Study Title:	Phase 3 Study of Sacituzumab Govitecan (IMMU-132) Versus Treatment of Physician's Choice (TPC) in subjects with Hormonal Receptor-Positive (HR+) Human Epidermal Growth Factor Receptor 2 (HER2) Negative Metastatic Breast Cancer (MBC) who have failed at least two prior chemotherapy regimens
Sponsor:	Gilead Sciences, Inc. (Immunomedics, Inc. is now part of the Gilead group of companies) 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	122694
EudraCT Number:	2018-004201-33
ClinicalTrials.gov Identifier:	NCT03901339
Indication:	Metastatic Breast Cancer
Protocol ID:	IMMU-132-09
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 21-Dec-2018 Amendment 01: 03-Jul-2019 (France specific) Amendment 02: 10-Jul-2019 (Germany specific) Amendment 03: 04-Feb-2020 (Global) Never Implemented Amendment 04: 13-Mar-2020 (Global) Amendment 05: 08-Oct-2020 (Global) Amendment 06: 27-Jan-2021 (Global) Amendment 07: 23-Aug-2021 (Global)

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 noninvestigational new drug application sites.

CONFIDENTIALITY STATEMENT

The information contained in this document, particularly unpublished data, is the property or under control of Gilead Sciences, Inc., and is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable institutional review board or independent ethics committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Gilead Sciences, Inc., except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

1. PROTOCOL SYNOPSIS

Name of Sponsor/Company:

Gilead Sciences, Inc. (Immunomedics, Inc. is now part of the Gilead group of companies)

Name of Investigational Product:

Sacituzumab govitecan is an antibody-drug conjugate composed of the humanized monoclonal antibody, hRS7 immunoglobulin G (IgG)1κ, which binds to trophoblastic cell-surface antigen-2 (Trop-2); the camptothecin-derived agent, SN-38, a topoisomerase I inhibitor; and CL2A, a linker, which couples SN-38 to hRS7 IgG1κ.

Title of Study:

Phase 3 Study of Sacituzumab Govitecan (IMMU-132) Versus Treatment of Physician's Choice (TPC) in subjects with Hormonal Receptor-Positive (HR+) Human Epidermal Growth Factor Receptor 2 (HER2-) Negative Metastatic Breast Cancer (MBC) who have failed at least two prior chemotherapy regimens

Study Center(s):

Approximately 125 centers worldwide

Study Duration:

Enrollment is expected to be completed in approximately 24 months and the overall duration of the study is expected to be 52 months.

Objectives:

Primary Objective:

- To assess and compare efficacy of sacituzumab govitecan to TPC as measured by progression-free survival (PFS) as determined by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in subjects with HR+/HER2- MBC who have progressed after cyclin-dependent kinase (CDK) 4/6 inhibitor, endocrine therapy, taxane, and after at least 2, but no more than 4 prior chemotherapy regimens for metastatic disease

Secondary Objectives:

- To assess and compare sacituzumab govitecan to TPC in overall survival (OS) in subjects with HR+/HER2- MBC who have progressed after CDK 4/6 inhibitor, endocrine therapy, taxane and at least 2, but no more than 4 prior chemotherapy treatment regimens for metastatic disease

- To assess and compare objective (overall) response rate (ORR), duration of response (DOR) and clinical benefit rate (CBR; complete response (CR)+partial response (PR)+stable disease (SD) with a duration of ≥ 6 months) between treatment arms as determined by local investigator review (LIR) and BICR using RECIST 1.1
- To assess and compare the impact of treatment on time to deterioration (TTD) of global health status/quality of life (QOL), pain, and fatigue domains as measured by European Organization for the Research and Treatment of Cancer (EORTC) quality of life of cancer patients, core questionnaire version 3.0 (QLQ-C30)
- To assess and compare the overall safety and tolerability

CCI [redacted]

Number of subjects planned:

Approximately 520 subjects

Methodology:

This is an open-label, randomized, multicenter, international Phase 3 study to compare the efficacy and safety of sacituzumab govitecan versus TPC in subjects with metastatic or locally-recurrent inoperable HR+/HER2- MBC who have progressed after a CDK 4/6 inhibitor, endocrine therapy, a taxane, and at least 2, but no more than 4 prior chemotherapy regimens for metastatic disease. Subjects will be randomized in a 1:1 ratio to either sacituzumab govitecan (Investigational Arm A) or TPC (Control Arm B; i.e., eribulin, capecitabine, gemcitabine, or vinorelbine). Randomization will be stratified based on prior chemotherapy regimens for treatment of metastatic disease (two vs. three/four lines), visceral metastasis (Y/N), and endocrine therapy in the metastatic setting for at least 6 months (Y/N).

The study will be conducted in two phases, a Pre-randomization Phase and a Randomization Phase:

- The Pre-randomization Phase will last no longer than 28 days and consists of the following two periods:
  - A Screening Period to establish study eligibility
  - A Baseline Period to confirm eligibility and establish disease characteristics prior to randomization and treatment
- The Randomization Phase will begin at the time of randomization of the first subject and will end on the data cut-off date for the final analysis of OS; the Randomization Phase consists of the following two periods:
  - A Treatment Period which begins at the time of randomization and ends with the completion of the End-of-Treatment (EOT) visit, which will occur at least 30 days after the final dose of study treatment
  - A Follow-up Period which begins the day after the EOT visit and continues as long as the subject is alive or until the data cut-off date of the final analysis of OS, unless the subject withdraws consent from the study or the Sponsor terminates the study

An independent Data Safety Monitoring Committee (DSMC) will be convened at regular intervals to assess the progress of this study and review safety.

Diagnosis and Criteria for Inclusion:

Inclusion Criteria

Subjects must meet all the following inclusion criteria:

1) Female or male subjects, adult or aged ≥ 18 years at the time of signing the informed consent form
2) Documented evidence of HR+/HER2- MBC confirmed by a local laboratory with the most recently available or newly obtained tumor biopsy (preferably within the last 12 months) from a locally recurrent or metastatic site(s) and defined per American Society of Clinical Oncologists/College of American Pathologists criteria as:
   - HR+ (a tumor is considered HR+ if at least 1% of the cells examined have estrogen and/or progesterone receptors)
   - HER2- defined as immunohistochemistry ≤ 2+ or fluorescence in situ hybridization negative
3) Availability of archival tumor tissue in a formalin fixed, paraffin embedded (FFPE) block (preferably within 12 months prior to consent) or newly acquired biopsy (FFPE block) from a metastatic site. Note: Bone biopsies are not allowed

4) Refractory to or relapsed after at least 2, but no more than 4 prior systemic chemotherapy regimens for metastatic disease. Adjuvant or neoadjuvant therapy for early stage disease will qualify as one of the required prior chemotherapy regimens if the development of unresectable, locally advanced, or metastatic disease occurred within a 12-month period of time of the therapy. Note: Treatments for bone metastases (e.g., bisphosphonates, denosumab, etc.) and hormonal therapy are not considered as prior systemic chemotherapy treatments for advanced disease.
5) Should have been previously treated with:
   - At least 1 taxane in any setting
   - At least 1 prior anticancer hormonal treatment in any setting
   - At least 1 CDK 4/6 inhibitor in any setting
6) Eligible for one of the chemotherapy options listed in the TPC arm
7) Documented disease progression after the most recent therapy by computed tomography (CT)/magnetic resonance imaging (MRI)
8) At least 1 measurable target lesion according to RECIST 1.1 (bony disease only is not allowed) that meets all of the following criteria:
   - Lymph node lesion that measures at least ≥ 1.5 cm in the short axis
   - Non-nodal lesion that measures ≥ 1.0 cm in the longest diameter in the plane of measurement
   - The lesion is suitable for repeat measurement using CT/MRI. Historical CT/MRI scans performed within 28 days of C1D1 may be used as screening scans to demonstrate eligibility as long as they meet minimum standards as separately defined by the central imaging vendor.
   - Lesions that have had external beam radiotherapy or locoregional therapy must show radiographic evidence of disease progression based on RECIST 1.1 to be deemed a target lesion.
   - Brain CT/MRI must be conducted for subjects with a history of brain metastasis. The subject must have had stable* brain metastasis for at least 4 weeks. Target lesions cannot be from brain.

     * Stable brain metastasis is defined as the following:
     - Prior local treatment by radiation, surgery, or stereotactic surgery
     - Imaging – stable or decreasing size after such local treatment
     - Clinically stable signs and symptoms for at least 4 weeks
     - ≥ 2 weeks from discontinuation of antiseizure medication
     - Low and stable doses of corticosteroids ≤ 20 mg prednisone or equivalent daily are permitted

9) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

10) Adequate renal function: calculated creatinine clearance ≥ 30 mL/minute according to the Cockcroft and Gault formula

11) Adequate bone marrow function, defined as:

— Absolute neutrophil count (ANC) ≥ 1,500 per mm^3

— Hemoglobin ≥ 9.0 g/dL

— Platelet count ≥ 100,000 per mm^3

Note: Blood transfusion or growth factor support is not allowed within 14 days prior to screening labs.

12) Adequate liver function, defined as:

— Total bilirubin ≤ 1.5× institutional upper limit of normal (IULN) or ≤ 3 IULN for patients with documented Gilbert's syndrome

— Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 2.5× IULN (in the case of liver metastases ≤ 5× IULN), and serum albumin ≥ 3 g/dL

— Alkaline phosphatase (ALP) ≤ 5.0× IULN unless there are bone metastases, in which case liver-specific ALP must be separated from the total and used to assess liver function instead of total ALP

13) Resolution of all systemic anticancer therapy-related or radiation-related toxicities to Grade 1 severity or lower, except for neuropathy (≤Grade 2) and alopecia. Subjects with Grade 2 neuropathy are eligible, but should not receive vinorelbine as TPC.

14) Females must not be lactating or pregnant at Baseline (as documented by a negative beta human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG [or hCG]). All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrhoeic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (i.e., bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

15) Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception (total abstinence [if it is her preferred and usual lifestyle], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 6 months after study drug discontinuation. For sites outside of the European Union (EU), it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, i.e., double barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide. If currently abstinent, the subject must agree to use a highly effective method as described above if she becomes sexually active during the study period or for

6 months after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 28 days before dosing and must continue to use the same contraceptive during the study and for 6 months after study drug discontinuation.

16) Male subjects who are partners of women of childbearing potential must use a condom and spermicide and their female partners, if of childbearing potential, must use a highly effective method of contraception (see methods described above in Inclusion Criterion 15) beginning at least 1 menstrual cycle prior to starting study drug, throughout the entire study period, and for 3 months after the last dose of study drug, unless the male subjects are totally sexually abstinent or have undergone a successful vasectomy with confirmed azoospermia or unless the female partners have been sterilized surgically or are otherwise proven sterile.

17) Must be willing and able to comply with all aspects of the protocol

18) Must voluntarily agree to provide written informed consent

19) Could have received an unlimited number of prior endocrine, biological, or targeted therapies in the absence of co-administered chemotherapy; all of these therapies must have been completed 14 days prior to randomization, except biological therapy which must have been completed 28 days prior to randomization

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1) Previous treatment with a topoisomerase 1 inhibitor as a free form or as other formulations

2) Current enrollment in another clinical study or used any investigational device or drug either within 5 half-lives or 28 days prior to randomization, whichever is longer

3) Treatment with chemotherapy, radiation, or small molecule targeted therapy within 2 weeks and biological therapy within 4 weeks prior to the first dose of study treatment

4) Existing anticancer treatment-related adverse events (AEs) of Grade ≥ 2 (except for alopecia and Grade 2 neuropathy) according to National Cancer Institute (NCI)-CTCAE v5.0

5) Any other malignancy that required treatment or has shown evidence of recurrence (except for non-melanoma skin cancer or histologically-confirmed complete excision of carcinoma in situ) during the 5 years prior to enrollment in this study

6) History of significant cardiovascular disease, defined as:

   — Congestive heart failure greater than New York Heart Association (NYHA) Class II according to the NYHA Functional Classification

   — Unstable angina or myocardial infarction within 6 months before enrollment

   — Serious cardiac arrhythmia

7) Clinically-significant electrocardiogram (ECG) abnormality, including any of the following:

   — Marked Baseline prolonged QT/QTc interval (i.e., a repeated demonstration of a QTc interval > 500 ms) demonstrated on ECG at Screening.

   $$QTc_F = \frac{QT}{\sqrt[3]{\frac{RR}{(1s)}}}$$

   QTcF is calculated by Fridericia's formula

   — History of risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of long QT Syndrome)

8) Has known active central nervous system metastases and/or carcinomatous meningitis. Subjects may participate provided they have stable brain metastasis. All subjects with carcinomatous meningitis are excluded regardless of clinical stability. Stable brain metastasis is defined in inclusion criterion 8

9) Active hepatitis B virus (positive hepatitis B surface antigen) or active hepatitis C virus (measurable viral ribonucleic acid (RNA) load with polymerase chain reaction) infection

10) Scheduled surgery during the study, other than minor surgery which would not delay study treatment

11) Has an active serious infection requiring antibiotics

12) Has active chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease) and subjects with a history of bowel obstruction

13) Have received a live vaccine within 30 days of randomization

14) Known hypersensitivity or intolerance to any of the study drugs or any of the excipients

15) Any medical or other condition which, in the opinion of the Investigator, causes the subject to be medically unfit to receive sacituzumab govitecan or unsuitable for any other reason

16) Is receiving any medication prohibited in combination with the study treatment(s) as described in the respective product labels, unless medication was stopped within 7 days prior to randomization

17) Locally-advanced MBC (stage IIIc) in subjects who are candidates for curative intent therapy at the time of study enrollment.

