missing critical efficacy data.

3.4.4. Safety and Survival Follow-up

After treatment discontinuation (Section 3.4.1), all patients must complete an EOT visit 30 days (± 7) after the last dose of study drug. Patients will enter the follow-up period after completing the EOT visit, unless the patient explicitly indicates their desire to forego survival follow-up in writing to their study investigator. Follow-up assessments will be performed according to the study procedures table (Table 1). All patients will be followed for survival until 1 of the discontinuation criteria from the study is met (Section 3.4.2). For any patient who dies during the follow-up period, primary cause of death must be reported to the sponsor.

Patients who complete or withdraw from all other study assessments (eg, tumor assessments, study treatment) will enter long-term follow-up. Follow-up visits should be conducted every 12 weeks from EOT visit (± 7 days) or more frequently until death or withdrawal of consent, whichever comes first. Visits will include documentation of survival status and documentation of subsequent anticancer therapy. For patients who discontinue from the study prior to completion of all protocol-required visits for study assessments or survival follow-up as described in the study procedures table (Table 1), the investigator may search publicly available records (where permitted by local laws and regulations) to ascertain survival status unless the patient withdraws consent for such follow-up. This ensures reduced risk of missing critical efficacy data.

3.5. Definitions for End of Study

Individual Patients: Patients are considered to have reached the end of the study when they are no longer followed for long-term or survival follow-up due to the following reasons: death, patient withdrew consent, lost to follow-up, the sponsor terminated study.

For any patient who dies during the follow-up period, primary cause of death must be reported to the sponsor.

All Patients: The end of the entire study for all patients is defined as the date on which the last patient remaining on study completes the last study visit/call or when the sponsor decides to end the study. The sponsor reserves the right to terminate the study at any time for any reason (including safety).

3.6. Poststudy Care

Patients who discontinue study drug and agree to remain in the study will follow the requirements outlined in Table 1 for continued follow-up.

3.7. Source Data

The source data for this study will be obtained from original records (eg, clinic notes, hospital records, patient charts), central laboratory, local laboratory, and/or specialty laboratory (for PK, ADA, and/or biomarker data) and/or additional biomarker testing, and interactive response technology (IRT).

4. PATIENT POPULATION

4.1. Number of Patients and Patient Selection

Approximately 580 eligible patients will be enrolled in this study.

4.1.1. Patient Replacement

Patients who discontinue before the end of the study will not be replaced.

4.2. Inclusion Criteria

Patients must meet all of the following inclusion criteria at screening/Day −1 to be eligible for participation in this study (no waivers for patient eligibility will be offered or permitted):

1) Female or male patients, 18 years of age or older, able to understand and give written informed consent

2) Life expectancy of 3 months or more

3) Pathologically documented NSCLC with documented evidence of Stage 4 NSCLC disease at the time of enrollment (based on the American Joint Committee on Cancer, Eighth Edition).

4) EGFR, ALK, and PD-L1 results are required prior to enrollment (see Section 6.3.10). Resulting for other actionable genomic alterations is recommended and to be performed as per local standard of care and availability of targeted treatment. For patients with squamous cell carcinoma, EGFR and ALK testing is optional.

5) Must have progressed after platinum-based chemotherapy in combination with anti-PD-1/PD-L1 antibody OR platinum-based chemotherapy and anti-PD-1/PD-L1 antibody (in either order) sequentially.

    - Note: Includes patients who received prior platinum-based chemoradiotherapy (with or without maintenance anti-PD-1/PD-L1 antibody) for Stage 3 disease. To be considered to have progressed during or after prior treatment with platinum-based chemotherapy, patients should have either received prior platinum-based chemotherapy in the recurrent/metastatic setting or have experienced disease progression within 6 months of last dose of platinum-based chemotherapy administered as part of concurrent chemoradiation for Stage 3 disease or as neoadjuvant or adjuvant therapy. To be considered to have progressed during or after prior treatment with an anti-PD-1/PD-L1 antibody, patients should have either received this therapy in the recurrent/metastatic setting or have experienced disease progression during “maintenance” treatment following concurrent chemoradiation for Stage 3 disease.

        a) No additional treatments are allowed in the recurrent/metastatic setting for patients with no actionable genomic alterations.

b) Patients with EGFR, ALK, or any other known actionable genomic alterations must have also received treatment with at least 1 locally approved and available TKI appropriate to the genomic alteration (see Appendix 8).

c) Documented radiographic disease progression while on or after receiving the most recent treatment regimen for advanced or metastatic NSCLC.

6) Measurable disease based on computed tomography (CT) or magnetic resonance imaging (MRI) as assessed by the investigator in accordance with per RECIST Version 1.1. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. Historical images within 28 days of the screening visit may be accepted as a screening image if deemed acceptable in the opinion of the investigator.

7) Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (Appendix 5) before randomization.

8) Adequate hematologic counts without transfusional or growth factor support within 2 weeks of study drug initiation (hemoglobin ≥ 9 g/dL, absolute neutrophil count ≥ 1500/mm^3, and platelets ≥ 100,000/μL).

9) Adequate hepatic function (bilirubin ≤ 1.5 upper limit of normal [ULN], aspartate aminotransferase and alanine aminotransferase ≤ 2.5 × ULN or ≤ 5 × ULN if known liver metastases, and serum albumin > 3 g/dL).

- Note: The investigator should follow local practice guidelines and/or the docetaxel label approved in the country of drug administration for assessing eligibility of patients for the study.

10) Creatinine clearance of at least 30 mL/min as assessed by the Cockcroft-Gault equation {Cockcroft 1976}.

11) Male patients and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 3.

4.3. Exclusion Criteria

Patients who meet *any* of the following exclusion criteria at screening/Day −1 are not eligible to be enrolled in this study (no waivers for patient eligibility will be offered or permitted):

1) Mixed small-cell lung cancer and NSCLC histology.

2) Positive serum pregnancy test (Appendix 3) or women who are lactating.

3) Known hypersensitivity to the study drugs, their metabolites, or formulation excipients.

4) Requirement for ongoing therapy with or prior use of any prohibited medications for SG and docetaxel as per Sections 5.6.1 and 5.11, respectively.

5) Received a prior anticancer biologic agent within 4 weeks prior to enrollment or have received prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to enrollment and have not recovered (ie, > Grade 2 is considered not recovered) from AEs at the time of study entry. Patients participating in observational studies are eligible.

6) Have not recovered (ie, > Grade 2 is considered not recovered) from AEs due to a previously administered agent.

   - Note: Patients with any grade alopecia are an exception to this criterion and will qualify for the study.

   - Note: If patients received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study drug.

7) Previously received treatment with any of the following:

   a) Topoisomerase 1 inhibitors. Any agent including an ADC containing a chemotherapeutic agent targeting topoisomerase 1

   b) Trop-2-targeted therapy

   c) Docetaxel as monotherapy or in combination with other agents

8) Active second malignancy

   - Note: Patients with a history of malignancy that have been completely treated, with no evidence of active cancer for 3 years prior to enrollment, or patients with surgically cured tumors with low risk of recurrence (eg, nonmelanoma skin cancer, histologically-confirmed complete excision of carcinoma in situ, or similar) are allowed to enroll.

9) NSCLC that is eligible for definitive local therapy alone.

10) Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (ie, pulmonary emboli within 3 months of enrollment, severe asthma, severe chronic obstructive pulmonary disease, restrictive lung disease, pleural effusion, etc); any autoimmune, connective tissue, or inflammatory disorders with pulmonary involvement (ie, rheumatoid arthritis, Sjogren syndrome, sarcoidosis, etc); or prior pneumonectomy.

11) Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they have stable CNS disease for at least 4 weeks prior to enrollment and all neurologic symptoms have returned to baseline, have no evidence of new or enlarging brain metastases, and are taking 10 mg/day or less of prednisone or its equivalent. All patients with carcinomatous meningitis are excluded regardless of clinical stability.

12) Met any of the following criteria for cardiac disease:

    a) Myocardial infarction or unstable angina pectoris within 6 months of enrollment.

    b) History of serious ventricular arrhythmia (ie, ventricular tachycardia or ventricular fibrillation), high-grade atrioventricular block, or other cardiac arrhythmias requiring antiarrhythmic medications (except for atrial fibrillation that is well controlled with antiarrhythmic medication); history of QT interval prolongation.

    c) New York Heart Association Class III or greater congestive heart failure or left ventricular ejection fraction of less than 40%.

13) Active chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease) or gastrointestinal perforation within 6 months of enrollment.

14) Active serious infection requiring antibiotics.

15) Positive HIV-1 or HIV-2 antibody with detectable viral load OR taking medications that may interfere with SN-38 metabolism.

16) Positive for hepatitis B surface antigen. Patients who test positive for hepatitis B core antibody will require hepatitis B virus DNA by quantitative polymerase chain reaction for confirmation of active disease.

17) Positive hepatitis C antibody and detectable hepatitis C viral load.

18) Other concurrent medical or psychiatric conditions that, in the investigator's opinion, may be likely to confound study interpretation or prevent completion of study procedures and follow-up examinations.

5. STUDY DRUGS

5.1. Randomization and Treatment Codes Access

Patients who meet randomization eligibility criteria will be randomized in a 1:1 ratio to receive either SG or docetaxel starting on Day 1 and assigned a patient number. Randomization will be stratified by the following:

1) Histology (squamous vs nonsquamous)

2) Response to last prior immune therapy received (best response PD/SD vs CR/PR on immune therapy)

3) Received prior therapy for actionable genomic alteration (yes vs no)

This is an open-label study. Treatment assignment data may be restricted to members of the sponsor team in accordance with sponsor processes for data handling.

5.2. Description and Handling of Sacituzumab Govitecan

5.2.1. Formulation

Sacituzumab govitecan is supplied as a sterile, off-white to yellowish lyophilized powder in single-dose glass vials. It is formulated in 2-(*N*-morpholino) ethane sulfonic acid buffer containing trehalose and polysorbate 80 and contains no preservatives. Following reconstitution, the concentration of SG is 10 mg/mL. The pH of the reconstituted solution is approximately 6.5.

5.2.2. Packaging and Labeling

Sacituzumab govitecan is packaged in single-use, 50R, glass vials, closed with coated elastomeric stoppers and capped with flip-off caps with aluminum over seals.