18) If required per local guidelines, any subject with a blood uracil level $\geq$ 150 ng/mL is excluded from receiving capecitabine as TPC (Note: blood uracil level will be assessed at Screening for all subjects eligible to be randomized to capecitabine as TPC)

Investigational Product, Dosage and Mode of Administration:

Sacituzumab govitecan 10 mg/kg administered as an intravenous (IV) infusion on Days 1 and 8 of repeating 21-day cycles. Protocol-defined dose reductions will be permitted. Subjects in this group will receive premedications (i.e., antipyretics, H_1 blockers, and H_2 blockers) for prevention of infusion reactions and a 2- or 3-drug combination regimen for prevention and treatment of chemotherapy-induced nausea, vomiting, and diarrhea.

Reference Therapy, Dosage and Mode of Administration:

TPC with one of the following:

- Eribulin - (1.4 mg/m^2 for North American sites, 1.23 mg/m^2 for EU sites or per institution) is to be administered IV on Days 1 and 8 of a 21-day cycle
- Capecitabine - (1000-1250 mg/m^2) is to be administered PO twice daily for 2 weeks followed by a 1-week rest period given as a 21-day cycle
- Gemcitabine - (800-1200 mg/m^2) administered IV on Days 1, 8, and 15 of each 28-day cycle or per institution
- Vinorelbine (25 mg/m^2 IV on Day 1 weekly cycle per institution) (Note: subjects with grade 2 neuropathy are eligible, but should not receive vinorelbine as TPC)

The use of premedications (i.e., antipyretics, H_1 blockers, and H_2 blockers) for prevention of infusion reactions and medications for prevention and treatment of chemotherapy-induced nausea, vomiting, and diarrhea for subjects in this group is based on the Investigator's discretion.

Duration of Treatment:

Subjects will continue to receive study treatment until RECIST 1.1 defined progressive disease (PD) by LIR, development of unacceptable toxicity, subject request, withdrawal of consent, Investigator decision, pregnancy, or study termination by the Sponsor, or another treatment discontinuation criteria is met (see Section 5.4 Criteria for Removal from Study Treatment)

Criteria for Evaluation:

Efficacy:

Efficacy analyses will be performed using tumor assessments by LIR and BICR using RECIST 1.1.

Primary Efficacy End Point:

- PFS as determined by BICR using RECIST 1.1

Secondary Efficacy End Points:

- OS
- ORR as determined by BICR using RECIST 1.1

- TTD in the global health status/QOL, pain and fatigue domains of EORTC QLQ-C30
- DOR as determined by LIR and BICR using RECIST 1.1
- CBR as determined by LIR and BICR using RECIST 1.1

Safety:

Safety and tolerability will be assessed based on the incidence of adverse events (AEs) and serious AEs (SAEs), review of clinical laboratory data (i.e., hematology, chemistry, and urinalysis), ECG monitoring, ECOG performance status, vital signs (i.e., heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature), and ADA.

Statistical Methods:

Sample Size Assumptions:

The sample size is estimated based on the primary end point of PFS, but also taking into consideration OS as the main secondary end point. An overall sample size of approximately 520 subjects were randomized in a 1:1 ratio to either sacituzumab govitecan or TPC.

For PFS, assuming a hazard ratio of 0.70 (medians of 5.3 months for sacituzumab govitecan and 3.7 months for TPC), a total of 350 PFS events will be used to detect a statistically significant difference at a 2-sided alpha of 0.05 with 92% power. With an estimated average accrual rate of 22 subjects per month, a total of 520 subjects will provide 350 PFS events approximately 27 months after the first subject is randomized, after accounting for events being censored because of subjects missing tumor assessments or starting subsequent anti-cancer therapies (see primary end point PFS definition in Section 9.5.1). The recruitment rate is assumed to be non-uniform so that half of the subjects are recruited 55% of the way through the recruitment period of approximately 24 months reflecting the change in sample size and actual recruitment rate that was affected by the global coronavirus disease 2019 (COVID-19) pandemic.

At PFS final analysis, OS will be summarized descriptively only. To be conservative, the nominal 2-sided alpha of 0.00001 will be spent even without formal hypothesis testing. For OS, assuming a hazard ratio of 0.73 (medians of 16.5 months in Arm A and 12 months in Arm B), a total of 438 OS events are needed to detect a statistically significant difference with 86.7% power at a 2-sided alpha of 0.04999 based on a recruitment period of approximately 24 months and 52 months of survival follow-up from the first subject randomized.

The Sponsor will closely monitor the number of subjects randomized and discontinued, including subjects who refuse study treatment assigned. As the primary analysis is triggered by a targeted number of PFS events, subjects who prematurely discontinue from the study or whose events are censored do not count toward the targeted number. To compensate for such cases, an additional number of subjects is necessary to be enrolled to ensure the targeted number of events is reached within a reasonable timeframe. If required, the additional number of subjects will be determined by the Sponsor on the basis of the number and pattern of accumulated and censored events at the appropriate times as the study progresses.

Multiplicity Adjustment:

The overall type I error rate for this study is strictly controlled at a 2-sided alpha of 0.05. The primary end point analysis of PFS assessed by BICR will serve as the gatekeeper for the secondary end point analyses and be tested at the 2-sided alpha of 0.05. At PFS final analysis, OS will be summarized descriptively only. To be conservative, the nominal 2-sided alpha of 0.00001 will be spent even without formal hypothesis testing. If the primary PFS analysis is positive, analysis of the main secondary end point of OS will be formally tested sequentially at the 2-sided alpha of 0.04999, ORR (assessed by BICR) and analysis for QOL will be formally tested sequentially at the 2-sided alpha of 0.05 respectively when the above hypotheses in the hierarchy are also statistically significant. For analysis of QOL, TTD of global health status/QOL, pain, and fatigue domains as measured by EORTC QLQ-C30 will be tested.

Analysis Populations:

The following populations will be defined and used for analysis:

- Screened Set is the group of all subjects who have signed an informed consent and participated in screening procedures at the investigative site to assess eligibility. This analysis population is used for selected tables and listings pertaining to subjects' disposition and eligibility criteria.
- Full Analysis Set (Intent-to-Treat Analysis [ITT] Population) is the group of all randomized subjects. This is the primary analysis population for all efficacy analyses which will be based on the ITT principle, with subjects analyzed according to the randomized treatment assignment.
- Safety Analysis Set is the group of subjects who received at least 1 dose of study drug. This is the analysis population for all safety analyses which will be based on the actual treatment received.
- HRQoL-Evaluable Set is the all ITT population who had an evaluable assessment of the HRQoL at baseline and at least one evaluable assessment at post-baseline visits. An evaluable assessment at a given visit will be defined as at least one of the 15 domains/scales were non-missing at that scheduled assessment visit.
- PK Set is defined as Safety population subjects who have completed at least one cycle of sacituzumab govitecan treatment and have at least one non-missing PK concentration of total SN-38, free SN-38, total antibody (hRS7 IgG) and/or SN-38G

Primary End Point (Primary Analysis)

PFS will be described using Kaplan-Meier (K-M) estimates. The primary analysis of PFS for the comparison between treatment arms will be performed using a stratified log rank test with the stratification factors used in the randomization. Median PFS and its 95% CI as determined by the Brookmeyer and Crowley method with log-log transformation will be presented and the K-M estimates of PFS will be plotted over time. Hazard ratio of PFS and its 95% CI will be estimated using Cox proportional-hazards model stratified by the same stratification factors used in the randomization.

Secondary End Points (Secondary Analyses)

OS will be described using K-M estimates. The primary analysis of OS for comparison between treatment arms will be performed using a stratified log rank test with the same stratification factors used in the randomization. Median OS and the associated 95% CI as determined by the Brookmeyer and Crowley method with log-log transformation will be presented. Hazard ratio and the associated 95% CI will be estimated using a Cox proportional-hazards model stratified by the same stratification factors used in the randomization.

ORR will be analyzed and compared between the treatment arms using the Cochran Mantel Haenszel (CMH) test stratified by the stratification factors used in the randomization. The 2-sided 95% CIs will be calculated using the Clopper-Pearson exact method.

CBR will be calculated with exact 95% CIs using the method of Clopper and Pearson. CBR will be compared between treatment arms using a CMH test stratified by the stratification factors used in the randomization. The differences and odds ratios of these rates between treatment arms and 95% CIs will be calculated respectively.

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

Time to deterioration of global health status/QOL, pain, and fatigue domains as measured by EORTC QLQ-C30 will be analyzed similarly as the primary analysis of PFS.

Safety Analyses

Safety analyses will be performed using the Safety Analysis Set and will be summarized using descriptive statistics. Categorical variables will be summarized by number and percentage. Continuous variables will be summarized using number of subjects, mean, standard deviation, median, upper and lower quartiles, and range (minimum and maximum).

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

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ADA	antidrug antibodies
ADC	antibody drug conjugate
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
AUC0-168	area under plasma concentration curve through 168 hours
BICR	blinded independent central review
β-HCG	beta human chorionic gonadotropin
BUN	blood urea nitrogen
CAP	College of American Pathologists
CBC	complete blood count
CBR	clinical benefit rate
CDK	cyclin-dependent kinase
CFR	Code of Federal Regulation
CI	confidence interval
Cl	clearance
Cmax	maximum concentration
CMH	Cochran Mantel Haenszel
COVID-19	coronavirus disease 2019
CR	complete response
CT	computed tomography
ctDNA	circulating tumor DNA
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
DSMC	Data Safety Monitoring Committee
EBRT	external beam radiotherapy
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organization for Treatment of Cancer
EOT	End-of-Treatment
ER	estrogen receptor
EU	European Union
EuroQOL	European Quality of Life
FDA	Food and Drug Administration
FFPE	formalin-fixed parafin embedded
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HER2-	human epidermal growth factor receptor 2 negative
HIPAA	Health Insurance Portability and Accountability Act

HR	hormonal receptor
HR+	hormonal receptor-positive
HRQOL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IULN	institutional upper limit of normal
IV	intravenous(ly)
IWRS	Interactive Web-Based Response System
K-M	Kaplan-Meier
LD	Longest diameter
LIR	local investigator review
LN	lymph node
MBC	metastatic breast cancer
MRI	Magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for AEs
NCCN	National Comprehensive Cancer Network
NYHA	New York Heart Association
OR	objective response, OR=CR+PR
ORR	objective (overall) response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PRO	patient-reported outcome(s)
PRO-CTCAE™	Patient Reported Outcomes version of the CTCAE
QLQ-C30	EORTC Quality of Life for Cancer Patients core questionnaire version 3.0
QOL	quality of life
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
t½	terminal elimination half-life
TPC	treatment of physician's choice

TROPiCS	Trop-2 Investigation in Cancer with sacituzumab govitecan
Trop-2	Trophoblastic cell-surface antigen 2
TNBC	Triple-Negative Breast Cancer
TTD	time to deterioration
UGT1A1	uridine diphosphate-glucuronosyl transferase 1A1
US	United States
Vz	volume of distribution of the terminal elimination phase
WBC	white blood cells

2. INTRODUCTION

2.1. Metastatic Breast Cancer

In 2018, an estimate of 266,120 new cases of breast cancer were diagnosed in the United States (US) with nearly 90% of these surviving 5 years or longer (SEER.cancer.gov). Approximately 41,000 breast cancer related deaths are estimated to occur in 2018. The most common breast cancer subtype is hormonal receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-), representing approximately 70-80% of all new cases {Setiawan 2009}.

The most common site of metastatic disease is bone, requiring use of bisphosphonates in conjunction with these other therapies. Once metastatic, patients become endocrine- and chemotherapy-refractory and there are no further treatment options. As per National Comprehensive Cancer Network (NCCN) guidelines, after no response to 3 sequential regimens including chemotherapy, palliative care is the only remaining option. European Society for Medical Oncology guidelines recommend sequential monotherapy. Only 24% of patients with metastatic disease survive more than 5 years and the disease often becomes refractory to treatment {Harb 2015}. Progression-free survival (PFS) after endocrine therapy in postmenopausal women ranges from 4.1-15.0 months (Table 1){Cortes 2015, Jones 1995, Kaufman 2015, Perez 2010a, Twelves 2016}.

First-line treatment for metastatic HR+/HER2- breast cancer is usually endocrine therapy (typically aromatase inhibitors), cyclin-dependent kinase (CDK) 4/6 inhibitors in combination with hormonal therapy, or, for patients with rapidly progressing or extensive visceral metastatic disease, chemotherapy. According to NCCN guidelines, preferred chemotherapy regimens include single-agent anthracyclines, taxanes, antimetabolites, and microtubule-inhibitors. Combination chemotherapy may also be used in some situations, such as high tumor burden, rapidly progressive disease (PD), or visceral crisis.

Efficacy in second- and third-line metastatic treatments continue to be significantly lower, with PFS ranging from 3-5.3 months, further representing an unmet clinical need (Table 1). Even with the recent approvals of CDK inhibitors, including CDK 4/6 inhibitors (palbociclib, ribociclib, and abemaciclib), PFS ranged from 9.5 months to 16.4 months in earlier lines of treatment and patients still became refractory, therefore requiring cytotoxic therapy {Cristofanilli 2018, Hortobagyi 1983, Sledge 2017}.

Table 1. Low Response Rates and Progression-Free Survival to Chemotherapy in Pre-Treated Metastatic Breast Cancer

Drug	N*	Population	HR+ (%)	ORR%	PFS months	OS months	Source
Ixabepilone	126	Prior A, T and Capecitabine	52	18.3	3.1	8.6	{Perez 2010b}
Capecitabine	548	Prior A, T ≤ 3 prior chemo (incl. adjuvant)	47	19.9	4.2	14.5	{Kaufman 2015}
Capecitabine HR+ subgroup	219	Idem	100	NA	5.3	16.8	{Twelves 2016}
Eribulin HR+ subgroup	198	Idem	100	NA	4.3	18.2	{Twelves 2016}
Eribulin	508	Prior A and T, ≥ 2 prior chemo	64	13	3.7	13.1	{Cortes 2015}
Vinorelbine	115	Prior A, ≤ 2 lines	51	13	3**	7.5	{Jones 1995}

Abbreviations: A= Anthracycline; HR+=hormonal receptor-positive; ER=estrogen receptor ORR=objective (overall) response rate; OS=overall survival; PFS=progression free survival; T=taxane
* N represents metastatic breast cancer population with includes HER2+ and/or triple negative breast cancer; ORRs are based on local review
** Time to treatment failure

2.2. Sacituzumab Govitecan

Sacituzumab govitecan (IMMU-132) is an antibody-drug conjugate (ADC) composed of hRS7, a humanized immunoglobulin G (IgG)1κ monoclonal antibody, SN-38, a camptothecin analog, and CL2A, a linker which couples SN-38 to hRS7. Trophoblastic cell-surface antigen-2 (Trop-2) is a cell surface antigen overexpressed in many epithelial cancers and has been linked to aggressive disease and a poor prognosis. The antibody component binds to Trop-2 such that the ADC concentrates on tumor cell surfaces. SN-38 is the active metabolite of irinotecan and a topoisomerase I inhibitor that induces single-stranded DNA breaks during replication. If unrepaired, these breaks progress to double-stranded DNA breaks and results in cell death. The CL2A linker is unique in that it is subject to pH-dependent hydrolysis. Following internalization of the ADC-antigen complex, SN-38 is released in the acidic lysosome and kills the target cells. In addition, SN-38 can be cleaved from extracellular, surface-bound ADC due to the acidic pH of the tumor microenvironment. The released drug diffuses into neighboring cells in an antigen-independent manner and this leads to the death of cells in the immediate proximity of target-expressing cells. These two mechanisms of action combine to enable sacituzumab govitecan to target and kill cancer cells that over-express Trop-2 as well as other cells in the tumor with low or no Trop-2 expression.

2.3. Summary of Nonclinical Findings

2.3.1. Pharmacology Studies

Sacituzumab govitecan showed significant cytotoxicity against 6 different epithelial tumor cell lines (i.e., PC-3 [prostate], Calu-3, COLO 205, Capan-1, SK-MES-1 and BxPC-3), with median inhibitory concentrations ranging from 1.95 nM to 23.14 nM {Cardillo 2011}.

Significant antitumor effects were seen with the hRS7-SN-38 conjugate compared to free SN-38, irinotecan, or an irrelevant IgG-SN-38 conjugate in murine xenografts of variety of human epithelial cancers {Cardillo 2015, Cardillo 2011, Goldenberg 2015}.

2.3.2. Pharmacokinetics

In a 3-month repeat-dose study in Cynomolgus monkeys, a dose-proportional increase in exposure (i.e., maximum concentration [C_{max}] and area under the curve [AUC]) was seen for sacituzumab govitecan, total antibody, total SN-38, and free SN-38, with no relevant gender differences after the first dose. Serum half-life ranged from 67.3 to 152 hours. On average the amount of free SN-38 in circulation was low (<3% free SN-38 compared with total SN-38 bound to sacituzumab govitecan), confirming that the majority of SN-38 administered as sacituzumab govitecan remains bound to ADC in serum and is not circulating as the free cytotoxic payload. The inactive metabolite, SN-38G, readily appeared in serum with mean time of maximum concentration ranging from 4.0 to 12 hours.

2.3.3. Toxicology

In acute toxicity studies in Swiss-Webster mice, sacituzumab govitecan at doses of up to 750 mg/kg/dose (i.e., cumulative doses of up to 1500 mg/kg) caused minimal loss (<10%) in body weight. There was no evidence of hematological toxicity and no abnormal histology findings. Transient increases in hepatic transaminases were observed that returned to normal by the end of the study.

In Cynomolgus monkeys, sacituzumab govitecan 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 the no-observed-adverse-effect level; a 120 mg/kg/dose administered 3 days apart was associated with lethality. Target organs in monkeys included the gastrointestinal tract (necrosis, erosions, inflammation, fibrosis, hemorrhage, 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).

Local tolerance was evaluated in the Good Laboratory Practices-compliant monkey studies. Changes were observed at the injection site, including mild to moderate perivascular hemorrhage, moderate hemorrhage in the dermis and subcutis, and minimal to mild perivascular mixed cell infiltration. These changes were interpreted as related to procedural trauma and not to study drug.

SN-38 was not mutagenic in a bacterial reverse mutation test or clastogenic in an in vitro mammalian cell micronucleus test. Carcinogenicity studies and fertility, early embryonic development, and pre- and post-natal development studies with sacituzumab govitecan have not been conducted. However, SN-38 is a camptothecin and hence is likely to be carcinogenic. Furthermore, SN-38 is a known developmental toxigen {CAMPTOSAR 2014}.

2.4. Summary of Clinical Studies

Three clinical studies with sacituzumab govitecan are ongoing: 1) a Phase 1/2 study, IMMU-132-01, in subjects with relapsed/refractory, metastatic epithelial cancers, including metastatic breast cancer (MBC); 2) a Phase 2 study, IMMU-132-06, in subjects with metastatic urothelial cancer who have failed either a platinum-based regimen or anti-PD1-based immunotherapy; and 3) a Phase 3 study IMMU-132-05 (ASCENT) comparing sacituzumab govitecan to treatment of physician's choice (TPC) in subjects with relapsed/refractory metastatic triple-negative breast cancer (TNBC). Data from the Phase1/2 study, IMMU-132-01, are provided below.

Study IMMU-132-01 is a multicenter study in the US to evaluate the safety, toxicity, and pharmacokinetics (PK) of sacituzumab govitecan. Over 500 subjects with relapsed/refractory, metastatic epithelial cancers have been enrolled in the study, including 215 heavily-pretreated subjects with MBC, 54 of whom are HR+/HER2-. The starting dose for the Phase 1 portion was 8 mg/kg administered on Days 1 and 8 of a 21-day cycle. After evaluation at this and higher doses in a 3+3 Phase 1 dose-finding design, 8 and 10 mg/kg sacituzumab govitecan administered on Days 1 and 8 of a 21-day cycle were chosen for further Phase 2 evaluation in patients with the following cancers: breast cancer, non-small-cell lung cancer, small-cell lung cancer, colorectal cancer, pancreatic cancer, urothelial cancer, endometrial cancer, and esophageal cancer.

Initially in Phase 2, subjects were recruited in a sequential manner to the 8 mg/kg dose and subsequently to the 10 mg/kg dose. An interim analysis was performed when 81 and 97 subjects with different tumor types had been treated at the two dose levels, respectively. The duration of treatment in the 8 and 10 mg/kg groups was similar and no important safety differences between the groups were seen. However, the 10 mg/kg dose was associated with a slightly better objective (overall) response rate (ORR) and clinical benefit rate (CBR) {Ocean 2017}. Based on these data, the Sponsor decided that further subject accrual would proceed at the 10 mg/kg dose level.

Additionally, sacituzumab govitecan has demonstrated promising tumor responses in multiple patient populations, including patients with advanced, relapsed/refractory MBC HR+/HER2- (31% [17/54]; {Bardia 2018}), urothelial carcinoma (30.6% [11/36]; {Tagawa 2017}), non-small lung cancer (19% [9/47];{Heist 2017}), small-cell lung cancer (14% [7/50]; {Gray 2017}), and others. Summaries of data from these trials are provided in the sacituzumab govitecan Investigator's Brochure (IB). In these studies, sacituzumab govitecan was more tolerable than when SN-38 is administered as the parent compound, irinotecan, or with other non-tumor-targeting SN-38 products.

2.4.1. Pharmacokinetics

The serum PK of sacituzumab govitecan and free SN-38 were evaluated in subjects with metastatic TNBC who received 10 mg/kg sacituzumab govitecan in the Phase 1/2 study, IMMU-132-01. PK parameters for sacituzumab govitecan and free SN-38 were determined by noncompartmental analysis and are presented in Table 2.

Table 2. Summary of Mean (± Standard Deviation) Sacituzumab Govitecan and Free SN-38

	Sacituzumab Govitecan					Free SN-38		
	C_{max} [ng/mL]	AUC_{0-168} [h ng/mL]	$t_{1/2}$ [h]	Vz [L/kg]	Cl [L/h/kg]	C_{max} [ng/mL]	AUC_{0-168} [h ng/mL]	$t_{1/2}$ [h]
	n=43	n=42	n=42	n=42	n=42	n=43	n=37	n=37
Mean	243,000	5,210,000	15.6	0.0450	0.00202	127	3,900	17.7
SD	45,600	1,230,000	2.90	0.0114	0.000477	59.7	1,830	4.74

AUC_{0-168}=area under plasma concentration curve through 168 hours; Cl= clearance; C_{max}=maximum plasma concentration; SD=standard deviation; $t_{½}$=terminal elimination half-life; Vz=volume of distribution of the terminal elimination phase

Distribution

The maximum concentrations of sacituzumab govitecan and SN-38 occurred close to the end of infusion. The mean volume of distribution of the terminal elimination phase (Vz) for sacituzumab govitecan was 0.0450 L/kg.

SN-38 is highly protein bound to human plasma proteins (approximately 95%). The plasma protein to which SN-38 predominantly binds is albumin. The relative amount of free SN-38 compared to total SN-38 was small and was less than or equal to 16.9% for all time points, averaging below 7.14%.

Elimination

Following administration of 10 mg/kg sacituzumab govitecan, the clearance of sacituzumab govitecan was calculated by noncompartmental analysis to be 0.00202 L/h/kg. SN-38 appeared to follow metabolite kinetics, with the elimination of SN-38 appearing to be limited by its rate of release from sacituzumab govitecan.

Metabolism

No metabolism studies with sacituzumab govitecan have been conducted. SN-38 is known to be metabolized via human uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1).

2.4.2. Immunogenicity

As with all therapeutic proteins, there is potential for an immune response to sacituzumab govitecan. Based on available data for 420 subjects in the Phase 1/2 study, IMMU-132-01, the rate of treatment-emergent and persistent antidrug antibodies (ADA) is very low and has been limited to 3 subjects (0.7%). An additional 17 subjects (4%) had transient ADA. None of the subjects with treatment-emergent, confirmed ADA had infusion-related hypersensitivity adverse events (AEs).

2.4.3. Efficacy in Metastatic Breast Cancer

Overall, 54 subjects with estrogen HR+/HER2- MBC have been treated with 10 mg/kg sacituzumab govitecan in the Phase 1/2 study, IMMU-132-01 {Bardia 2018}. Demographic data are summarized in Table 3.

All subjects were treated at a starting dose of 10 mg/kg, with a median of 11 doses (range: 1-74); median time on treatment was 4.0 months (0.2 – 26.0 months). Twelve (22%) subjects had a dose reduction to 7.5 mg/kg; 9% occurring in the first cycle. Thirty-four subjects are in long-term follow-up, with 11 subjects still on treatment; 18 subjects have died; 1 subject is lost to follow-up after 5.3 months; and data for 1 subject are currently not available.

ORR based on investigator assessment and Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) was 31% (17/54 subjects; 95% confidence interval [CI]: 19.5%, 45.6%) (Table 4 and Figure 1). All responses were partial responses (PRs); no complete responses (CR) were seen. An additional 31% of subjects had stable disease (SD), with 9 of 17 subjects having SD for ≥ 6 months, for a CBR of 48%. CBR was also 48% in subjects with liver involvement. Median duration of response (DOR) is currently 7.4 months (95% CI: 4.4, 18.3), with a median onset of response of 2.3 months (1.5 to 7.8 months). Fourteen of the 17 responders were on-study for 6+ months and 7 are still receiving treatment (Figure 2). Of the remaining 20 subjects, 14 reported objective progression of disease and 6 discontinued the study without a post-treatment tumor assessment. Median PFS was 6.8 months (95% CI: 4.6, 9.3; Figure 3).