Study drug to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US Food and Drug Administration (FDA), European Union (EU) Guideline to Good Manufacturing Practice–Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

The glass vials of SG must be stored under refrigeration (2-8 °C) and protected from light until use. Since the formulated drug product contains no preservative, vials should be used only once. After reconstitution, the infusion should be initiated as soon as possible.

Refer to the current version of the Pharmacy Manual for additional details.

5.3. Premedication and Prophylaxis for Sacituzumab Govitecan

Guidance for premedication for prevention of toxicities associated with SG is presented in Table 2.

Table 2. Guidance for Premedication and Prophylaxis for Toxicities Associated With Sacituzumab Govitecan

Potential Reaction	Premedication and Prophylaxis Guidance
Infusion-related reaction	• Antipyretics and H1/H2 blockers should be administered before each SG infusion. • Corticosteroids (hydrocortisone 50 mg or equivalent PO or IV) may be administered prior to infusions.
Nausea and vomiting	• Premedication with a 2-drug antiemetic regimen is recommended. • If nausea and vomiting are persistent, a 3-drug regimen may be used, including a 5-HT3 inhibitor (ondansetron or palonosetron, or other agents according to local practices), an NK1-receptor antagonist (fosaprepitant or aprepitant), and dexamethasone (10 mg PO or IV). • Anticipatory nausea can be treated with olanzapine.
Neutropenia	• Complete blood counts must be obtained prior to each SG infusion and treatment should be administered only if ANC meets the following criteria: — Day 1: ANC $\geq 1500/mm^3$ — Day 8: ANC $\geq 1000/mm^3$ • The routine prophylactic use of growth factors is not required; however, prophylactic administration should comply with current ASCO/ESMO guidelines for use of growth factors.

ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; IV = intravenous; PO = orally; SG = sacituzumab govitecan

All patients should be given medications to take home with clear instructions for the prevention and treatment of nausea, vomiting, and diarrhea. At the onset of diarrhea, promptly initiate treatment with antidiarrheals (eg, loperamide at 4 mg initially followed by an additional 2 mg with every episode of diarrhea for a maximum of 16 mg daily or follow local label guidelines for loperamide). Discontinue antidiarrheals 12 hours after diarrhea resolves. Additional supportive measures (eg, fluid and electrolyte substitution) may also be employed as clinically indicated. Patients who exhibit an excessive cholinergic response to treatment with SG (eg, abdominal cramping, diarrhea, salivation, etc) can receive appropriate premedication (eg, anticholinergics such as atropine) for subsequent infusions.

5.4. Dosage and Administration of Sacituzumab Govitecan

Sacituzumab govitecan is administered at 10 mg/kg as an intravenous (IV) infusion on Days 1 and 8 of a 21-day cycle.

The dose of SG will be calculated based on actual weight at enrollment (using weight obtained either at screening or on Cycle 1 Day 1) and remains constant throughout the study, unless there is a > 10% change in body weight from baseline. Modifications to the study treatment doses administered should be made for a > 10% change in body weight from baseline. Dose modifications for changes in body weight < 10% may be made according to local institutional guidelines.

Sacituzumab govitecan is administered via IV infusion as described below with additional information available in the current version of Pharmacy Manual. Sacituzumab govitecan should not be administered as an IV push or bolus. Sacituzumab govitecan is a cytotoxic drug and applicable special handling and disposal procedures should be followed.

- Administer the first infusion over 3 hours. Subsequent infusions may be administered over 1 to 2 hours if previous infusions were well tolerated. Monitor the patient during, and for at least 30 minutes after infusion.
- Protect the infusion bag from light.
- An infusion pump may be used.
- Confirm compatibility with polypropylene infusion bags.
- In-line filters and other ancillary infusion equipment are not recommended for use.
- Do not mix SG, or administer as an infusion, with other medicinal products.
- Upon completion of the infusion, flush the IV line with 20 mL 0.9% Sodium Chloride Injection, United States Pharmacopeia.

5.5. Dose Modification and Treatment Delays of Sacituzumab Govitecan

The major toxicities of SG are expected to be gastrointestinal symptoms and neutropenia. Premedication and prophylaxis for the prevention of SG-associated toxicities is described in Section 5.3. Management of toxicities should be in accordance with best clinical practices, standard institutional guidelines, and current American Society of Clinical Oncology/European Society for Medical Oncology guidelines. All patients will be closely monitored over the course of their treatment and aggressively medically managed, including dose reduction and interruption, to prevent the need for treatment discontinuation and serious complications of these toxicities. In particular, patients with known reduced UGT1A1 activity should be closely monitored for adverse reactions (see Section 1.2.3.1). All efforts to avoid dose reduction should be taken to address toxicity prior to initiation of dose reduction. Instructions for dose modification and discontinuation of SG for treatment-related toxicities are provided in Section 5.5.1 and instructions for treatment delays are provided in Section 5.5.2.

5.5.1. Dose Reductions and Discontinuation of Sacituzumab Govitecan

Table 3 summarizes recommendations for SG dose reductions and discontinuations for treatment-related toxicities.

Sacituzumab govitecan dose reductions and interruptions will be managed based on toxicity severity. Leukopenia or lymphopenia in the absence of neutropenia does not require dose modification. The SG dose must not be re-escalated following a dose reduction.

The SG treatment must be discontinued if there is a 3-week dose delay from the planned treatment date due to treatment-related toxicity or 5-week dose delay for all other reasons.

Table 3. Recommended Dose Modification Schedule for Sacituzumab Govitecan

Adverse Reaction	Occurrence	Dose Modification or Action
Severe neutropenia		
Grade 4 neutropenia ≥ 7 days, OR	First	25% dose reduction and administer G-CSF
Grade 3-4 febrile neutropenia, OR	Second	50% dose reduction
At time of scheduled treatment, Grade 3 or 4 neutropenia that delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1	Third	Discontinue Treatment
At time of scheduled treatment, Grade 3 or 4 neutropenia that delays dosing beyond 3 weeks for recovery to ≤ Grade 1	First	Discontinue treatment
Severe nonneutropenic toxicity		
Grade 4 nonhematologic toxicity of any duration, OR	First	25% dose reduction
	Second	50% dose reduction
Any Grade 3 or 4 nausea, vomiting, or diarrhea due to treatment that is not controlled with antiemetics and antidiarrheal agents OR Other Grade 3 or 4 nonhematologic toxicity persisting > 48 hours despite optimal medical management, OR At time of scheduled treatment, Grade 3 or 4 nonneutropenic hematologic or nonhematologic toxicity that delays dose by 2 or 3 weeks for recovery to ≤ Grade 1	Third	Discontinue treatment
In the event of Grade 3 or 4 nonneutropenic hematologic or nonhematologic toxicity that does not recover to ≤ Grade 1 within 3 weeks	First	Discontinue treatment
Infusion-related toxicities		
Grade 2 or Grade 3 infusion-related reaction despite optimal management	Recurrent	Discontinue treatment
Grade 4 infusion-related reaction	First	Discontinue treatment

G-CSF = granulocyte-colony stimulating factor; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events
Refer to Section 7 for the NCI-CTCAE severity grading details.

5.5.2. Treatment Delays of Sacituzumab Govitecan

Sacituzumab govitecan will be administered in 21-day cycles on Days 1 and 8; the next cycle should start a minimum 14 days after the Day 8 dose (ie, the Day 8 infusion will be counted as the first day of that 14-day period). However, visit windows of 1 day prior to and 2 days after the scheduled infusion are permitted. The scheduled Day 1 and Day 8 infusions may be delayed for up to 3 weeks for treatment-related toxicities.

Instructions for dose delays and dose reductions for specific toxicities are summarized below. See Table 2 for when SG can be administered based on absolute neutrophil count. Withhold SG for Grade 3 nausea or Grade 3 or 4 diarrhea or vomiting at the time of scheduled treatment administration and resume dosing when resolved to Grade 1 or less. For toxicities not specifically addressed in Table 2, dosing may be delayed for toxicities higher than Grade 2 for a maximum of 3 weeks per investigator assessment. If the toxicity has improved to Grade 2 or less, the dose should be administered at that time. For a toxicity that delays Day 8 dosing, if dosing is delayed for more than 1 week, dosing should resume as Day 1 of next cycle to minimize treatment gap. Regardless of whether the Day 8 dose is delayed for toxicity, there should be a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

Palliative radiotherapy is permitted. If there is clear evidence of clinical benefit, treatment may be continued after completion of palliative radiotherapy. In this case, SG administration should be interrupted 1 week before the procedure and reinstated no earlier than 2 weeks after the procedure. In the event a patient requires surgery, SG should be interrupted 1 week before the procedure if clinically feasible and dosing should be held for 2 weeks after the procedure. Dosing may resume thereafter if the patient is clinically stable. Extensive surgical procedures (eg, abdominal, cranial surgeries) may require suspension of dosing for 4 weeks to allow for an adequate period for healing before dosing may resume. The study medical monitor must approve continuation of therapy with SG before resumption of dosing (see Section 3.4.1 for discontinuation criteria).

Treatment interruptions for reasons other than resolution of toxicities/procedures are not permitted outside of the permitted visit windows. Refer to Appendix 2 for further details on the risks and risk mitigation strategy for study drug dose delays as a result of the pandemic.

5.6. Prior and Concomitant Medications With Sacituzumab Govitecan

Premedication and prophylaxis are permitted while on SG as described in Section 5.3. Medications that are excluded are listed in Section 5.6.1. Palliative and/or supportive medications, such as pain medications, bone-modifying medications (bisphosphonates or denosumab), antiemetics or antidiarrheal medications, transfusions, and growth factor support are allowed at the investigator's discretion. Palliative radiotherapy is permitted; refer to Section 6.3.7 for the response assessment details regarding palliative radiotherapy allowed in this study.

5.6.1. Prior and Concomitant Medications That are Prohibited or Used With Caution With Sacituzumab Govitecan

No anticancer therapies, aside from the study drugs, are permitted during this study.

SN-38 (the active metabolite of SG) is metabolized via human UGT1A1. Concomitant administration of strong inhibitors or inducers of UGT1A1, with SG, should be avoided because of the potential to either increase (inhibitors) or decrease (inducers) the exposure to SN-38.

For details on the risk and mitigation strategy for concurrent administration of the coronavirus disease 2019 vaccine, refer to Appendix 2.