Table 3. Demographics and Subject Characteristics of HR+/HER2- MBC Subjects from IMMU-132-01 Basket Study

Demography	N=54
Female/male, n	54/0
Median age, years (range)	54 (33-79)
ECOG performance status, %	
0	35
1	56
Missing	9
Median time from metastatic disease to study entry, years (range)	3.50 (0.14-18.11)
≥ 1 prior chemotherapy for metastatic disease	96
≥ 2 prior chemotherapy regimens for metastatic disease	76
Median number of metastatic chemotherapy lines (range)	2 (0-11)
Prior chemotherapy for metastatic disease, %	
Taxanes – any setting	93
Anthracyclines – any setting	69
Taxane and Anthracyclines – any setting	67
Metastatic Taxane	57
Platinum agents	24
Fluoropyrimidine agents	78
Eribulin	33
Hormonal agents for metastatic disease	100
CDK 4/6 inhibitors, %	69
mTOR inhibitor, %	54
Number of metastatic sites at study entry, %	
1	24
2	38
3+	33
Sites of metastatic disease at study entry, %	
Lung/mediastinum	31
Bone	100
Chest wall	37
Brain	0
Liver	81

CDK=cyclin-dependent kinase; ECOG=Eastern Cooperative Oncology Group; HER2-=human epidermal growth factor receptor 2 negative; HR=hormonal receptor; mTOR=mammalian target of rapamycin

Table 4. Overall Response Assessment Analyses in Various Subject Subsets

Subject Subset	ORR, % (n/N)
Overall	31 (17/54)
Age	
<65	29 (12/42)
≥ 65	42 (5/12)
Onset of metastatic disease from diagnosis	
< 1 year	15 (2/3)
≥ 1 year	37 (15/41)
≥ 2 prior chemos for metastatic disease	29 (12/41)
< 2 prior chemos for metastatic disease	38 (5/13)
Prior CDK 4/6 inhibitors	24 (9/37)
No prior CDK 4/6 inhibitors	47 (8/17)
Visceral involvement at study entry (Liver/Lung)	
Yes	27 (13/48)
No	67 (4/6)
Liver involvement	
(More than 2 Metastates=95%)	27 (12/44)

CDK=cyclin-dependent kinase; ORR=objective (overall) response rate

Figure 1. Waterfall Graph of Subjects with at Least 1 Computerized Tomography Assessment of Response to Sacituzumab Govitecan (N=54)

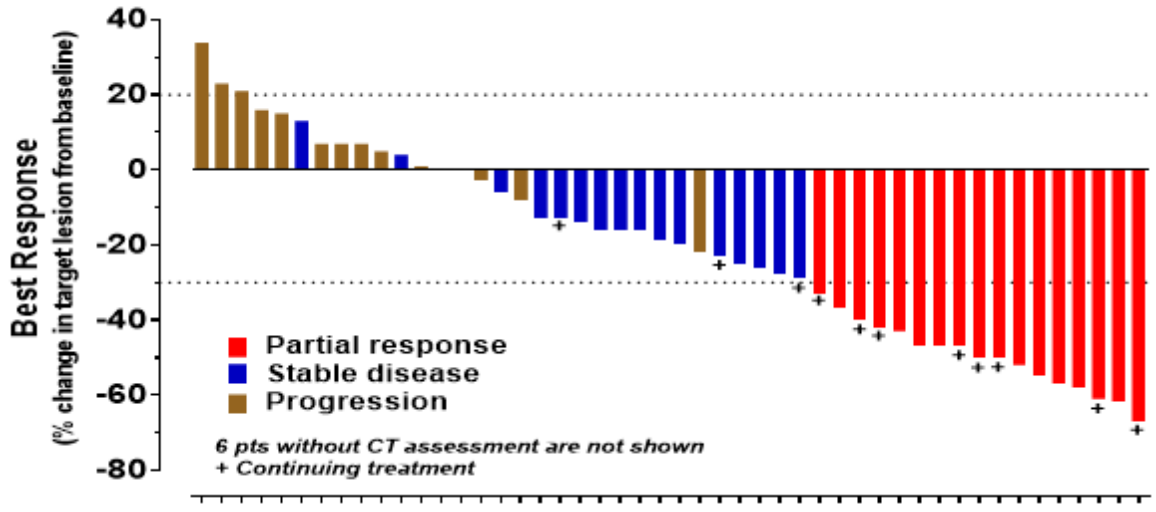


Figure 2. Response Onset and Durability of Response (N=17)

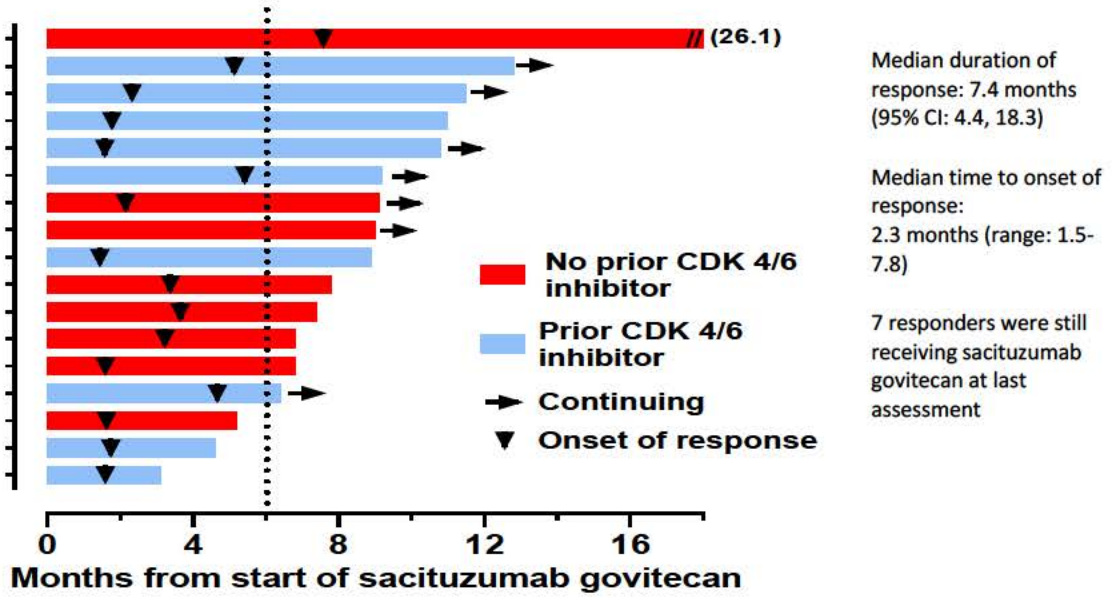
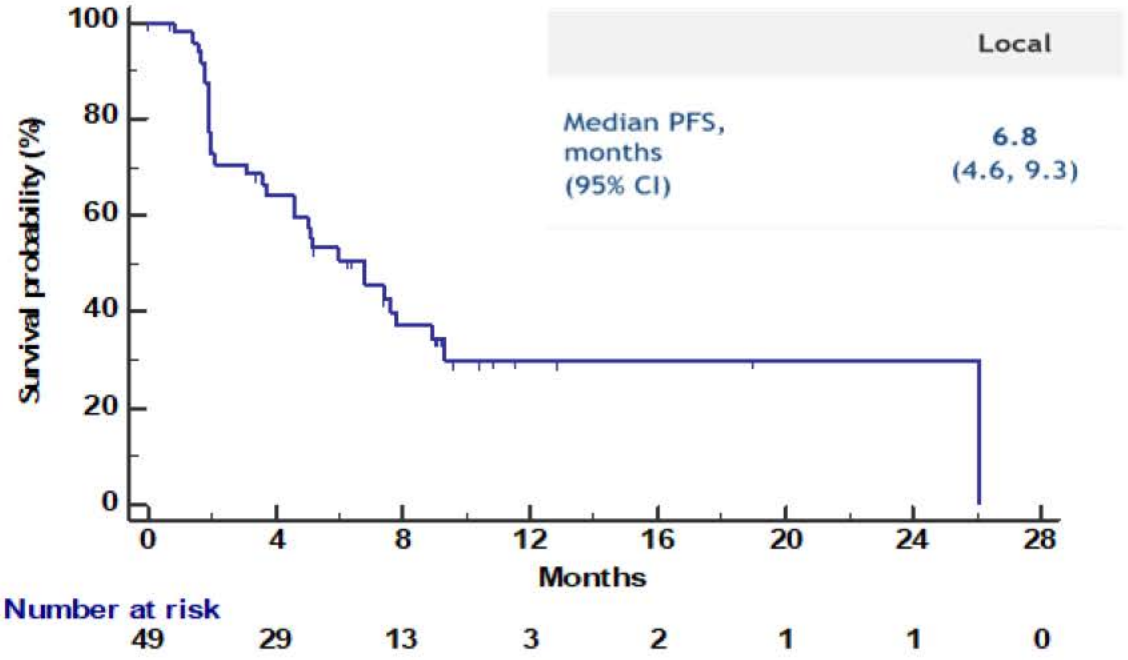


Figure 3. Progression-free Survival for 54 HR+/HER2-Negative Metastatic Breast Cancer Subjects: Administered Sacituzumab Govitecan (ITT Population)



HER2-=human epidermal growth factor receptor 2 negative; HR=hormonal receptor; ITT=Intent-to-Treat.

2.4.4. Safety Data

The safety profile of sacituzumab govitecan has been characterized based on 420 patients included in the Overall Safety Population in Study IMMU-132-01. As described in Section 2.6, subjects were treated with doses of 8 mg/kg, 10 mg/kg, 12 mg/kg, and 18 mg/kg. This population included 164 patients with breast cancer (including 108 patients with metastatic TNBC treated with 10 mg/kg), 45 patients with urothelial cancer, 110 patients with lung cancer (small cell lung cancer and non-small cell lung cancer), and 101 patients with other epithelial cancers (including cervical, colorectal, endometrial, epithelial ovarian, esophageal, gastric, glioblastoma multiforme, head and neck, hepatocellular, prostate, pancreatic, and renal). As of 01 Dec 2017, the mean treatment duration in these patients was 160 days (7.7 cycles). The following is a summary of the safety data; additional details can be found in the sacituzumab govitecan IB.

Nearly all subjects experienced at least one AE, with 75% with one ≥National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) Grade 3 AE. Overall, 41% had a serious AE (SAE). AEs leading to treatment interruption occurred in 48% of subjects; however, only 11% of subjects discontinued due to an AE. Fatal AEs (within 30 days of last dose) occurred in 6.7% of subjects; however, nearly all of these deaths were in the setting of disease progression.

The most frequent AEs were gastrointestinal (nausea, vomiting, and diarrhea) and myelosuppressive (neutropenia and anemia). Nausea occurred in 67% (5% ≥Grade 3); vomiting occurred in 44% (4% ≥Grade 3); and diarrhea occurred in 62% (9% ≥Grade 3) of patients. All subjects were administered prophylactic antiemetic treatments and nausea, vomiting, and diarrhea were managed according to standard treatment guidelines. With aggressive management of these toxicities, few subjects required treatment discontinuation.

The most frequent myelosuppressive AEs were neutropenia (41% overall; ≥Grade 3, 28%) and anemia (41% overall; ≥Grade 3, 11%). Neutrophil count decreased occurred in 18% of subjects (13% ≥Grade 3) and febrile neutropenia occurred in 6%. Although treatment was interrupted due to neutropenia in 21% of subjects, only one subject discontinued treatment because of neutropenia.

Infections occurred in 43% of subjects (10% ≥Grade 3); the most frequent infections were common, and community-acquired, such as urinary tract infections (12%) and upper respiratory tract infections (10%). Pneumonia occurred in 5% (3% ≥Grade 3) of subjects, sepsis in 1.4% (6 subjects), and septic shock in 0.5% (2 subjects).

Other frequent AEs included fatigue (53%) and alopecia (42%). Only 2 subjects had infusion-related hypersensitivity reactions requiring permanent discontinuation of treatment (anaphylaxis in one subject and wheezing, cough, and nasal congestion in a second subject). These subjects were ADA negative.

As noted previously in Section 2.3, SN-38 (the active metabolite of irinotecan) is metabolized by UGT1A1. Irinotecan-treated subjects who are homozygous for the UGT1A1 *28 allele are at increased risk for neutropenia and diarrhea {CAMPTOSAR 2014}. Preliminary results from Study IMMU-132-01 suggest that the frequency of some exposure-related AEs (i.e., neutropenia and febrile neutropenia) may also be higher in subjects homozygous for the *28 allele; however, the frequencies of neutrophil count decreased and other treatment-related AEs, notably diarrhea, did not differ among homozygous compared with heterozygous subjects.

2.5. Rationale for the Study

MBC has a high unmet medical need. Sacituzumab govitecan has been generally safe and well tolerated in nonclinical and clinical studies. Additionally, in a Phase 1 study in subjects with HR+/HER2- MBC, subjects treated with sacituzumab govitecan had an ORR of 31%, a median DOR of 7.4 months, with a CBR of 48% in all subjects. Taken together, these results suggest that sacituzumab govitecan is a promising agent for HR+/HER2- breast cancer patients. The study described herein will be conducted to assess and compare the efficacy and safety of sacituzumab govitecan to TPC in previously-treated subjects with relapsed/refractory HR+/HER2- MBC.

2.6. Rationale for Dose Regimen

In the Phase 1 part of study IMMU-132-01, dose escalation was performed according to a standard 3+3 design and based on planned initial sacituzumab govitecan dose levels of 8, 12, and 18 mg/kg. A sacituzumab govitecan dose of 12 mg/kg was formally identified as the maximum tolerated dose (MTD), but was associated with dose delays and reductions in several subjects. In order to determine a maximum acceptable dose, additional subjects were treated at the 8 mg/kg dose level and an intermediate dose cohort of 10 mg/kg was added. Both 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. Interim analyses demonstrated that subjects receiving the 10 mg/kg dose had a comparable treatment duration as subjects receiving 8 mg/kg. However, there was no worsening of AE incidence nor severity with the 10 mg/kg dose compared with the 8 mg/kg dose. ORR and CBR were higher and PFS was longer with the 10 mg/kg dose compared with the 8 mg/kg dose, specifically in TNBC patients {Ocean 2017}. Based on these results, 10 mg/kg was chosen as the dose for further study. Additional information regarding safety and efficacy of sacituzumab govitecan can be found in current edition of the sacituzumab govitecan IB.

2.7. Risk/Benefit Assessment for the Study

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 10 for further details on the risks and risk mitigation strategy.

2.8. Compliance

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

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of the study is:

- To assess and compare the efficacy of sacituzumab govitecan to TPC as measured by PFS as determined by blinded independent central review (BICR) using RECIST 1.1 (see Appendix 6) in subjects with HR+/HER2- MBC who have progressed after CDK 4/6 inhibitor, endocrine therapy, taxane, and at least 2, but no more than 4 prior chemotherapy regimens for metastatic disease

3.2. Secondary Objectives

The secondary objectives of the study are:

- To assess and compare sacituzumab govitecan to TPC in overall survival (OS) in subjects with HR+/HER2- MBC who have progressed after CDK 4/6 inhibitor, endocrine therapy, taxane and at least 2, but no more than 4 prior chemotherapy treatment regimens for metastatic disease
- To assess and compare ORR, DOR, and CBR between treatment arms as determined by LIR and BICR using RECIST 1.1
- To assess and compare the impact of treatment on time to deterioration (TTD) of global health status/QOL, pain, and fatigue domains as measured by European Organization for the Research and Treatment of Cancer (EORTC) quality of life for cancer patients, core questionnaire version 3.0 (QLQ-C30)
- To assess and compare the overall safety and tolerability

CCI [redacted]

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

Study IMMU-132-09 (TROPiCS 02 [Trop-2 Investigation in Cancer with sacituzumab govitecan]) is an open-label, randomized, multicenter, international Phase 3 study to compare the efficacy and safety of sacituzumab govitecan versus TPC in subjects with metastatic or locally recurrent inoperable HR+/HER2- MBC who have progressed after CDK 4/6 inhibitor, endocrine therapy, taxane, and at least 2, but no more than 4 prior chemotherapy treatment regimens for metastatic disease.

Approximately 520 eligible subjects will be randomized in a 1:1 ratio to either sacituzumab govitecan (Investigational Arm A) or TPC (Control Arm B; i.e., eribulin, capecitabine, gemcitabine, or vinorelbine). Randomization will be stratified based on prior chemotherapy regimens for treatment of metastatic disease (two vs. three/four lines), visceral metastasis (Y/N), and endocrine therapy in the metastatic setting for at least 6 months (Y/N).

The study will be conducted in two phases, a Pre-randomization Phase and a Randomization Phase:

- The Pre-randomization Phase will last no longer than 28 days and consists of the following two periods:
  - A Screening Period to establish study eligibility
  - A Baseline Period to confirm eligibility and establish disease characteristics prior to randomization and treatment
- The Randomization Phase will begin at the time of randomization of the first subject and will end on the data cut-off date for the final analysis of OS; the Randomization Phase consists of the following two periods:
  - A Treatment Period which begins at the time of randomization and ends with the completion of the End-of-Treatment (EOT) visit, which will occur at least 30 days after the final dose of study treatment
  - A Follow-up Period which begins the day after the EOT visit and continues as long as the subject is alive or until the data cut-off date of the final analysis of OS, unless the subject withdraws consent from the study or the Sponsor terminates the study

4.2. Data Safety Monitoring Committee

An independent Data Safety Monitoring Committee (DSMC) will be convened at regular intervals to assess the progress of this study and review safety per an approved DSMC charter.

4.3. End Points

4.3.1. Efficacy

Efficacy analyses will be performed using tumor assessments by LIR and BICR using RECIST 1.1.

The primary efficacy end point is:

- PFS as determined by BICR using RECIST 1.1

The secondary efficacy end points are:

- OS
- ORR as determined by BICR using RECIST 1.1
- TTD in the global health status/QOL, pain and fatigue domains of EORTC QLQ-C30
- DOR as determined by LIR and BICR using RECIST 1.1
- CBR as determined by LIR and BICR using RECIST 1.1

4.3.2. Safety

Safety and tolerability will be assessed based on the incidence of AEs and SAEs, review of clinical laboratory data (i.e., hematology, chemistry, and urinalysis), electrocardiogram (ECG) monitoring, Eastern Cooperative Oncology Group (ECOG) performance status, vital signs (i.e., heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature), and ADA.

4.4. Duration of Study

Enrollment is expected to be completed in approximately 24 months. The overall duration of the study is expected to be 52 months.

5. SUBJECT POPULATION

5.1. Inclusion Criteria

1) Female or male subjects, adult or aged ≥ 18 years at the time of signing the informed consent form (ICF)

2) Documented evidence of HR+/HER2- MBC confirmed by a local laboratory with the most recently available or newly obtained tumor biopsy (preferably within the last 12 months) from a locally recurrent or metastatic site(s) and defined per American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) criteria as:

   — HR+ (a tumor is considered HR+ if at least 1% of the cells examined have estrogen and/or progesterone receptors)

   — HER2- defined as immunohistochemistry ≤ 2+ or fluorescence in situ hybridization negative

3) Availability of archival tumor tissue in a formalin-fixed, paraffin embedded (FFPE) block (preferably within 12 months prior to consent) or newly acquired biopsy (FFPE block) from a metastatic site. Note: bone biopsies are not allowed.

4) Refractory to or relapsed after at least 2, but no more than 4 prior systemic chemotherapy regimens for metastatic disease. Adjuvant or neoadjuvant therapy for early stage disease will qualify as one of the required prior chemotherapy regimens if the development of unresectable, locally advanced, or metastatic disease occurred within a 12-month period of time of the therapy. Note: treatments for bone metastases (e.g., bisphosphonates, denosumab, etc.) and hormonal therapy are not considered as prior systemic chemotherapy treatments for advanced disease

5) Should have been previously treated with:

   — At least 1 taxane in any setting

   — At least 1 prior anticancer hormonal treatment in any setting

   — At least 1 CDK 4/6 inhibitor in any setting.

6) Eligible for one of the chemotherapy options listed in the TPC arm.

7) Documented disease progression after the most recent therapy by computed tomography (CT)/magnetic resonance imaging (MRI)

8) At least 1 measurable target lesion according to RECIST 1.1 (bony disease only is not allowed) meeting all of the following criteria:

   — Lymph node lesion that measures at least ≥ 1.5 cm in the short axis.

   — Non-nodal lesion that measures ≥ 1.0 cm in the longest diameter in the plane of measurement

   — The lesion is suitable for repeat measurement using computerized tomography (CT)/MRI. Historical CT/MRI scans performed within 28 days of C1D1 may be used as screening scans to demonstrate eligibility by local radiology review as long as they meet minimum standards as separately defined by the central imaging vendor.

   — Lesions that have had external beam radiotherapy (EBRT) or locoregional therapy must show radiographic evidence of disease progression based on RECIST 1.1 to be deemed a target lesion.

   — Brain CT/MRI must be conducted for subjects with a history of brain metastasis. The subject must have had stable* brain metastasis for at least 4 weeks. Target lesions cannot be from brain.

      * Stable brain metastasis is defined as the following:

      ■ Prior local treatment by radiation, surgery, or stereotactic surgery.

      ■ Imaging – stable or decreasing size after such local treatment.

      ■ Clinically stable signs and symptoms for at least 4 weeks.

      ■ ≥ 2 weeks from discontinuation of antiseizure medication

      ■ Low and stable doses of corticosteroids ≤ 20 mg prednisone or equivalent daily are permitted

9) ECOG performance status of 0 or 1

10) Adequate renal function: calculated creatinine clearance ≥ 30 mL/minute according to the Cockcroft and Gault formula

11) Adequate bone marrow function, defined as:

   — Absolute neutrophil count (ANC) ≥ 1,500 per mm^3

   — Hemoglobin ≥ 9.0 g/dL

   — Platelet count ≥ 100,000 per mm^3

      Note: Blood transfusion or growth factor support is not allowed within 14 days prior to screening labs.

12) Adequate liver function, defined as:

- Total bilirubin ≤ 1.5× institutional upper limit of normal (IULN) or ≤ 3 IULN for patients with documented Gilbert's syndrome
- Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 2.5× IULN (in the case of liver metastases ≤ 5× IULN), and serum albumin ≥ 3 g/dL
- Alkaline phosphatase (ALP) ≤ 5.0× IULN unless there are bone metastases, in which case liver-specific ALP must be separated from the total and used to assess liver function instead of total ALP

13) Resolution of all systemic anticancer therapy-related or radiation-related toxicities to Grade 1 severity or lower, except for neuropathy (≤Grade 2) and alopecia. Subjects with Grade 2 neuropathy are eligible, but should not receive vinorelbine as TPC.

14) Females must not be lactating or pregnant at Baseline (as documented by a negative beta human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG [or hCG]). All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrhoeic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (i.e., bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

15) Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception (total abstinence [if it is her preferred and usual lifestyle], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 6 months after study drug discontinuation. For sites outside of the European Union (EU), it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, i.e., double barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide. If currently abstinent, the subject must agree to use a highly effective method as described above if she becomes sexually active during the study period or for 6 months after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 28 days before dosing and must continue to use the same contraceptive during the study and for 6 months after study drug discontinuation

16) Male subjects who are partners of women of childbearing potential must use a condom and spermicide and their female partners, if of childbearing potential, must use a highly effective method of contraception (see methods described above in Inclusion Criterion 15)) beginning at least 1 menstrual cycle prior to starting study drug, throughout the entire study period, and for 3 months after the last dose of study drug, unless the male subjects are totally sexually abstinent or have undergone a successful vasectomy with confirmed azoospermia or unless the female partners have been sterilized surgically or are otherwise proven sterile.

17) Must be willing and able to comply with all aspects of the protocol

18) Must voluntarily agree to provide written informed consent

19) Could have received an unlimited number of prior endocrine, biological, or targeted therapies in the absence of co-administered chemotherapy; all of these therapies must have been completed 14 days prior to randomization, except biological therapy which must have been completed 28 days prior to randomization

5.2. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1) Previous treatment with a topoisomerase 1 inhibitor as a free form or as other formulations

2) Current enrollment in another clinical study or used any investigational device or drug either within 5 half-lives or 28 days prior to randomization, whichever is longer

3) Treatment with chemotherapy, radiation, or small molecule targeted therapy within 2 weeks and biological therapy within 4 weeks prior to the first dose of study treatment

4) Existing anticancer treatment-related AEs of Grade ≥ 2 (except for alopecia and Grade 2 neuropathy) according to NCI-CTCAE v5.0

5) Any other malignancy that required treatment or has shown evidence of recurrence (except for non-melanoma skin cancer or histologically-confirmed complete excision of carcinoma in situ) during the 5 years prior to enrollment in this study

6) History of significant cardiovascular disease, defined as:

   — Congestive heart failure greater than New York Heart Association (NYHA) Class II according to the NYHA Functional Classification

   — Unstable angina or myocardial infarction within 6 months before enrollment

   — Serious cardiac arrhythmia

7) Clinically-significant ECG abnormality, including any of the following:

   — Marked Baseline prolonged QT/QTc interval (i.e., a repeated demonstration of a QTc interval > 500 ms) demonstrated on ECG at Screening. QTcF is calculated by Fridericia's formula

$$QTc_F = \frac{QT}{\sqrt[3]{\frac{RR}{(1s)}}}$$

— History of risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of long QT Syndrome)

8) Has known active central nervous system metastases and/or carcinomatous meningitis. Subjects may participate provided they have stable brain metastasis. All subjects with carcinomatous meningitis are excluded regardless of clinical stability. Stable brain metastasis is defined in inclusion criterion 8)

9) Active hepatitis B virus (positive hepatitis B surface antigen) or active hepatitis C virus (measurable viral ribonucleic acid (RNA) load with polymerase chain reaction) infection

10) Scheduled surgery during the study, other than minor surgery which would not delay study treatment

11) Has an active serious infection requiring antibiotics

12) Has active chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease) and subjects with a history of bowel obstruction

13) Have received a live vaccine within 30 days of randomization.