5.6.1.1. UGT1A1 Inhibitors

Coadministration of SG with inhibitors of UGT1A1 may increase systemic exposure to the active metabolite, SN-38. UGT1A1 inhibitors should not be administered concomitantly with SG unless there are no therapeutic alternatives. A list of example UGT1A1 inhibitors is provided in Appendix 7.

5.6.1.2. UGT1A1 Inducers

Exposure to SN-38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers. UGT1A1 inducers should not be administered concomitantly with SG unless there are no therapeutic alternatives. A list of example UGT1A1 inducers is provided in Appendix 7.

Should patients have a need to initiate treatment with any prohibited concomitant medication, the Gilead medical monitor must be consulted, and approval granted before initiation of the new medication. In instances where a prohibited medication is initiated before discussion with the Gilead medical monitor, the investigator must notify Gilead as soon as he/she is aware of the use of the prohibited medication.

5.7. Description and Handling of Docetaxel

5.7.1. Formulation

Docetaxel is commercially sourced. Information regarding the formulation can be found in the current full prescribing information or summary of product characteristics for each country where the study will be conducted.

5.7.2. Packaging and Labeling

Commercial product of docetaxel will be used for this study where docetaxel is approved for the treatment of locally advanced or metastatic NSCLC after platinum therapy failure. Study drug to be distributed to centers in other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice–Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.7.3. Storage and Handling

Docetaxel is commercially sourced. Information regarding the storage and handling can be found in the current prescribing information.

5.8. Premedication and Prophylaxis for Docetaxel

For docetaxel treatment, patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (eg, 8 mg twice daily) for 3 days starting 1 day before docetaxel administration to reduce the incidence and severity of fluid retention as well as severity of hypersensitivity reactions.

5.9. Dosage and Administration of Docetaxel

The docetaxel dosing regimen is described in Section 3.2.

5.10. Dose Modification and Treatment Delays for Docetaxel

Docetaxel is known to cause neutropenia, hepatotoxicity, peripheral neuropathy, fluid retention, and hypersensitivity reactions. Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions. Patients developing peripheral edema may be treated with standard measures (eg, salt restriction, oral diuretics).

Docetaxel dose delays and resumption of treatment as well as dose reductions and treatment discontinuation decisions should be conducted in accordance with the current local docetaxel label and treatment guidelines. The docetaxel dose must not be re-escalated following a dose reduction.

Recommended initial dose and dose reductions for docetaxel:

- Initial dose: 75 mg/m^2
- First dose level reduction: 55 or 60 mg/m^2 (as per local label and guidelines for docetaxel)
- Second dose level reduction: Per investigator's discretion (as per local label and guidelines for docetaxel)

Docetaxel should not be administered to patients who have significant liver dysfunction or a neutrophil count of less than 1500 cells/mm^3 (refer to local label for liver function requirements for dosage and dose modification for hematologic toxicities).

Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils less than 500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or other Grade 3/4 nonhematologic toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity and then resume dosing at the next dose level reduction.

Criteria for permanent discontinuation of docetaxel

- Grade 3 or higher peripheral neuropathy
- Cystoid macular edema
- Severe hypersensitivity reaction to docetaxel
- Consider discontinuation for severe cutaneous AEs (eg, Stevens Johnson syndrome)

Docetaxel treatment must be discontinued if there is more than a 5-week dose delay from the last dose or failure to resolve a toxicity within 3 weeks of the last dose of docetaxel.

5.11. Prior and Concomitant Medications With Docetaxel

The current local docetaxel prescribing information should be followed for permitted and prohibited concomitant medications.

5.12. Accountability for Study Drugs

The investigator is responsible for ensuring adequate accountability of all used and unused study drug vials. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition).

Each study site must keep accountability records that capture:

- The date received, quantity, and condition of study drug vials
- The date, patient number, and the study drug quantity or medication number dispensed.
- The date, quantity of used and unused study drug vials returned, along with the initials of the person recording the information

5.12.1. Study Drug Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate standard operating procedure for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved procedural documents. A copy of the site's approved procedural document will be obtained for the electronic trial master file. If study drug is destroyed at the site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be provided to Gilead.

If the site does not have an appropriate standard operating procedure for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

6. STUDY PROCEDURES

The study procedures to be conducted for each patient screened or enrolled in the study are presented in tabular form in Table 1 and described in the sections below.

The investigator must document any deviation from the protocol procedures and notify Gilead or the contract research organization.

6.1. Informed Consent

The investigator is responsible for obtaining written informed consent from each patient participating in this study after adequate explanation of the rationale, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The informed consent form (ICF) will inform patients about genomic testing and/or planned sample retention. In addition to the study-specific ICF to be signed by each patient participating in the study, patients will be required to document agreement to provide additional samples or to allow the use of the remainder of their already-collected specimens for optional future research in accordance with applicable regulations. In addition to the study-specific ICF to be signed by each patient participating in the study, patients will be required to document agreement to provide additional samples and/or to allow the use of the existing samples for optional genomic research. The results of the tests performed on the samples will not be given to the patient or the investigator.

6.2. Screening, Patient Enrollment, and Treatment Assignment

Patients will be screened within 28 days prior to enrollment to determine eligibility for participation in the study. Patients meeting all of the inclusion criteria and none of the exclusion criteria will return to the study site within 28 days after screening for enrollment into the study. Enrollment occurs upon receipt of randomization number via IRT. Randomization must occur on or before Cycle 1 Day 1. Dosing must commence within 3 days after randomization.

No waivers for patient eligibility will be offered or permitted.

Patient screening laboratory assessments may be repeated beyond the initial screening assessments within the 28-day screening period.

Patients who fail to meet eligibility criteria may be rescreened once if there is a reasonable expectation that the patient will meet eligibility after repeat screening. Entry into screening does not guarantee enrollment into the study. To manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study wide at any time.

6.3. Instructions for Study Procedures

Study procedures, including instructions for standard procedures (eg, medical history, physical examination, vital signs) are presented in Table 1. Assessments requiring additional detail are presented below.

6.3.1. Adverse Events

From the time informed consent is obtained through the first dose of study drug, record all SAEs, as well as any AEs related to protocol-required procedures on the AE electronic case report form (eCRF). All untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history. After the first dose of study drug, report all AEs and SAEs. See Section 7 for additional details.

6.3.2. Prior and Concomitant Medications

Medications administered prior to the first dose of study drug will be recorded as prior medications, whereas medications initiated after administration of the first dose of study drug until 30 days after treatment discontinuation will be captured as concomitant medications. Medication information will be entered in the appropriate eCRF with information regarding dose, indication, route of administration, and dates of administration. Medications used for prophylaxis of anticipated study drug AEs as outlined in the protocol should be documented along with the rationale for prophylactic intent.

Additional information regarding concomitant medications is located in Sections 5.6 and 5.11.

6.3.3. Vital Signs

Vital signs will be recorded according to the study procedures table (Table 1). Additional collection of vital signs will be needed in the event of suspected infusion-related reactions. Vital signs will include blood pressure, pulse, respiratory rate, and body temperature and will be recorded after the patient has been resting for at least 5 minutes.

6.3.4. Electrocardiograms

Local 12-lead ECGs will be obtained for all patients according to the study procedures table (Table 1). Abnormal findings should be evaluated as clinically indicated, including repeated ECGs. ECGs may be performed at other time points during the study if clinically indicated.

ECGs are to be performed at rest in the supine position. Clinically significant abnormal findings should be noted and the appropriate clinical work-up initiated until the condition has stabilized.

The following will be measured or calculated: heart rate, PR, QRS, QT, QTcF, and rhythm.

6.3.5. Clinical Laboratory Assessments

All clinical laboratory samples for safety are required to be collected and analyzed by a central laboratory at screening and every subsequent study visit (per Table 1) with appropriate clinical action taken based on the investigator's clinical judgment. Local laboratory test results may be used in addition to central laboratory tests for immediate clinical decisions. Eligibility determination is based on the central laboratory test results. All investigations will be assessed for all patients according to the study procedures table (Table 1). Additional and more frequent tests may be performed at the investigator's discretion. Clinically significant abnormal results should be repeated within 24 to 48 hours to confirm abnormality and followed until resolution. Results of unscheduled tests should be documented. The panels of laboratory tests to be performed are shown in Table 4.

Table 4. Laboratory Tests

Safety Laboratory Measurements				Other Laboratory Measurements
Serum Chemistry	**Hematology**	**Coagulation**	**Urinalysis**	
Albumin	Hemoglobin	INR	Blood	FSH[a]
ALP	Platelet count	PT	Glucose	LDH[b]
ALT	WBC count and differential with (ANC)	PTT	pH	Pregnancy test[c]
AST			Protein	Uric acid[b]
Bicarbonate (CO_2/HCO_3-)			Ketones	HBV surface antigen
Urea nitrogen				HBV core antibody
Calcium				HBV DNA, as applicable[d]
Chloride				HCV antibody
Creatinine				HCV RNA, as applicable[e]
Glucose				HIV-1 antibody
Magnesium				HIV-2 antibody
Phosphorus				HIV RNA, as applicable[f]
Potassium				
Sodium				
Total bilirubin				
Total protein				

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell
Refer to Table 1 for collection time points.

a Conduct as needed per Appendix 3 for determination of childbearing potential.
b May be tested more frequently at the discretion of the managing physician if abnormal results warrant follow-up. Results of unscheduled tests should be documented.
c In female patients of childbearing potential, pregnancy testing will be performed according to the study procedures table (Table 1) and as discussed in Appendix 3.
d Perform HBV DNA testing if the patient tests positive for HBV core antibody.
e Perform HCV RNA testing if the patient tests positive for HCV antibody.
f Perform HIV RNA testing if the patient tests positive for HIV-1 antibody or HIV-2 antibody.

6.3.6. ECOG Performance Status

Eastern Cooperative Oncology Group performance status will be assessed according to the study procedures table (Table 1). Appendix 5 presents the performance status criteria.