14) Known hypersensitivity or intolerance to any of the study drugs or any of the excipients

15) Any medical or other condition which, in the opinion of the Investigator, causes the subject to be medically unfit to receive sacituzumab govitecan or unsuitable for any other reason

16) Is receiving any medication prohibited in combination with the study treatment(s) as described in the respective product labels, unless medication was stopped within 7 days prior to randomization

17) Locally-advanced MBC (stage IIIc) in subjects who are candidates for curative intent therapy at the time of study enrollment

18) If required per local guidelines, any subject with a blood uracil level ≥ 150 ng/mL is excluded from receiving capecitabine as TPC (Note: blood uracil level will be assessed at Screening for all subjects eligible to be randomized to capecitabine as TPC)

5.3. Number of Subjects and Treatment Assignment

Approximately 520 subjects will be enrolled and randomized in a 1:1 ratio to receive either sacituzumab govitecan or a preselected TPC using an Interactive Web-Based Response System (IWRS), with stratification by number of prior chemotherapy regimens for treatment of metastatic disease (two vs. three/four lines), visceral metastasis (Y/N), and endocrine therapy in the metastatic setting for at least 6 months (Y/N).

5.4. Criteria for Removal from Study Treatment

A subject will remain on study treatment until one or more of the following events occur(s):

- Unacceptable study drug-related AEs (see Section 6.1.7)
- Subject request
- First documentation of PD or symptomatic deterioration, indicating treatment failure in the absence of clinical benefit
- Note: Subjects will be permitted to continue in the Treatment Period beyond initial RECIST 1.1-defined progression as long as investigator-assessed clinical benefit is observed and the subject is tolerating study drug. Subjects will discontinue study treatment upon evidence of further progression and/or loss of clinical benefit as judged by the Investigator.
- Treatment delay for any reason > 3 weeks
- Withdrawal of consent
- Termination of the study by the Sponsor
- Pregnancy
- Investigator decision
- Death
- Lost to follow-up

6. TREATMENT OF SUBJECTS

6.1. Investigational Product, Dosage, and Mode of Administration

6.1.1. Description

Sacituzumab govitecan is formulated as a sterile, non-pyrogenic, lyophilized powder consisting of 10 mg/mL sacituzumab govitecan in 25 mM MES, pH 6.5, together with the excipients 25 mM trehalose and 0.01% Polysorbate 80. The formulated drug product contains no preservative. Sacituzumab govitecan is supplied in a 50-mL clear glass vial.

6.1.2. Packaging and Labeling

Sacituzumab govitecan will be supplied in individual cartons, each containing 1 vial.

Study drug(s) to be distributed to centers in the US and 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.

CCI [redacted]

[redacted]

6.1.4. Preparation

Refer to the Pharmacy Manual for instructions on preparing sacituzumab govitecan.

6.1.5. Premedications

Premedications for prevention of infusion related reactions should be administered before each sacituzumab govitecan infusion, including antipyretics and H1 and H2 blockers. Corticosteroids (hydrocortisone 50 mg or equivalent orally [PO] or IV) may be administered prior to subsequent infusions if the subject has experienced an infusion-related reaction with a previous infusion.

Sacituzumab govitecan is considered to be moderately emetogenic and premedication with a two-drug antiemetic regimen is recommended. If nausea and vomiting are persistent, a three-drug regimen, 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 intravenously [IV]), may be used. Anticipatory nausea can be treated with olanzapine.

6.1.6. Administration

Sacituzumab govitecan is administered at 10 mg/kg as an IV infusion on Days 1 and 8 of a 21-day cycle. Dosing is based on the subject's body weight on Day 1 of each cycle (or at each dosing day if change in body weight is >10% from last measurement or if required by institutional policy). Dose modifications for changes in body weight ≤ 10% may be made according to local institutional guidelines.

Do not administer as an IV push or bolus. Sacituzumab govitecan is administered IV as a slow infusion as described below.

Intravenous access must be well established prior to initiating infusion. At the time of dosing, the IV line will be connected to an infusion container containing the prepared volume of sacituzumab govitecan. Either gravity or an infusion pump may be used. Only normal saline should be used as the infusion base solution since the Sponsor has not examined the compatibility of sacituzumab govitecan with other infusion diluents.

Initiate the infusion within 1 hour of reconstitution/dilution. If infusion is delayed beyond 1 hour, refrigerate at 2-8°C for no more than 4 hours from reconstitution/dilution prior to infusion. Once reconstituted and diluted into the IV bag, a paper sleeve should be put over the IV bag during administration or if stored at 2-8°C to protect from light until administered to the subject. If refrigerated, allow the diluted solution to come to room temperature prior to administration. If infusion is not initiated within 4 hours after reconstitution/dilution, dispose of the original preparation and prepare a new infusion bag by reconstituting and diluting from new vials. Discard any unused portion in the vial.

The initial infusion should proceed over 3 hours. Subsequent infusions can either be administered over 3 hours or 1-2 hours if vital signs remain stable and no infusion reactions occur. Monitor the patient during and for at least 30 minutes after infusion. Following infusion completion, the IV line should be flushed slowly with 20 mL normal saline and the end-of-infusion time recorded. In the event of infusion reactions or vital sign changes, the infusion rate may be slowed, interrupted, or terminated as considered appropriate by the managing physician.

6.1.7. Management of Sacituzumab Govitecan Toxicity

Section 6.1.7.1 provides guidance for modification of the sacituzumab govitecan dose and discontinuation for management of toxicity. Section 6.1.7.2 provides guidance on the management of toxicities known to occur with sacituzumab govitecan. Toxicities should be managed in accordance with standard institutional practices and accepted treatment guidelines.

6.1.7.1. Dose Delays, Dose Reductions, and Study Drug Discontinuations

Dose Delays

Sacituzumab govitecan is to be administered in 21-day cycles on Day 1 and Day 8; the next cycle should start a minimum of 14 days after the Day 8 dose. Visit windows of ±2 days from the scheduled infusion are permitted. Scheduled Day 1 dosing may be delayed for up to 1 week for treatment-related toxicities. Instructions for dose delays and dose reductions for specific toxicities are summarized below. Day 8 dosing could be delayed for up to 1 week for treatment-related toxicities, however, if the toxicity has not resolved to ≤Grade 2 within 1 week of Day 8, then the scheduled Day 8 dosing may be cancelled and dosing should resume with the Day 1 of the following cycle. There should be a minimum of 14 days and a maximum of 21 days between the Day 8 infusion and the Day 1 infusion of the next cycle. No other treatment interruptions are permitted.

Dose Reductions and Discontinuation

The major toxicities of sacituzumab govitecan are expected to be gastrointestinal symptoms and hematologic suppression. All subjects will be closely monitored over the course of their treatment and aggressively medically managed, including dose reduction and interruption, in order to prevent the need for treatment discontinuation and serious complications from these toxicities. Sacituzumab govitecan dose reductions and interruptions will be managed based on toxicity severity assessed by NCI-CTCAE v5.0. The sacituzumab govitecan dose must not be re-escalated following a dose reduction. Table 5 summarizes recommendations for sacituzumab govitecan dose reductions and discontinuations for treatment-related toxicities.

Table 5. Recommended Dose Reduction Schedule for Sacituzumab Govitecan

Event NCI-CTCAE v5.0	Occurrence	Recommended dose reduction or action
Severe Neutropenia		
Grade 4 neutropenia ≥ 7 days, OR Grade 3-4 febrile neutropenia OR At time of scheduled treatment, ≥Grade 3 neutropenia which has delayed dosing by 1 week	First	Administer granulocyte-colony stimulating factor or sooner, if clinically indicated
	Second	25% dose reduction
	Third	50% dose reduction
	Fourth	Discontinue treatment
≥Grade 3 neutropenia which delays dosing beyond 3 weeks	First	Discontinue treatment
Severe Non-Neutropenic Toxicity		
Grade 4 non-hematologic toxicity of any duration, OR Any ≥Grade 3 nausea, vomiting or diarrhea due to treatment that is not controlled with antiemetics and anti-diarrheal agents, OR Other ≥Grade 3 non-hematologic toxicity persisting >48 hours despite optimal medical management, OR At time of scheduled treatment, ≥Grade 3 non-neutropenic hematologic or non-hematologic toxicity, which has delayed dosing by 1 week	First	25% dose reduction
	Second	50% dose reduction
	Third	Discontinue treatment
≥Grade 3 non-neutropenic hematologic or non-hematologic toxicity, which has delayed dosing for more than 3 weeks	First	Discontinue treatment

6.1.7.2. Management of Specific Toxicities

6.1.7.2.1. Infusion-Related Reactions

Infusion-related reactions can occur at any cycle and are defined as symptoms that occur during and within the first 6 hours after the infusion of sacituzumab govitecan. Symptoms can include fever, chills, rigors, arthralgias, myalgias, urticaria, pruritus, rash, diaphoresis, hypotension, dizziness, syncope, hypertension, dyspnea, cough, and wheezing, as well as severe hypersensitivity reactions, including anaphylactic reactions. Infusion-related reactions should be treated in accordance with best clinical practices and standard institutional guidelines. Because of the potential for life threatening infusion-related reactions, sacituzumab govitecan should only be administered in a setting in which appropriately trained medical staff, emergency equipment, and medications are available in the event that resuscitation is required. NCI-CTCAE v5.0 is used to grade the severity of all infusion-related AEs. Premedication for the prevention of infusion related-reactions is described in Section 6.1.5.

Grade 3 and Grade 4 Events

Grade 3 and Grade 4 infusion-related reactions can include severe or clinically-significant cardiopulmonary events and severe allergic reactions, such as symptomatic bronchospasm and anaphylactic reactions. Grade 3 infusion-related reactions are defined as those which are prolonged and do not improve with symptomatic treatment and/or brief interruption of treatment; reactions that recur following treatment; and reactions that require hospitalization. Grade 4 reactions include potentially life-threatening reactions requiring urgent intervention. Severe allergic and anaphylactic reactions should be treated in accordance with best clinical practices and standard institutional guidelines. If Grade 3 or Grade 4 infusion-related reactions occur, sacituzumab govitecan should be permanently discontinued.

Grade 2 Events

Grade 2 infusion-related reactions are defined as those that require infusion interruption and respond to symptomatic treatment; prophylactic medications are indicated for ≤ 24 hours. For Grade 2 infusion-related reactions, the infusion should be interrupted for at least 15 minutes until symptoms resolve. After symptoms resolve, the infusion should be resumed at a slower infusion rate. Recommended infusion rates are provided in Section 6.1.6. For recurrent Grade 2 infusion reactions that fail to recover within 6 hours, despite optimal management, sacituzumab govitecan should be permanently discontinued.

6.1.7.2.2. Gastrointestinal Toxicities

Nausea, vomiting, and diarrhea are frequent sacituzumab govitecan-associated toxicities. Appropriate treatment, including, as needed, fluid and electrolyte replacement, is required to minimize the risk of serious consequences such as dehydration. Instructions for sacituzumab govitecan dose reduction for treatment-related gastrointestinal toxicities are provided in Section 6.1.7.2.2.

Nausea and Vomiting

Instructions for the use of premedications for prophylactic treatment of nausea and vomiting and anticipatory nausea are provided in Section 6.1.5. Do not hold the dose of sacituzumab govitecan for Grade 3 nausea unless Grade 3 nausea persists despite maximal optimal medical management. Subjects should be treated for delayed nausea and vomiting on Days 2 and 3 with 5-HT_3 receptor antagonist (ondansetron or palonosetron) monotherapy and other agents if needed. Steroids may be added if symptoms do not resolve with these agents. Consider olanzapine for persistent or anticipatory nausea; an olanzapine dose of 2.5 mg or 5 mg at bedtime is recommended. NK1 receptor antagonists (fosaprepitant and aprepitant) may be administered.

Diarrhea

Dietary modification should be recommended for the management of diarrhea, including a bland diet, small frequent meals, adequate fluid intake of clear liquids to maintain hydration, and discontinuation of lactose-containing foods and drinks containing alcohol. Loperamide should be administered at the onset of treatment-related diarrhea at an initial dose of 4 mg, followed by 2 mg with every episode of diarrhea to a maximum dose of 16 mg/day. If diarrhea is not resolved after 24 hours, add diphenoxylate/atropine or opium tincture as clinically indicated. Add octreotide 100-150 µg subcutaneously 3 times per day if diarrhea persists. For Grade 4 diarrhea, consider subject hospitalization and treatment with IV fluids and octreotide. Antibiotics can be administered as clinically indicated.

Subjects who exhibit an excessive cholinergic response to treatment with sacituzumab govitecan (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g., atropine) for subsequent treatments.

6.1.7.2.3. Neutropenia

Complete blood counts must be obtained prior to each sacituzumab govitecan infusion and should be administered if ANC meet 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 recommended; however, they may be used in subjects who have experienced febrile neutropenia or Grade 3 or Grade 4 neutropenia following previous infusions. Growth factors may also be administered in the setting of neutropenia in subjects at high risk of poor clinical outcomes, including those with prolonged neutropenia, ANC $< 1000/mm^3$, febrile neutropenia, and serious infections.