6.3.7. Efficacy Assessments

Computed tomography or MRI scans with IV contrast (unless contrast use is medically contraindicated) of chest, abdomen, pelvis, and any other involved disease sites are required in all patients at screening and every 6 weeks for first 12 months, and then every 9 weeks from the date of randomization until the occurrence of radiologic PD per RECIST Version 1.1 criteria requiring discontinuation of further treatment. Patients with known brain metastasis must have a brain MRI. For each patient, the same imaging technique should be used throughout the study for tumor assessment. Patients who discontinue treatment due to toxicity or for any reason other than objective progression will continue to obtain radiologic response assessments according to the protocol-required schedule until radiologic PD or initiation of subsequent anticancer therapy. Visit windows are ± 7 days for imaging (Table 1). The timing of imaging is based on calendar time from the date of randomization. Dose delays and cycle delays should not result in delays in the timing of imaging.

If the use of IV contrast is medically contraindicated for a patient, 1 of following options may be used (listed in order of preference): CT without contrast, MRI without contrast, or attempt to desensitize the patient with steroids.

Target and nontarget lesions must be determined by the clinical site at baseline according to the RECIST Version 1.1 criteria (Appendix 6). Clinical progression leading to patient discontinuation should be documented by CT or MRI scan of target lesions if clinically feasible. Patients who discontinue treatment due to toxicity or for any reason other than objective progression will continue to obtain radiologic response assessments according to the protocol-required schedule until radiologic PD or initiation of subsequent anticancer therapy. For patients with evidence of CR and PR, a confirmatory scan must be obtained a minimum of 4 to 6 weeks after initial documentation of response. Additional CT or MRI scans may be performed at the discretion of the investigator to assess disease status as medically indicated. These results should be recorded. Tumor response and progression will be determined using RECIST Version 1.1 (Appendix 6).

If palliative radiotherapy is given (Section 5.6), the presence of new or worsening metastases will be considered progression. Palliative radiation of a target lesion will render that target lesion and subsequent tumor assessments “not evaluable” and should be avoided. If the radiologic assessment does not confirm PD, patients should continue to be assessed per the study procedures table.

If a patient has known or suspected bone metastasis, a bone scan (99m-technetium polyphosphonate scintigraphy, whole body bone MRI, or 18F-NaF/fluorodeoxyglucose [18F] [FDG] positron emission tomography [PET]) to assess bone metastases will be performed according to the study procedures table (Table 1). In patients whose body CT/MRI scans indicate

that CR has been achieved, a bone scan or 18F-NaF/FDG PET will be required at confirmation of CR to exclude the presence of new bone metastases or if clinically indicated, and will occur within 1 week, but not more than 2 weeks following a CR as assessed by the investigator. For each patient, the same imaging technique used at screening should be used throughout the study to ensure comparability. Lesions detected on bone scans must be followed with cross-sectional imaging.

All radiology images and reports for screening, response, and progression will be provided to the central imaging vendor and held for potential further blinded independent central review based upon regulatory feedback or at the sponsor's discretion.

6.3.8. Pharmacokinetics

Serum samples for PK analysis will be collected from all patients who receive SG according to the study procedures table (Table 1). Following PK analytes will be measured at the specified time points: SG, total SN-38, free SN-38, and total antibody.

6.3.9. Immunogenicity Assessments

Serum samples for immunogenicity (ADA) analysis will be collected from all patients who receive SG according to the study procedures table (Table 1). Serum samples will be evaluated using a validated ADA assay. Based on the results from the ADA assay, the samples may be assessed using a validated nAb assay, if available.

6.3.10. Immunohistology Evaluation of Tumor

Preferably, local testing will be conducted according to the study procedures table (Table 1) if EGFR, ALK, or PD-L1 status is unknown. If local testing is unavailable, tumor tissue testing can be performed by the central laboratory.

See Appendix 9 for United Kingdom and EU specific text.

6.3.11. UGT1A1 Genotype

UGT1A1 genotype will be evaluated from a blood sample collected according to the study procedures table (Table 1).

6.3.12. Biomarker Testing

6.3.12.1. Biomarker Samples to Address the Study Objectives

The following biological specimens will be collected from all patients who have provided consent to participate in this study and may be used to evaluate the association of systemic and/or tissue-based biomarkers with study drug response (including efficacy and/or AEs) and dosage selection, and to better understand the biological pathways, biology of NSCLC, and/or the validation of a companion diagnostic for SG. Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it may not be possible to prospectively specify all tests that may be performed on the specimens provided. The specific analyses will include but may not be limited to the biomarkers and assays listed below.

The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon new state-of-the-art knowledge.

Archival tumor tissue (formalin-fixed, paraffin-embedded [FFPE] block) that was obtained preferably within 12 months prior to initial dosing (Cycle 1 Day 1) or newly acquired tumor tissues from an evaluable core or excisional biopsy collected from patients within signing of the informed consent to prior to initial dosing (Cycle 1 Day 1) may be submitted to the central laboratory. Tissue samples older than 12 months are acceptable. If tumor blocks are not available, it is recommended to submit freshly-cut unstained slides, sections of 4-5-micron thickness, serially cut from a single FFPE block and mounted on positively charged slides. Refer to the Laboratory Manual for further details. All efforts should be made to submit tumor tissue to the central laboratory. Consult with the sponsor if a sample is unavailable and the patient is unwilling to undergo a biopsy procedure.

Mandatory blood specimen will be collected for the extraction of circulating tumor DNA for genomic testing and genotyping to test for polymorphisms of genes that could regulate or be involved in the disposition of SG. These samples should be collected at screening and at predose on Day 1 of Cycles 2 and 3.

Trop-2 testing on archival/new tissue sample obtained prior to treatment will be performed to assess if efficacy varies by Trop-2 expression.

Biomarkers (in blood and tissue) may include, but are not limited to, protein expression, analyses of specific immune and tumor signatures (RNA), as well as tumor mutational burden and specific tumor mutations (DNA). Tumor and blood samples will be collected to measure biomarkers of response and resistance and better understand molecular attributes predictive of SG response in NSCLC. Examples may include, but will not be limited to, Trop-2 expression, mutations/gene expression related to the DNA damage repair pathways including TOP1 and SLFN11, tumor mutational burden, oncogenic mutations, PD-L1 expression, composition of immune subsets in the tumor microenvironment, clearance of circulating tumor DNA, pathological features of the tumor, and spatial heterogeneity of Trop-2 expression. Biomarker samples will be collected at the time points specified in Table 1.

Some of the samples may not be collected at a site if there are local laws or regulations preventing collection or if an IRB/IEC does not approve the collection of the sample.

Samples collected for biomarker assessments will be destroyed no later than 15 years after the end of the study or per country requirements (Section 9.1.4).

6.3.12.2. Biomarker Samples for Optional Future Research

In addition to the study-specific ICF to be signed by each patient participating in the study, patients will be required to document agreement to provide additional samples or to allow the use of the remainder of their already-collected biomarker and PK specimens and data collected on the study for optional future research in accordance with applicable regulations.

The specimens collected for optional future research in conjunction with collected data may be used to advance development of the study drug and/or increase our knowledge and understanding of the biology of the disease under investigation and related diseases. These specimens may also be used to study the association of biomarkers with biological pathways, disease pathogenesis, progression, and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. In addition, these specimens may be used to develop biomarker and/or diagnostic assays and establish the performance characteristics of these assays. The collection and analysis of optional future research specimens may facilitate the design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

The specimens collected for optional future research will be destroyed no later than 15 years after the end of study or per country requirements (Section 9.1.4).

6.3.12.3. Biomarker Samples for Optional Genomic Research

In addition to the study-specific ICF to be signed by each patient participating in the study, patients will be required to document agreement for use of existing and new samples for optional genomic research. A single blood sample will also be obtained from patients who agree to participate and provide their additional specific consent. The planned genetic analysis sample may not be collected at a site if there are local laws or regulations preventing collection or if an IRB/IEC does not approve the collection of the sample.

These samples should be collected at the Cycle 1 Day 1 visit before administration of the first dose of study drug but may be collected at any time during the study or at a separate poststudy visit, if necessary.

The specimens collected for optional genomic research and data collected on the study may be used to advance the development of the drug and/or increase our knowledge and understanding of the biology of the disease under investigation or related diseases. These specimens may also be used to study the association of biomarkers with biological pathways, disease pathogenesis, progression, and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. These samples may be used as a germline control with the main study biomarker samples. In addition, these specimens may be used to develop biomarker and/or diagnostic assays and establish the performance characteristics of these assays. The collection and analysis of optional genomic research specimens may facilitate the design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

The samples collected for optional genomic research will be destroyed no later than 15 years after the end of study or per country requirements (Section 9.1.4).

6.3.13. Quality of Life Assessments

Quality of life assessments will be performed according to the study procedures table (Table 1). The QOL assessments will be conducted before other study procedures occur, including study drug administration. The following QOL instruments will be completed in the following sequence from first to last.

- EQ5D3L {EuroQol Research Foundation 2018}
- NSCLC Symptom Assessment Questionnaire (NSCLC-SAQ) {Pro Consortium 2021}
- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Version 3 (EORTC QLQC30 v3) {European Organisation For Research And Treatment Of Cancer (EORTC) 2021}
- PGIS with a recall period of 7 days
- PGIC since the start of the study
- PRO-CTCAE item library (mouth/throat sores, abdominal pain, rash, hair loss, itching, numbness, and tingling) {National Institutes of Health (NIH) 2021}

6.4. Assessments for Discontinuation From Study Treatment

If a patient discontinues study drug (see Section 3.4 for discontinuation criteria), every attempt should be made to keep the patient in the study and continue to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the patient or investigator, the patient may be withdrawn from the study. In the absence of PD, scans should continue to be performed as described in the study procedures table (Table 1), until PD or initiation of subsequent anticancer therapy, whichever is earlier. After development of PD, or the initiation of subsequent anticancer therapy, the patient should still be followed for survival.

A patient who discontinues study drug early will be asked to return to the study site 30 days (± 7) after the last dose of study drug to attend an EOT visit. See the study procedures table (Table 1) for the assessments to be performed at the EOT visit and beyond.

6.5. Sample Storage

The stored biological samples may be used by Gilead or its research partner for additional testing to provide supplemental data to answer questions that relate to the main study. At the end of this study, these samples may be retained in storage by Gilead for a period up to 15 years or per country requirements. If patients provide additional specific consent for optional future research, residual biologic samples may be retained in storage no later than 15 years after the end of the study or per country requirements (Section 9.1.4).

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study patient administered a study drug that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, or transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae (Section 7.1.3).
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented as medical history.