6.1.8. Drug Interactions

No formal drug-drug interaction studies with sacituzumab govitecan have been conducted. SN-38 (the active metabolite of sacituzumab govitecan) is metabolized via human UGT1A1. Concomitant administration of inhibitors or inducers of UGT1A1 with sacituzumab govitecan should be avoided due to the potential to either increase (inhibitors) or decrease (inducers) the exposure to SN-38.

UGT1A1 Inhibitors

Co-administration of sacituzumab govitecan with inhibitors of UGT1A1 (e.g., atazanavir, gemfibrozil, indinavir) may increase systemic exposure to the active metabolite, SN-38. Do not administer UGT1A1 inhibitors with sacituzumab govitecan unless there are no therapeutic alternatives.

UGT1A1 Inducers

Exposure to SN-38 may be substantially reduced in subjects concomitantly receiving UGT1A1 enzyme inducers. Do not administer UGT1A1 inducers with sacituzumab govitecan unless there are no therapeutic alternatives.

6.1.9. Drug Accountability and Destruction

Study drug must be stored under refrigerated conditions (2-8ºC) in a locked room that can be accessed only by the pharmacist, the study Investigator, or another duly authorized study/site personnel. Study medication must not be used outside of the context of this protocol. Under no circumstances should the Investigator or other site personnel supply study drug to other Investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol. Records documenting receipt, use, return, loss, or other disposition of study drug vials must be kept. A complete drug accountability record supplied by the Sponsor (or its designee or National Cancer Institute drug accountability forms) or computer records used by the pharmacy at the investigational site can be used to provide drug accountability. In all cases, information describing study medication disposition, subject-by-subject, must be provided and signed by the Investigator (or the pharmacist or other person who dispensed the drug) and collected by the Study Monitor. Requisite data include relevant dates, quantities, batches or code numbers, and subject identification for subjects who received trial product. At the end of the study, following authorization by the Study Monitor, study medication may be destroyed at the site as dictated by the appropriate standard operating procedures at the participating sites. Destruction must be documented with the signature of either the site's pharmacist or delegate. Alternatively, after notification, all unused product will be collected by the Study Monitor and returned to the Sponsor or its designee.

If abnormalities of the drug vial, reconstituted product, or specific AEs are noted that are thought to be attributed to study drug, under no circumstances are additional testing or procedures to be performed on the affected study drug vial or infusion bag and study drug should not be discarded. Entire study drug should be retained at the site and the Sponsor or Sponsor's representative should be immediately notified. Please refer to the Laboratory Manual for further instructions.

6.2. Treatment of Physician's Choice

TPC is single-agent treatment determined before randomization from one of the following:

- Eribulin - (1.4 mg/m^2 for North American sites, 1.23 mg/m^2 for EU sites or per institution) is to be administered IV on Days 1 and 8 of a 21-day cycle

- Capecitabine - (1000-1250 mg/m^2) is to be administered PO twice daily for 2 weeks followed by a 1-week rest period given as a 21-day cycle

- Gemcitabine - (800-1200 mg/m^2) administered IV on Days 1, 8, and 15 of each 28-day cycle or per institution

- Vinorelbine (25 mg/m^2 IV on Day 1 weekly cycle per institution) (Note: subjects with grade 2 neuropathy are eligible, but should not receive vinorelbine as TPC)

No combination or crossovers of the 4 choices is permitted.

The use of premedications (i.e., antipyretics, H_1 blockers, and H_2 blockers) for prevention of infusion reactions and medications for prevention and treatment of chemotherapy-induced nausea, vomiting, and diarrhea for subjects in this group is based on the Investigator's discretion.

TPC dosing is based upon body surface area as per local standard of care and should be administered using the recommended doses and schedules in the locally-approved prescribing information or according to NCCN guidelines (with dose/schedule modifications either according to locally-approved prescribing information or institutional standard practices; https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf).

6.3. Concomitant Medications and Procedures

Medications initiated prior to the first dose of study drug will be recorded as prior medications and medications initiated following receipt 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 electronic Case Report Form (eCRF) with information regarding dose, indication, route of administration, and dates of administration. Medications used for prophylaxis of anticipated AEs should be documented with the rationale for prophylactic intent (see Section 6.1.5).

6.3.1. Prohibited Concomitant Medications and Procedures

Subjects are prohibited from receiving the following therapies during the Pre-Randomization Period (Baseline/Screening) and Treatment Period of this study:

- Anticancer therapies: No anticancer therapies, aside from study drug, are permitted during this study
- Radiation therapy: Radiation therapy is prohibited within 2 weeks prior to randomization.

  Note: Radiation therapy to a symptomatic solitary non-target lesion or to the brain may be allowed while on study treatment after consultation with Sponsor provided that palliative radiotherapy is not indicated for tumor progression. Such radiation therapy would be considered a progression event in efficacy analyses.
- High-dose systemic corticosteroids are not allowed within 2 weeks of randomization. Low and stable doses of corticosteroids ≤ 20 mg prednisone or equivalent daily are permitted if the subject entered the study on low-dose steroids for treated brain metastasis or if medically indicated as part of premedication for infusions. (Topical steroids and corticosteroid inhalers are allowed)
- Herbal supplements are not recommended

6.3.2. Permitted Concomitant Medications and Procedures

Palliative and/or supportive medications, such as pain medications, bone-modifying medications (bisphosphonates or denosumab), anti-emetics or anti-diarrheal medications, transfusions and growth factor support, continuing or initiating the use of low-dose corticosteroids, and other palliative medications for complications of disease, including medications for pain and dietary support, are allowed at the Investigator's discretion. Palliative external radiotherapy is permitted, but presence of new or worsening metastases will be considered progression.

There is not substantial safety data regarding the concurrent administration of the coronavirus disease 2019 (COVID-19) vaccine and sacituzumab govitecan. Patients are allowed to receive the COVID-19 vaccine to reduce the risk and complications of COVID-19 infection. The study visits should continue as planned if possible, and clinically appropriate if vaccination occurs while the patient is on the study.

6.3.3. QT-Prolonging Drugs

Subjects receiving QT-prolonging drugs should be carefully monitored as some of the study medications may increase the QT interval. When possible, the Investigator should consider avoiding these medications and using alternative medications that do not affect the QT interval. While 5-HT3 receptor antagonist compounds can prolong the QT interval, they are effective for prophylaxis/treatment of nausea associated with sacituzumab govitecan and investigators are advised to monitor subjects closely when used. See Appendix 8 for a list of medications that affect the QT interval.

7. STUDY PROCEDURES

7.1. Informed Consent

No study-specific study procedure or alteration of subject care will be undertaken until informed consent has been obtained either from the subject or his/her legally authorized representative. The Investigator will explain the nature and scope of the study, potential risks and benefits of participation, and answer questions for the subject and/or legally authorized representative.

If the subject agrees to participate, the ICF must be signed, dated, and witnessed, with a copy given to the subject. The consenting process must be well documented by each investigational site.

If the subject decides to stop all protocol procedures and withdraw consent for treatment, the subject will be asked to sign an additional ICF for the collection of follow-up information regarding further lines of therapy and survival.

If a subject is allowed to continue treatment after progression, the subject will be required to sign an additional ICF to ensure awareness that he/she is foregoing other therapies, including other clinical trials that may be available.

7.2. Subject Registration

At such time as a subject has been deemed eligible for the study and all required screening evaluations have been completed, the subject can be randomized using the IWRS.

Randomization must occur on or before C1D1, such that dosing commences within 5 days after randomization.

7.3. Demographics, Medical History, Prior and Concomitant Medications

Each subject's demographic and medical/surgical history, all prior anti-cancer treatments, including treatment response and also time to progression for last therapy regimen (if available), and all prior therapies are to be collected within 28 days prior to randomization. Mutational status, including breast cancer susceptibility gene 1 and 2, will also be collected, if known.

All prior and concomitant medications (including over-the-counter medicines, herbal treatments, supplements, vitamins, and substance use) and treatments taken from 28 days prior to signing consent until at least 30 days after the last dose of study drug will be recorded.

7.4. Tumor Assessments

7.4.1. Screening

Target and non-target lesions must be determined by the clinical site at the time of randomization. Note: brain lesions cannot be target lesions.

- Screening tumor assessments using CT/MRI of the chest, abdomen, and pelvis and other areas of known disease or newly suspected disease should be performed within 28 days prior to C1D1

  — Scans of the abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast

  — Historical CT/MRI scans performed within 28 days before C1D1 may be used as screening scans to demonstrate eligibility by local radiology review as long as they meet minimum standards as separately defined by the central imaging vendor

- 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 prior to C1D1 (historical scans are acceptable)

- Brain CT/MRI in subjects with known or suspected brain metastases. Historical brain CT/MRI scans performed within 28 days before C1D1 may be used as screening scans to demonstrate eligibility, as long as they meet minimum standards as separately defined by the central imaging vendor

- Histology or cytology review locally to confirm HR+/HER2- MBC according to ASCO/CAP criteria

- Tumor sample from either an FFPE archival block (preferably within 12 months prior to consent) or a newly acquired biopsy are to be sent to the Sponsor's designee for assessment of Trop-2 expression. A newly-acquired biopsy cannot be taken from any target lesion being used for tumor assessments. Alternatively, a minimum of 6 freshly sectioned unstained slides of archived biopsy/surgical specimens (outlined above) may be submitted. Tumor blocks may be returned to the clinical site after being processed, if requested.

7.4.2. CT or MRI Tumor Assessments

Tumor assessments during the study should use the same methodology (CT or MRI) and scan acquisition techniques (including use or non-use of IV contrast) as used for the screening assessments. Tumor assessments will be performed by LIR and BICR review of CT/MRI scans using RECIST 1.1 (Appendix 6). Tumor assessments during the study include:

- CT or MRI tumor assessments of the chest, abdomen, pelvis and other areas where scans were performed at screening or of sites with newly suspected disease should be performed every 6 weeks ±1 week after the start of study treatment (or sooner if there is evidence of PD) through 54 weeks then every 12 weeks ±1 week until the occurrence of progression of disease as determined by LIR using RECIST 1.1. Assessment intervals should not be changed in case of delays in dose administration.

- Bone scans (99m-technetium polyphosphonate scintigraphy, whole body bone MRI, or 18F-NaF/FDG PET) will be performed during the Treatment Period if clinically indicated and within a target of 1 week, but no more than 2 weeks after a subject achieves a CR to exclude new bone metastases. The same bone scan methodology and acquisition techniques used at screening should be used throughout the study to ensure comparability. Lesions detected on bone scans must be followed with cross-sectional imaging.

- Brain CT/MRI in subjects with known brain metastases. During the Treatment Period, CT/MRI of the brain will be performed if clinically indicated and within a target of 1 week after a subject achieves a CR. For subjects with history of treated brain metastases, brain scans will be performed at tumor assessment time points if clinically indicated. The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability.

Investigator-determined response assessments will be performed at each assessment time point and entered onto the eCRF. Copies of all tumor assessment scans, as well as any unscheduled scans, will be sent to the central imaging vendor designated by the Sponsor. Tumor assessments will be carried out following the guidelines provided by the central imaging vendor.

In most cases, disease progression will be based on LIR using RECIST 1.1 criteria. If disease progression is based on the subject's symptoms, every effort should be made to document progression using objective criteria.

7.5. Quality of Life

HRQOL will be assessed prior to study drug administration and before other assessments and procedures (see Appendix 4) using the following subject questionnaires:

- EORTC QLQ-C30, 30-item instrument assesses 15 scales:

  — Global health status/Quality of Life scale;

- Five functional scales: physical, role, cognitive, emotional, and social; and
- Nine symptom/item scales: fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties.

- EQ-5D-5L, health status instrument comprised of 2 parts:
  - The descriptive system with which patients rate the severity of their experience in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) along 5 levels of severity. A utility value for each health state is assigned on the basis of a set of preference weights (tariffs) elicited from the general population and is specific for each country; and
  - The EQ-5D visual analogue scale (EQ-VAS) for patients to self-rate their health state.

- PRO-CTCAE™, subjects will be asked about 9 selected symptoms, based on the previously reported AE profile for TPC and sacituzumab govitecan, including decreased appetite, nausea, vomiting, constipation, diarrhea, abdominal pain, shortness of breath, hair loss, and fatigue. Responses are scored from 0 to 4 with no standardized scoring rules

See Appendix 5 for each of the questionnaires.

7.6. Assessment of Safety

7.6.1. Physical Examinations

A full physical examination and total body examination of all major body systems (e.g., general appearance, skin, neck [including thyroid], ears, eyes, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities and a clinical neurological examination), and weight must be performed. Post-screening physical examinations may be targeted based on findings present at screening or subject complaints (see Appendix 4).

Clinically-significant physical examination findings at screening should be recorded either as medical history or as an AE as appropriate. Clinically-significant new findings at post-screening visits should be recorded as AEs.

7.6.2. Vital Signs

Vital signs, including heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature, will be measured throughout the study (see Appendix 4).