Preexisting events that increase in severity or change in nature after study drug initiation or during or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death
- A life-threatening situation (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization.

- Persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.
- A medically important event or reaction: Such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.2.1. Protocol-Specific Serious Adverse Event Clarifications

To maintain study integrity, the following events that are assessed as unrelated to study drug will not be considered SAEs:

- Progression of disease
- Deaths related to progression of disease

Disease progression is an efficacy endpoint and should not be reported as an SAE unless assessed as related to study drug. Expected disease progression refers to an event that is unequivocally related to disease progression and that the clinical course is consistent with what would be expected for the patient's disease. A clinical event in the setting of disease progression would be considered an SAE if it could not unequivocally be attributed to or is not consistent with expected course of disease progression. Refer to Section 6.3.7 for additional details about disease progression.

7.1.3. Study Drugs and Gilead Concomitant Medications Special Situations Reports

Special situations reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a patient.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively that is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the patient in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the patient has taken the excess dose(s). Overdose cannot be established when the patient cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the patient has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine is defined as any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes**: There is reasonable possibility that the AE may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol procedures (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0. For each episode, the highest grade attained should be reported as defined in the NCI-CTCAE Toxicity Scale (Appendix 4).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Before Study Drug Initiation

After informed consent, but before initiation of study drug, the following types of events must be reported on the applicable eCRFs: all SAEs and any AEs that are related to protocol-required procedures.

7.3.2. Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship, until 30 days after the last dose of study drug and report the AEs on the eCRF as instructed.

All AEs and clinically significant laboratory abnormalities should be followed until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the patient first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported on the applicable eCRFs and to Gilead Patient Safety as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the ICF is signed.

Any SAEs (including deaths, see Section 7.1.2.1 for exclusions) that occur up to 30 days after the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead Patient Safety.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead Patient Safety (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance with the AE and SAE reporting guidance (Section 7.3).

7.3.5. Concomitant Medications Reports

7.3.5.1. Gilead Concomitant Medications Special Situations Report

Special situation reports involving a Gilead concomitant medication (not considered study drug), that occur after the patient first consents to participate in the study (ie, signing of the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead Patient Safety utilizing the paper SSR form (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Medications Report

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE eCRF.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE eCRF. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situations Reports

7.4.1. Serious Adverse Event Reporting Process

For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal patient identification, maintaining the traceability of a document to the patient identifiers.

Additional information may be requested to ensure the timely completion of accurate safety reports.

Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the patient’s eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

Site personnel will record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead Patient Safety within 24 hours of the investigator's knowledge of the event from the time of the ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If for any reason it is not possible to record and transmit the SAE information electronically, record the SAE on the paper SAE reporting form and transmit within 24 hours to:

Gilead Patient Safety
Email: PPD
or
Fax: PPD
PPD

If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to Gilead Patient Safety.

7.4.2. Special Situations Reporting Process

7.4.2.1. Electronic Special Situations Reporting Process for Study Drug

Site personnel will record all SSR data on the applicable eCRFs and from there transmit the SSR information within 24 hours of the investigator's knowledge to Gilead Patient Safety from study drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If for any reason it is not possible to record and transmit the SSR information electronically, record the SSR on the paper SSR form and transmit within 24 hours to:

Gilead Patient Safety
Email: PPD
or
Fax: PPD
PPD

If a SSR has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SSR reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to Gilead Patient Safety.

See Section 7.4.2.2 for instructions on reporting special situations with Gilead concomitant medications.

7.4.2.2. Reporting Process for Gilead Concomitant Medications

Special situations that involve Gilead concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to Gilead Patient Safety utilizing the paper SSR form and transmitted to:

Gilead Patient Safety
Email: PPD
or
Fax: PPD
PPD

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs due to a non-Gilead concomitant medication, must be reported on the AE eCRF.

7.4.2.3. Pregnancy Reporting Process

The investigator should report pregnancies in female study patients who are identified after initiation of study drug and throughout the study, up to 6 months after the last dose of study drug (in female patients), whichever is longer, to Gilead Patient Safety within 24 hours of becoming aware of the pregnancy using the pregnancy report form.

The investigator should report pregnancies in female partners of male patients who are identified after initiation of study drug and throughout the study, up to 3 months after the last dose of study drug (in male patients with female partners), whichever is longer, to Gilead Patient Safety within 24 hours of becoming aware of the pregnancy using the pregnancy report form.

Contact details for transmitting the pregnancy report form are as follows:

Gilead Patient Safety
Email: PPD
or
Fax: PPD
PPD

The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.

All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome after the study must be reported to the Gilead Patient Safety.

The patient should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to Gilead Patient Safety using the pregnancy outcome report form. If the end of the pregnancy/partner pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead Patient Safety. Gilead Patient Safety contact information is as follows: email: PPD and fax: PPD

Refer to Appendix 3 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs which may be in the form of line listings, serious adverse drug reactions, or suspected unexpected serious adverse reactions. In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable suspected unexpected serious adverse reactions as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant suspected unexpected serious adverse reaction reports associated with any study drug. The investigator should notify the IRB or IEC of suspected unexpected serious adverse reaction reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

To minimize the possibility of exposing patients to unusual risk, the safety information from this study will also be reviewed periodically by an independent DMC. The DMC may have access to data and will make recommendations regarding the study according to the DMC charter.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the NCI-CTCAE Version 5.0. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Toxicity Management

The investigator is responsible for monitoring of AEs and laboratory parameters for graded toxicities. Refer to Sections 5.5 and 5.10 (Dose Modifications and Treatment Delays of SG and docetaxel, respectively).

Management of AEs and laboratory toxicities not covered in Sections 5.5 and 5.10 is at the discretion of the investigator. For Grade 3 and 4 toxicities, relationship to study drugs, clinical status of patient, and investigator assessment of patient safety should inform patient withdrawal from dosing. Abnormal laboratory values should be repeated when necessary and followed until resolution and as clinically appropriate. Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead medical monitor, and the appropriate course of action will be discussed and decided. Whether or not considered treatment related, all patients experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels, or they are considered irreversible, or until there is satisfactory explanation for the changes observed.

Any questions regarding toxicity management or management of specific laboratory values should be directed to the Gilead medical monitor.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

Objectives and endpoints are listed in Section 2.

8.2. Planned Analyses

8.2.1. Interim Analyses

There will be 1 planned interim superiority analysis and 1 final analysis based on the primary endpoint of OS for this study.

The superiority interim efficacy analysis will be performed when approximately 242 death events (72% of the final target OS events) have occurred across the SG and docetaxel treatment arms. This is predicted to occur approximately 23 months after the first patient is randomized.

The Lan-DeMets spending function that approximates an O'Brien-Fleming approach will be used to account for multiplicity introduced by including an interim analysis for superiority. The alpha level applied at the interim depends upon the proportion of information available. If 242 death events (72% of the target 336 events with 42% maturity) have occurred at the time of the analysis, the 1-sided significance level to be applied for the OS at the interim and final analysis would be 0.82% and 2.25%.

To ensure the integrity of the study and to oversee the planned efficacy interim analysis, an independent DMC will review the interim analysis results and may recommend changes in the conduct of the study.

Details of the DMC plan and communication process will be provided in the DMC charter.

8.2.2. Final Analysis

The final analysis of the primary endpoint of OS will be conducted in the ITT Analysis Set when approximately 336 death events have occurred for across the treatment arms of SG versus docetaxel (336/580 events with 58% maturity), which is projected for approximately 29 months of survival follow-up after the first patient is randomized

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

The ITT Analysis Set will include all randomized patients according to the treatment arm to which the patient is randomized, unless otherwise specified. This is the primary analysis set for all efficacy analyses.

8.3.1.2. Safety

The Safety Analysis Set will include all patients who received at least 1 dose of any study drug, with treatment assignments designated according to the actual treatment received. This is the primary analysis set for all safety analyses.

8.3.1.3. Pharmacokinetics

The PK analysis will be conducted on Pharmacokinetic Analysis Set, defined as all randomized patients who received at least 1 dose of SG per the protocol and have at least 1 measurable posttreatment serum concentration of SG.

8.3.1.4. Immunogenicity

The immunogenicity analysis will be conducted on Immunogenicity Analysis Set, defined as all randomized patients who received at least 1 dose of SG and have at least 1 evaluable posttreatment anti-SG antibody test result.

8.3.1.5. Biomarkers

The biomarker analysis will be conducted on the Biomarker Analysis Set, defined as all patients who received any study drug and have at least 1 evaluable posttreatment biomarker measurement available.

8.3.1.6. Quality of Life Assessments

Quality of life assessments will be analyzed for patients in the ITT Analysis Set.

8.3.2. Data Handling Conventions

By-patient listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in analysis set), n (number with data), mean, standard deviation, 95% CIs on the mean, median, minimum, and maximum. Summary tables for categorical variables will include N, n, percentage, and 95% CIs on the percentage. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided.

Data will be described and summarized by treatment arm. The baseline value used in each analysis will be the last (most recent) pretreatment value before or on the first dosing date of study drug. As appropriate, changes from baseline to each subsequent time point will be described and summarized. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized. Graphical techniques (ie, waterfall plots, Kaplan-Meier curves, and line plots) may be used when such methods are appropriate and informative. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline characteristics will be summarized using standard descriptive methods by treatment arm. Categorical variables will be summarized by number and percentage. Continuous variables will be summarized using number of patients, mean, standard deviation, median, and range (minimum and maximum), unless otherwise specified. Details will be provided in the SAP.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary analysis of OS for comparing SG versus docetaxel will be performed in the ITT Analysis Set using the log-rank test stratified by randomization stratification factors (see Section 5.1). The HR and its 95% CI estimated using a Cox proportional hazard regression model stratified by randomization stratification factors will also be presented. Overall survival will be summarized by treatment arm using Kaplan-Meier estimates, which will include median and the proportion of patients alive at benchmark time points such as 12 and 18 months. Kaplan-Meier plots will be provided.

8.5.2. Secondary Analyses

At the time of the OS interim analysis, PFS, ORR, and other secondary endpoints will be mature for the final analysis, which will be approximately 23 months after the first patient is randomized.

The secondary endpoint PFS assessed by the investigator per RECIST Version 1.1 will be performed using the same methods as described for the primary OS analysis. Patients who have not progressed or died at the time of analysis will be censored according to the censoring rules similar to those described in the US FDA Guidance for Industry Clinical Trial Endpoints for the Approval of NSCLC Drugs and Biologics {U.S. Department of Health and Human Services (DHHS) 2015}. The detailed PFS censoring rules will be described in the SAP.

The ORR will be based on RECIST Version 1.1 using investigator-assessed response data. The ORR will be analyzed and compared between the treatment arms using the Cochran Mantel-Haenszel test stratified by the stratification factors used for randomization. The 2-sided 95% CIs for each treatment will be calculated using the Clopper-Pearson exact method.

Kaplan-Meier estimates of median DOR and its 95% CI will be calculated for responders (CR or PR) in each treatment arm.

Disease control rate will be analyzed using the same methods as described for ORR.

8.5.2.1. Quality of Life Analyses

The NSCLC-SAQ instrument will generate scores for 5 domains and a total score for each assessment visit. The analysis of time to first symptom deterioration in NSCLC-SAQ total score and time to first deterioration in NSCLC-SAQ shortness of breath domain will be conducted between the 2 treatment groups using the log-rank test stratified by randomization stratification factors in the ITT Analysis Set.

8.5.3. Exploratory Analyses

The analysis of the exploratory QOL endpoints will include the following:

- Mean change from baseline of total score and all domains of NSCLC-SAQ not assessed as secondary endpoints.
- Mean change from baseline of all domains of EORTC QLQ-C30 v3.
- The proportion of patients with meaningful change in each QOL domain while on treatment will be assessed in between-treatment comparisons.
- Time to first improvement and time to first deterioration in each QOL domain not assessed as secondary endpoints will be assessed in between-treatment comparisons.
- PRO-CTCAE scores for each attribute (frequency, severity, or interference) will be assessed in between-treatment comparisons.
- Further details for the exploratory QOL endpoints analyses will be outlined in the SAP.

8.6. Safety Analysis

Safety analyses will be performed using the Safety Analysis Set. Safety data will be summarized by treatment arm using descriptive statistics for TEAEs, clinical laboratory tests, vital signs, and concomitant medications. Information regarding study drug administration, study drug compliance, and other safety variables will also be summarized descriptively by treatment arm.

8.6.1. Extent of Exposure

A patient's extent of exposure to study drug data will be generated from the study drug administration data. Exposure data will be summarized by treatment arm.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities. System organ class, high-level group term, high-level term, preferred term, and lower-level term will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of study drug through 30 days after the last dose of study drug.

Summaries (number and percentage of patients) of treatment-emergent AEs (by system organ class and preferred term) will be provided by treatment arm.

8.6.3. Laboratory Evaluations

Selected laboratory test data (using conventional units) will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized by treatment arm.

Graded laboratory abnormalities will be defined according to NCI-CTCAE Version 5.0 (Appendix 4).

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time point postbaseline will be summarized by treatment arm. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment-emergent.

Laboratory abnormalities that occur before the first dose of study drug through 30 days after the last dose of study drug will be included in a data listing.

8.6.4. Other Safety Evaluations

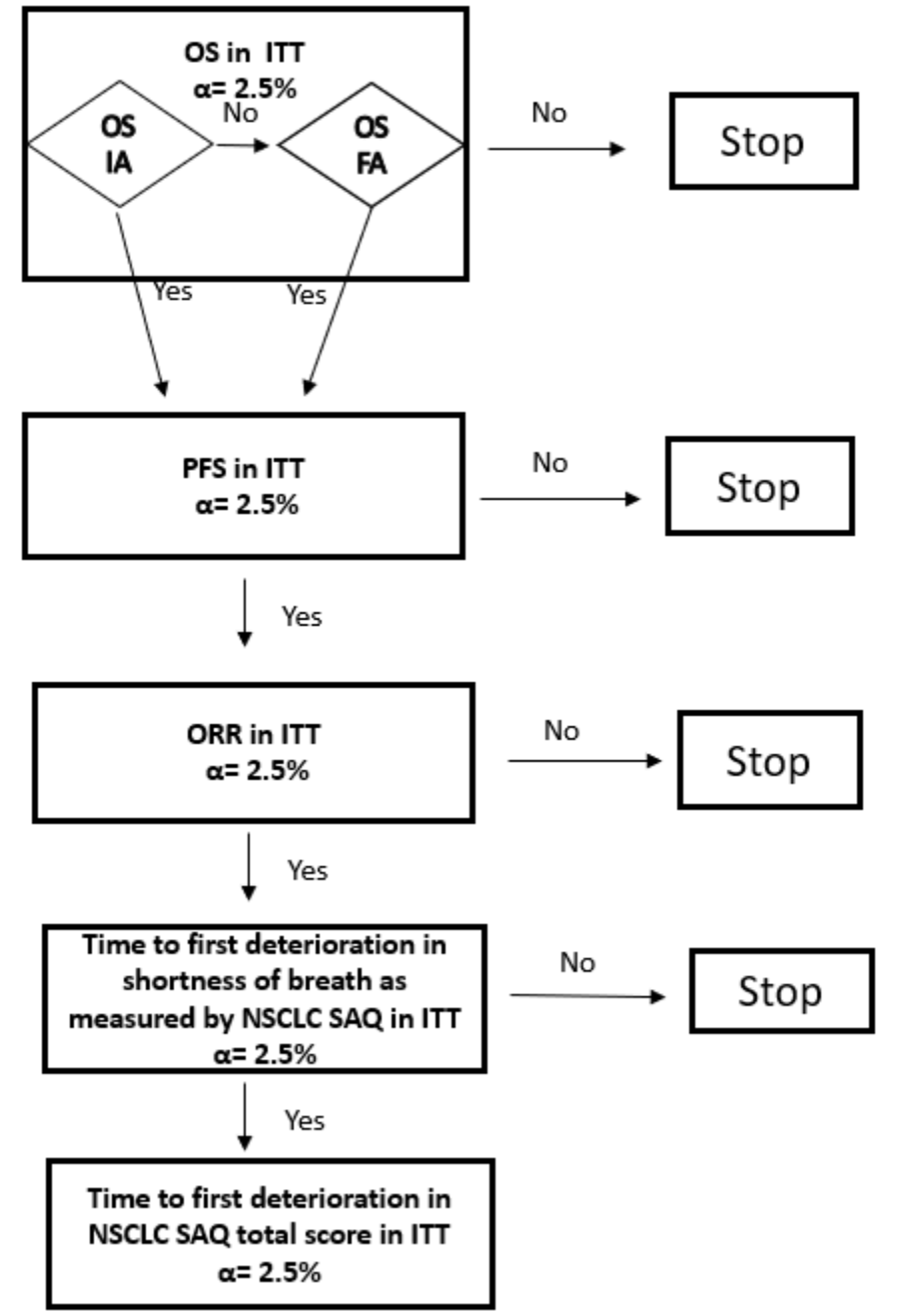
Vital signs, ECOG performance status, and concomitant medications will be summarized by treatment arm. Physical examination findings may be provided in a listing.

8.7. Adjustments for Multiplicity

The overall Type I error rate for this study is strictly controlled at a 1-sided alpha of 2.5%. A Lan-DeMets alpha spending function that approximates an O'Brien-Fleming approach will be used to account for multiplicity introduced by including an interim analysis for superiority. The OS efficacy interim analysis will be tested at the 1-sided significance level of 0.82% if 72% of the death events (242/336) is available at the time of the analysis. If the OS interim analysis is not positive, the OS final analysis will be tested at the 1-sided significance level of 2.25%. Note that alpha levels for the OS interim and final analysis are based on the actual observed events and will be adjusted accordingly.

If the primary OS analysis is positive at either interim or final, the final analysis based on the full dataset of the key secondary efficacy endpoints of PFS, ORR, time to first deterioration in shortness of breath, and time to first deterioration in NSCLC-SAQ total score, as measured by NSCLC-SAQ will be formally tested sequentially at the 1-sided alpha of 2.5% when the above hypotheses in the hierarchy were also statistically significant (Figure 2). All of the secondary efficacy endpoints will be mature and the final analysis could be performed at the time of the OS interim analysis.

Figure 2. Hierarchical Testing Procedures



FA = final analysis; IA = interim analysis; ITT = intent to treat; NSCLC-SAQ = non-small cell lung cancer Symptom Assessment Questionnaire; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

8.8. Pharmacokinetic Analysis

Serum samples for PK analysis will be collected for patients who receive SG. Plasma concentrations and PK parameters (ie, C_{max}, C_{trough}) will be listed and summarized for SG, total SN-38, free SN-38, and total antibody using descriptive statistics.

8.9. Immunogenicity Analysis

Serum samples for ADA analysis will be collected for patients who receive SG. The impact of immunogenicity, if detected, will be evaluated in relation to PK and clinical responses, safety/tolerability, and efficacy.

8.10. Biomarker Analysis

Baseline Trop-2 analysis will be performed and correlated with clinical outcomes. The baseline level, absolute level, and change from baseline level over time will be summarized using descriptive statistics for each biomarker at the sample collection time point by treatment arm, as appropriate. Exploratory analyses may be performed to evaluate the association of each biomarker or combination of biomarkers with clinical outcomes.

8.11. Sample Size

Global Study

Approximately 580 eligible patients will be randomly assigned in a 1:1 ratio to receive either SG or docetaxel over a planned nonuniform accrual period of 19 months.

The sample size is estimated based on the primary endpoint of OS. The assumed OS treatment effect under the alternative hypothesis is an average HR of 0.70 for SG versus docetaxel, which is characterized by a median OS of 11 months on docetaxel treatment {Paz-Ares 2021} {Fossella 2002}and a median OS of 15.7 months on SG treatment assuming OS is exponentially distributed. A total of 336 death events are required to detect a statistically significant difference at overall 1-sided alpha of 2.5% with 90% power based on a log-rank test. It is estimated that approximately 580 patients will provide 336 death events after approximately 29 months of survival follow-up after the first patient is randomized. EAST® 6.5 was used to calculate the sample size.

China Extension Study

Following completion of global enrollment, additional patients from sites in mainland China may be enrolled in a China Extension Cohort in the China-specific amendment (if needed). Patients randomized in the China extension study will not be included in the above primary efficacy population.

8.12. Data Monitoring Committee

A multidisciplinary DMC, consisting of therapeutic area experts and biostatisticians who are not employed by Gilead, are not investigators for this study, and do not have any major conflict of interest, will review the progress of the study, perform interim reviews of safety data at intervals of approximately every 6 months after the first patient is randomized unless otherwise specified, and will perform the efficacy interim analyses. The DMC will provide recommendation to Gilead whether the nature, frequency, and severity of AEs associated with study drugs warrant the early termination of the study in the best interests of the patient, whether the study should continue as planned, or whether the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with the sponsor or proprietary interests in the study drug. This documentation must be provided before the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last patient completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study patient activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the patient after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study patients.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explaining the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB/IEC-approved ICF for documenting written informed consent. Each ICF (or assent as applicable) will be appropriately signed and dated by the patient or the patient's legally authorized representative, the person conducting the consent discussion, and an impartial witness (if required by IRB/IEC or local requirements).

The ICF will inform patients about genomic testing and/or planned sample retention. In addition to the study-specific ICF to be signed by each patient participating in the study, patients will be required to document additional consent to provide additional samples and/or to allow the use of the remainder of their already-collected specimens for optional future research, in accordance with applicable regulations. In addition to the study-specific ICF to be signed by each patient participating in the study, patients will be required to document additional consent to provide additional samples and/or to allow the use of the existing samples for optional genomic research. The results of the tests performed on the samples will not be given to the patient or the investigator. The stored biological samples will be destroyed no later than 15 years after the end of study or per country requirements, but patients may at any time request that their stored samples be destroyed.

9.1.5. Confidentiality

The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB/IEC, or the laboratory. Laboratory specimens must be labeled in such a way as to protect patient identity while allowing the results to be recorded to the proper patient. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log with details for all patients screened and enrolled in the study, in accordance with the site procedures and regulations. Patient data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, eCRFs, study drug information, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRFs, IRB/IEC, and governmental approval with correspondence, the ICF(s), drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each patient:

- Patient identification
- Documentation that patient meets eligibility criteria (ie, medical history, physical examination, and confirmation of diagnosis [to support inclusion and exclusion criteria])
- Documentation of the reason(s) a consented patient is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (start and end date; dose if relevant; dose changes)
- Date of study completion and reason for discontinuation, if it occurs

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, the US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the patient, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each patient consented, an eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the electronic data capture (EDC) system. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a non-EDC vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the case report form Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the investigator will apply their electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. For studies with sites in countries following the EU Regulation No. 536/2014, a CSR will be submitted within 1 year (6 months for pediatric studies, in accordance with Regulation [EC] No. 1901/2006) after the global end of study (as defined in Section 3.5).

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media in accordance with the Gilead clinical trial agreement. .

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study personnel may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal and/or travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation and any patient records to verify the adherence to the protocol and the accuracy of the data recorded in the eCRF. The study monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The investigator agrees to cooperate with the study monitor to ensure that any problems detected through any type of monitoring (central, off-site, on-site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the Gilead study monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the patients, appropriate regulatory authorities, and IRB/IEC. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGMENT

Open-Label, Global, Multicenter, Randomized, Phase 3 Study of Sacituzumab Govitecan Versus Docetaxel in Patients With Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) With Progression on or After Platinum-Based Chemotherapy and Anti-PD-1/PD-L1 Immunotherapy

GS-US-577-6153, Amendment 2, 22 December 2022

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD	*[See appended electronic signature]*
Director, Clinical Development	Signature
[See appended electronic signature]	
Date	

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)	Signature
Date	Site Number

Appendix 2. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with patients being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Study drug supplies to patients and sites:

   a) Patients may be unable to return to the site for a number of visits to get the study drug, or the site may be unable to accept any patient visits. Without study drugs, the patient would not be able to continue receiving the study drug as planned per protocol.

      Mitigation plan: If permitted by local ethics committee (EC)/institutional review boards (IRBs) noninvestigational product as determined by sponsor (ie, docetaxel) can be administered at a clinic closer to the patient, under the supervision of a licensed physician. If necessary, a dosing delay for SG must be discussed with the sponsor in this instance. A virtual study visit, via phone or video conferencing, must be performed prior to remote dosing. At the earliest opportunity, the site will schedule in-person patient visits and return to the protocol's regular schedule of assessments. A qualified courier may be considered to ship the drug from sites to the alternate clinic.

   b) Shipments of study drug could be delayed because of transportation issues. Without study drug, the patient would not be able to continue receiving the study drug as planned per protocol.

      Mitigation plan: The site's study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and investigational sites. Manual shipments will be triggered as necessary.

2) Patient safety monitoring and follow-up:

   a) Patients may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

      Mitigation plan: For patients who may be unable or unwilling to visit the study site for their scheduled study visits as required per protocol, the principal investigator or qualified delegate will conduct a remote study visit, via phone or video conferencing, to assess the patient within the target visit window date whenever possible. During the remote study visit, the following information at minimum will be reviewed:

      i) Confirm if patient has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow up on any unresolved AEs/SAEs.

      ii) Review the current list of concomitant medications and document any new concomitant medications.

b) Patients may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central laboratory analyses.

Mitigation plan: Local laboratories or other vendors may be utilized as appropriate to monitor patient safety until the patient can return to the site for their regular follow up per protocol. Any changes in the party conducting laboratory assessments for the study due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

c) Patients may be unable or unwilling to attend the study visit to sign an updated informed consent form version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with the local EC/IRB and national laws and regulations. Remote consent will be allowed if has been approved by the local EC/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

d) The safety of study patients is important and testing of coronavirus disease 2019 (COVID-19) infection will be based on local clinical guidelines for testing based on signs/symptoms and/or suspected exposure to COVID-19.

Mitigation plan: If patient has a diagnosis of COVID-19 while on this clinical study, study drug may be held until clinical improvement or resolution in accordance with the treating physician's judgment and general SG dose delay guidance in the protocol. Additional supportive care and treatment measures for COVID-19 infection on the study will be performed in accordance with local institutional guidelines. Patients with a COVID-19 infection while participating in the clinical study will have this event documented as an AE in the clinical database.

3) Protocol and monitoring compliance:

a) Protocol deviations may occur in case study visits cannot be conducted as planned per protocol.

Mitigation plan: If it is not possible to complete a required procedure, a study visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed patient visits or deviation to the protocol due to the pandemic must be reported in the electronic case report form (eCRF)and described in the clinical study report. Any remote study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

b) Study monitors may be unable to carry out source data review or source data verification, or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in source data verification, an increase in protocol deviations, or under reporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. Remote source data verification may be arranged if allowed by local regulation and the Study Monitoring Plan. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct an off-site monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or patients on-site, must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

There may be an increased amount of missing data due to patients missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (eg, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

5) Concurrent administration of the COVID-19 vaccine:

There may be potential safety issues due to concurrent administration of the COVID-19 vaccine and study drugs.

Mitigation plan: There is not substantial efficacy or safety data regarding the concurrent administration of the COVID-19 vaccine and SG or docetaxel. Patients are allowed to receive the COVID-19 vaccine to reduce the risk and complications of COVID-19 infection. Investigators and study personnel should provide close surveillance of patients after COVID-19 vaccine administration and the institutional guidelines should always be followed. The administration of specific COVID-19 vaccine must be documented in the clinical database and AEs associated with COVID-19 vaccine administration should be recorded in the AE eCRF. COVID-19 vaccine administration should be recorded in the prior or concomitant medication eCRF as appropriate. The study visits should continue as planned, if possible, and clinically appropriate if vaccination occurs while the patients is on the study.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of patients who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of SG in study patients remains unchanged.

Appendix 3. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female-born patient is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the patient is permanently sterile or has medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are at least 54 years of age with cessation of previously occurring menses for at least 12 months without an alternative cause. In addition, women younger than 54 years with amenorrhea of at least 12 months also may be considered postmenopausal if their follicle-stimulating hormone level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female patient of any age.

b. Definition of Male Fertility

For the purposes of this study, a male-born patient is considered fertile after the initiation of puberty unless the patient is permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Patients

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Sacituzumab govitecan (SG) is contraindicated in pregnancy because a malformative effect has been demonstrated/suspected or is unknown, taking into consideration class effects, and genotoxic potential. Based on the assessment of published data related to cytochrome P450 enzyme inhibition and induction experiments for SN-38, efficacy of hormonal contraception is not expected to be impacted due to SG administration. A dedicated oral contraceptive drug-drug interaction clinical study has not been conducted. Refer to the latest version of the investigator's brochure for additional information.

Based on the mechanism of action and findings in animals, docetaxel can cause fetal harm when administered to a pregnant woman. In nonclinical studies, docetaxel has genotoxic effects. Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant during therapy with docetaxel. If the patient becomes pregnant while receiving docetaxel, the patient should be apprised of the potential hazard to the fetus. There is no contraindication to hormonal contraception according to the docetaxel prescribing information. Refer to the docetaxel prescribing information for additional information.

b. Contraception Requirements for Female Patients of Childbearing Potential

The inclusion of female patients of childbearing potential requires the use of highly effective contraceptive measures that have a failure rate of less than 1% per year. Patients must have a negative serum pregnancy test at screening and a negative urine pregnancy test is required prior to study drug administration on Cycle 1 Day 1. Pregnancy tests will be performed thereafter on Day 1 of each treatment cycle starting at Cycle 2 through the last cycle and every 28 days after the last dose of study drug up to 6 months after the last dose of study drug until the end of contraception requirement. If a urine pregnancy test is positive or equivocal, a confirmatory serum pregnancy test will be required.

Duration of required contraception for female patients in this clinical study should start from the screening visit until 6 months after the last dose of study drug.

Female patients must agree to 1 of the following contraceptive methods:

Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the patient's preferred and usual lifestyle.

Or

Consistent and correct use of 1 of the following methods of birth control listed below:

- Nonhormonal intrauterine device (IUD)
- Hormonal IUD (must be used in conjunction with a barrier method)
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Or

Female patients who wish to use a hormonally based method must use it in conjunction with a barrier method, preferably a male condom. Hormonal methods are restricted to those associated with the inhibition of ovulation. Hormonally based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods (each method must be used with a barrier method, preferably male condom)
  - — Oral contraceptives (either combined or progesterone only)
  - — Injectable progesterone*
  - — Subdermal contraceptive implant*
  - — Transdermal contraceptive patch*
  - — Contraceptive vaginal ring*

- Barrier methods (each method must be used with a hormonal method)
  - — Male condom (with or without spermicide)
  - — Female condom (with or without spermicide)
  - — Diaphragm with spermicide*
  - — Cervical cap with spermicide*
  - — Sponge with spermicide
  - * Not approved in Japan.

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female patients must also refrain from egg donation, cryopreservation of germ cells, and in vitro fertilization during treatment and until the end of contraception requirement. If needed, female patients should be advised to seek advice about egg donation and cryopreservation of germ cells before treatment.

3) Contraception Requirements for Male Patients

It is theoretically possible that a relevant systemic concentration of study drug may be achieved in a female partner from exposure of the male patient's seminal fluid and pose a potential risk to an embryo/fetus. Therefore, male patients with female partners of childbearing potential must use condoms during treatment and until 6 months after last dose of study drug. If the female partner of childbearing potential is not pregnant, additional contraception recommendations should also be considered.

Male patients must also refrain from sperm donation, and/or cryopreservation of germ cells during treatment and until the end of contraception requirement. If needed, male patients should be advised to seek advice about sperm donation and cryopreservation of germ cells before treatment.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Female patients will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study and throughout the study, up to 6 months after the last dose of study drug (in female patients), whichever is longer. Sacituzumab govitecan must be discontinued immediately upon discussion with the medical monitor.

Male patients whose partner has become pregnant or suspects she is pregnant from start of study and throughout the study, up to 3 months after the last dose of study drug (in male patients with female partners), whichever is longer, must also report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.4.2.3.

Appendix 4. Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Appendix 5. Eastern Cooperative Oncology Group Performance Status Criteria

Grade	Description
0	Normal activity Fully active, able to carry on all predisease performance without restriction
1	Symptoms, but ambulatory Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 6. Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1)

New Response Evaluation Criteria in Solid Tumors: Revised RECIST criteria {Eisenhauer 2009} are summarized below. Timing of assessments has been modified to fit this protocol.

Measurable/Nonmeasurable Lesions: Each tumor lesion or site of disease identified at baseline is categorized as either a measurable lesion or a nonmeasurable lesion according to the following definitions.

Lesion type	Qualifying definition
Measurable	Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by CT scan (CT scan slice thickness no greater than 5 mm.) • 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable). • 20 mm by chest x-ray. Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
Nonmeasurable	All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with 10 to < 15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

CT = computed tomography

Special considerations regarding lesion measurability:

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, positron emission tomography scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or magnetic resonance imaging can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.

- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions With Prior Local Treatment: Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days before the beginning of the treatment.

Target Lesions: Target lesions are selected from measurable lesions at baseline on the basis of their size and suitability for accurate repeated measurements by imaging techniques or clinical judgment. The sum of the longest diameter for all target lesions provides a quantitative means of characterizing objective tumor response to treatment as follows:

Evaluation Criteria Used for Categorizing Treatment Response of Target Lesions

Response category	Definition
CR	Disappearance of all target lesions
PR	> 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
PD	> 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

CR = complete response; LD = longest diameter; PD = progressive disease; PR = partial response; SD = stable disease

Nontarget Lesions: Nontarget lesions are other lesions (or sites of disease) not identified as target lesions at baseline. These include both nonmeasurable lesions as well as measurable lesions exceeding the maximum number allowed per organ or in total. The response of nontarget lesions to treatment is evaluated on the basis of their presence or absence as follows:

Evaluation Criteria Used for Categorizing Treatment Response of Nontarget Lesions	
Response category	**Definition**
CR	Disappearance of all nontarget lesions and normalization of tumor marker levels initially above upper limits of normal
PD	Appearance of 1 or more new lesions and/or unequivocal progression of existing nontarget lesions
SD	Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits

CR = complete response; PD = progressive disease; SD = stable disease

New Lesions: New lesions not present at baseline should be recorded at time of occurrence.

Overall Response: The overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease (PD) the smallest measurements recorded since the treatment started). To be assigned a status of partial response (PR) or CR, changes in tumor measurements must be confirmed by repeat assessments 4 to 6 weeks after initial documentation. In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once with a minimum interval of at least 6 to 8 weeks from enrollment.

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR[a]
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD[b]
Any	PD	Yes or No	PD[b]
Any	Any	Yes	PD[b]

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

a When evaluation of possible CR depends on distinguishing residual disease from normal tissue, fine needle aspirate/biopsy is recommended before confirming the complete response status.

b Patients without objective evidence of disease progression, but with globally deteriorated health status requiring discontinuation of treatment, should be classified as having "symptomatic deterioration" at that time, with every effort made to document the objective progression, even after discontinuation of treatment.

Duration of Response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started). Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Appendix 7. UGT1A1 Inhibitors and Inducers

Inducers of UGT1A1	Inhibitors of UGT1A1
Carbamazepine	Amitriptyline
Efavirenz	Atazanavir
Ethinylestradiol	Dacomitinib
Lamotrigine	Dasabuvir
Phenobarbital	Deferasirox
Phenytoin	Eltrombopag
Primidone	Enasidenib
Rifampicin	Erlotinib
Ritonavir	Flunitrazepam
Tipranavir	Flurbiprofen
	Fostamatinib
	Gemfibrozil
	Glecaprevir
	Indinavir
	Indomethacin
	Ketoconazole
	Nilotinib
	Ombitasvir
	Paritaprevir
	Pazopanib
	Pexidartinib
	Pibrentasvir
	Probenecid
	Propofol
	Regorafenib
	Rucaparib
	Silibinin
	Sorafenib
	Valproic acid

Appendix 8. Required Prior Treatment With Targeted Therapy Requirement for Patients With Known Actionable Genomic Alterations

Prior treatment with at least ONE of the options listed below is required for known specific genomic alteration if at least 1 of the listed medications for the genomic alteration is approved and available locally. If a patient has received a locally approved medication that is not listed here, sponsor consultation is required for confirmation of eligibility.

Activating Genomic Alteration	Required Prior Therapy
EGFR sensitizing	erlotinib, gefitinib, afatinib, dacomitinib, osimertinib, lazertinib
$EGFR^{T790M}$	osimertinib, lazertinib
EGFR exon 20 insertion	amivantamab
ALK	crizotinib, ceritinib, alectinib, lorlatinib, brigatinib
ROS1	entrectinib, larotrectinib, crizotinib
NTRK	entrectinib, larotrectinib
$BRAF^{V600E}$	dabrafenib and trametinib (in combination)
MET exon 14 skipping	capmatinib, tepotinib
RET	selpercatinib, pralsetinib
$KRAS^{G12C}$	sotorasib

ALK = anaplastic lymphoma kinase; BRAF = proto-oncogene B-raf; EGFR = epidermal growth factor receptor; KRAS = Kirsten rat sarcoma virus; MET = mesenchymal-epithelial transition; NTRK = neurotrophic tyrosine receptor kinase; RET = rearranged during transfection; ROS1 = ROS proto-oncogene 1

Appendix 9. Additional Country-Specific Requirements for United Kingdom and European Union

Reflects the changes to the global Amendment 1 protocol dated 15 September 2021 and reflected in Amendment 1.1 (United Kingdom) dated 29 November 2021.

Country-specific Requirements	Protocol Section
In the United Kingdom and EU, diagnostic testing for EGFR, ALK, and PD-L1 to determine eligibility at screening will be performed with tests that are approved for use in the EU. EGFR testing will be performed using the Cobas® EGFR Mutation Test (Roche). For ALK, the Vysis ALK Break Apart FISH probe test (Abbott) will be used. PD-L1 testing will be performed with the PD-L1 IHC 22C3 pharmDx test (Dako).	Section 6.3.10

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; EU = European Union, PD-L1 = programmed death ligand 1

Appendix 10. Amendment History

A high-level summary of this amendment is provided in tabular form in the subsection below, with changes listed in order of importance. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

Earlier separate summaries of changes are available upon request.

A separate tracked change (red-lined) document comparing Amendment 1 to this amendment will be made available upon the publication of this protocol.

Appendix Table 1. Amendment 2 (22 December 2022)

Rationale for Key Changes Included in Amendment 2	Affected Sections
The sample size was updated to 580 patients and the study power is increased to 90% due to change in the assumptions for activity of the control arm (docetaxel) from recent data outside of this protocol.	Synopsis, Study Schema, Sections 3.1, 4.1, 8.11, and 8.2
Secondary PRO endpoints were updated to time to first deterioration for NSCLC-SAQ shortness of breath domain and total score to align with approaches used for the primary endpoints and increase likelihood of generating a significant difference between treatment arms,	Synopsis, Sections 2, 3.1, 8.5.2.1, and 8.7
Exploratory PRO endpoints were updated to mean change from baseline for NSCLC-SAQ shortness of breath domain and total score.	Synopsis, Section 2
Additional text was added to describe the extension study in China.	Synopsis, Sections 3.1, and 8.11
Clarification was added on follow-up requirements for patients who complete or withdraw from the study.	Sections 3.4.4 and 6.3.7
Inclusion criterion was updated to indicate testing for patients with squamous cell carcinoma. EGFR and ALK testing is optional because among the patients with squamous cell carcinoma, mutation rates for EGFR and ALK are very low or rare.	Section 4.2
Criteria for discontinuation and timing of dose reductions of sacituzumab govitecan have been updated to align with current guidelines.	Section 5.5.1
The interim futility analysis was removed since the study is enrolling ahead of projected schedule and enrollment would likely be completed around the time of DMC meeting for futility evaluation. Overall safety and efficacy will continue to be monitored by an independent DMC.	Sections 8.2.1, 8.7, and 8.12
Country-specific requirements from Amendments 1.1 for the UK were included in the global protocol.	Appendix 9
Biomarker analysis was updated to include “Baseline Trop-2 analysis will be performed and correlated with clinical outcomes” to strengthen language for Trop-2 analysis.	Section 8.10
Text was updated to align with reporting requirements.	Section 9.2.2

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; NSCLC-SAQ = non-small cell lung cancer Symptom Assessment Questionnaire; PRO = patient-reported outcomes; Trop-2 = trophoblast cell surface antigen-2; UK = United Kingdom.

Prot GS-US-577-6153 amd-2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	22-Dec-2022 18:38:22