7.6.3. ECGs

Standard 12-lead ECGs will be recorded throughout the study (see Appendix 4) and at additional time points if clinically indicated.

7.6.4. Laboratory Assessments

Blood and urine will be collected for analysis of the laboratory parameters specified in Table 6 according to the Schedule of Assessments (see Appendix 4).

Table 6. Laboratory Assessments

Hematology	Complete blood count including platelet count, with white blood cell differential in absolute cell counts
Chemistry	Glucose, creatinine, BUN[1], total bilirubin, ALT, AST, lactate dehydrogenase, ALP, creatinine clearance[2], serum albumin, total protein, sodium, potassium, calcium, chloride, magnesium phosphorus, and blood uracil level[3]
Urinalysis	Glucose, ketones, pH, protein, white blood cells, hemoglobin (or red blood cells), and specific gravity. Microscopic examination if there are positive findings for blood, protein, leukocytes, or nitrite on the dipstick analysis[4]
Others	Serum β–HCG tests (women of childbearing potential only), hepatitis B surface antigen test, hepatitis C (either antibody test or viral testing)

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen.
1 Sites that do not perform BUN testing can calculate BUN from urea using the following standard formula: BUN (mg/dL) = Urea (mg/dL)/2.1428.
2 May be calculated using Cockcroft-Gault equation.
3 Drawn at Screening if required by local guidelines on all subjects eligible to be randomized to the TPC capecitabine arm in order to exclude subjects from receiving TPC capecitabine if blood uracil level is ≥ 150 ng/mL.
4 If urinalysis suggests a urinary tract infection or if clinically indicated, culture and sensitivity should be performed at the institution's laboratory.

7.6.5. ECOG Performance Status

ECOG performance status (Appendix 2) will be assessed per the Schedule of Assessments (see Appendix 4).

7.6.6. Adverse Events and Serious Adverse Events Reporting

All subjects must be carefully monitored for AEs, including SAEs (defined in Section 7.6.6.1 and Section 7.6.6.2). Sufficient information must be obtained by the Investigator to determine whether the event meets criteria for immediate reporting to the Sponsor (i.e., SAEs and pregnancies). All AEs should be assessed in terms of their seriousness (Section 7.6.6.2), severity (Section 7.6.6.7), and relationship to the study drug (Section 7.6.6.8).

7.6.6.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject administered a medicinal product that does not necessarily have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational medicinal product.

AEs may include worsening or exacerbation of preexisting conditions or events; intercurrent illnesses; or drug interactions.

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. Anticipated fluctuations of preexisting conditions that do not represent a clinically significant exacerbation or worsening are not considered AEs.

- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).

- Overdose without clinical sequelae.

- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form 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.

In this protocol, disease progression is an efficacy end point and should not be reported as an AE. It is important to differentiate expected disease progression from an AE. Events that are clearly consistent with the expected pattern of disease progression should not be considered AEs. Expected disease progression refers to an event that is unequivocally related to disease progression and has a clinical course consistent with what would be expected for the subject's disease. A clinical event in the setting of disease progression would be considered an AE if it could not be unequivocally attributed to or is inconsistent with expected disease progression.

AEs should be recorded using medical terminology and, whenever possible, a diagnosis should be provided for clearly associated signs, symptoms, and/or abnormal laboratory results. If the final diagnosis is not known at the time of initial detection, the provisional diagnosis or signs or symptoms should be recorded and updated when the final diagnosis is available.

7.6.6.2. Definition of a Serious Adverse Event

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 subject 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.)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect (in the child of a subject who was exposed to the study treatment)
- A medically important event or reaction: Such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject 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.

7.6.6.3. Protocol-Specific Serious Adverse Event Reporting Exemptions

An SAE does not include:

- Progression of disease
- Hospitalization for a routine clinical procedure as stipulated by the protocol
- Pre-planned treatments or surgical procedures requiring hospitalization (the conditions should be documented as appropriate in the eCRF)
- Hospitalization due to signs and symptoms of disease progression
- Hospitalization for nonmedical reasons (i.e., social admissions, hospitalizations for social, convenience, or respite care)

Death is an outcome of an SAE and not, in itself, an SAE. When death is an outcome, the event(s) resulting in death should be reported (e.g., "pulmonary embolism" with a fatal outcome). The appropriate diagnosis (i.e., cause of death) should be recorded and assigned severity Grade 5. Fatal AEs meeting these criteria are SAEs and should be reported to the Sponsor or the Sponsor's designee in accordance with the timelines specified in Section 7.6.6.4.

Deaths related to progression of underlying disease during the study will not be reported as an SAE if, in the Investigator's judgment, the event is unequivocally due to the expected course of progression of the underlying disease and not due to another cause.

7.6.6.4. Follow-up of Adverse Events

All subjects will be followed for AEs until 30 days post-treatment or until resolution or stabilization of all treatment-related AEs to either ≤Grade 2 or baseline, whichever is longer, or until the subject is lost to follow-up.

Any SAE that occurs >30 days from the last dose of study treatment and is assessed as possibly related to study drug must be reported and should be followed to resolution or, if resolution is unlikely, to stabilization.

7.6.6.5. Recording of Adverse Events

All AEs from the time the subject signs the informed consent and until 30 days after the last dose of study drug must be recorded. During the period after informed consent has been obtained and before the first dose of study drug has been administered, only SAEs caused by a protocol-mandated intervention (e.g., biopsy) should be reported. Any SAE that occurs 30 days after the last dose of study drug and is assessed as possibly related to study drug must be reported.

It is the responsibility of the Investigator to document all AEs that occur during the study. All AEs regardless of seriousness, severity, or relationship to the study drug, that occur during the safety reporting period, must be recorded in the AE page of the eCRF. AEs should be elicited by asking the subject a non-leading question (e.g., "have you experienced any new or changed symptoms since we last asked/since your last visit?"). AEs can also represent abnormal findings from physical examinations; laboratory tests; and other study procedures (i.e., ECGs). The Investigator must review all laboratory and test data; abnormal findings should be assessed to determine if they meet the criteria for AEs (Section 7.6.6.1 and Section 7.6.6.2).

For all AEs, the investigator must pursue and obtain information adequate to assess whether it meets the criteria for classification as an SAE (Section 7.6.6.2) and, therefore, requires immediate notification to the Sponsor or its designated representative.

To assist in the Sponsor's assessment of each case, further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical trial.

7.6.6.6. Reporting Requirements

All SAEs and pregnancies must be reported to the Sponsor or the Sponsor's designee **immediately**, and **no later than 24 hours** of becoming aware of the event. All SAEs and pregnancies should be reported to the Sponsor as per the reporting instructions provided on the Completion Guidelines and as stated on the SAE Form, Pregnancy Report Form, and Pregnancy Outcome Report Form.

The initial SAE report should be as complete as possible; however, reporting should not be delayed in order to obtain more information. All follow-up information should be reported within 24 hours of the Investigator's awareness of the information. The Investigator is required to provide follow-up information in response to queries from the Sponsor or Sponsor's designee. Hospital discharge summaries should be provided for subjects who are hospitalized and autopsy findings, if available, should be provided for subjects who die; however, reporting should not be delayed in order to obtain more information. All follow-up information should be reported within 24 hours of the Investigator's awareness of the information. The Investigator is required to provide follow-up information in response to queries from the Sponsor or Sponsor's designee.

Pregnancy occurring in a female subject during dosing or within 1 month after the end of treatment should be reported to the Sponsor or Sponsor's designee on the Pregnancy Form within 24 hours of the Investigator becoming aware of the event. Pregnancy occurring in female partners of male subjects while the male partner is receiving study drug and within 1 month after the final dose should be reported to the Sponsor or Sponsor's designee within 24 hours of becoming aware of the event.

The Investigator should counsel the subject, and in the case of a male subject, the subject's partner, regarding the risks of continuing with the pregnancy and the possible effects on the fetus.

If the female partner of a male subject becomes pregnant, the investigator should obtain informed consent of the pregnant partner prior to monitoring the pregnancy, so that information regarding the pregnancy outcome can be reported to the Sponsor or Sponsor's designee.

Information regarding the pregnancy should include estimated date of conception, duration of study drug exposure (or number of days/months after treatment discontinuation) as of the estimated conception date, expected delivery date, date of last menstrual period, all concomitant medications (including recreational drug use such as alcohol, tobacco, and illicit drugs), and other maternal medical conditions.

The Investigator should make every effort to follow the subject (or female partner of a male subject) through the resolution of the pregnancy (i.e., delivery or pregnancy termination). If the pregnancy results in abortion (spontaneous or induced), premature birth, or if the infant is born with a congenital anomaly, these events are considered SAEs and should be reported. The outcome of all pregnancies must be reported to the Sponsor or Sponsor's designee, even for normal births. The condition of the infant at birth should be reported, including any anomalies, and the infant should be followed until 3 months of age and any illnesses should be reported.

All information regarding the pregnancy in a female subject or female partner of a male subject and the infant should be reported on the Pregnancy Form.

The Investigator must notify his/her local Institutional Review Board (IRB)/Independent Ethics Committee (IEC) about certain AEs, including suspected unexpected serious adverse reactions (SUSARs) in accordance with the IRB/EC's policies and procedures and GCP/International Council for Harmonisation (ICH) guidelines.

7.6.6.7. Assessment of Adverse Event Severity

The severity of AEs will be graded using NCI-CTCAE Version 5.0. For each SAE, the highest severity grade should be reported. If a CTCAE criterion does not exist, the Investigator should assess the severity according to the criteria in Table 7.

Table 7. Grading for Adverse Events Not Listed in NCI-CTCAE

CTCAE Grade	Severity	Definition
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily life[1]
Grade 3	Severe	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care activities of daily life[2,3]
Grade 4	Life-threatening	Life-threatening consequences; urgent intervention indicated[3]
Grade 5	Death	Results in death

1 Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
2 Self- care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
3 These events should be assessed to determine if they meet the definition of SAEs.

7.6.6.8. Assessment of Adverse Event Causality

The Investigator's causality assessment is required for all AEs, including both non-serious and serious AEs. The causality assessment is the determination of whether there exists a reasonable possibility that the study treatment caused or contributed to an AE. In order to determine causality, the Investigator should consider the temporal relationship of event onset to the start of study drug; the course of the event and, in particular, whether the event resolves or improves with dose reduction or study drug discontinuation; the known toxicities of the study drug; events expected to occur in subjects with the disease under study; and concomitant medications and comorbidities which may have a known association with the event. Causality is to be assessed as follows:

- Related: Plausible time relationship to study treatment administration; plausible time relationship of improvement or resolution with study drug dose reduction or discontinuation; event cannot be explained by the underlying disease, comorbidities, or concomitant medications

- Possibly related: a reasonable time sequence to administration of study drug, but which could also be explained the underlying disease, comorbidities, or concomitant medications

- Unlikely related: a temporal relationship to drug administration which makes a causal relationship improbable and the underlying disease, comorbidities, or concomitant medications provide a plausible explanation

- Not related: a causal relationship to the study drug can be easily ruled out

7.6.6.9. Adverse Events Based on Abnormal Test Findings

An abnormal laboratory test finding that meets any 1 of the following criteria should be considered an AE:

- Test result is associated with accompanying symptoms

- Test result requires additional diagnostic testing or medical/surgical intervention

- Test result leads to a change in study treatment dosing (e.g., dose modification, interruption, or permanent discontinuation) or concomitant drug treatment (e.g., addition, interruption, or discontinuation) or any other change in a concomitant medication or therapy

- Test result leads to any of the outcomes included in the definition of an SAE (see Section 7.6.6.2; Note: this would be reported as an SAE)

- Test result is considered an AE by the Investigator

Laboratory results that fall outside the reference range and do not meet 1 of the criteria above should not be reported as AEs. Repeating an abnormal test, in the absence of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Any abnormal test finding that meets the criteria for an SAE (Section 7.6.6.2) should be reported as such.

7.6.6.10. Study Drug Action Taken

The Investigator will determine the study drug action taken with regard to the AE. The action taken should be classified according to the categories shown in Table 8.

Table 8. Classification for Study Drug Action Taken with Regard to an Adverse Event

Classification	Definition
Dose Not Changed	Study drug dose or frequency not changed in response to an AE
Dose Reduced	Study drug dose reduced in response to an AE
Drug Interrupted	Study drug administration interrupted in response to an AE
Drug Withdrawn	Study drug administration permanently discontinued in response to an AE
Not Applicable	Action taken regarding study drug administration does not apply. "Not applicable" should be used in circumstances such as when the investigational treatment had ended before the AE began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible.

AE = adverse event

7.6.6.11. Adverse Event Outcome and Treatment Given

An AE should be followed until the Investigator has determined and provided the final outcome. The outcome should be classified according to the categories shown in Table 9.

Table 9. Classifications for Outcome of an Adverse Event

Classification	Definition
Recovered/Resolved	Resolution of an AE with no residual signs or symptoms
Recovered/Resolved with Sequelae	Resolution of an AE with residual signs or symptoms
Recovering/Resolving (Ongoing)	Improvement of an AE but not yet resolved
Not Recovered/Not Resolved (Ongoing)	No improvement of an AE, such that it remains ongoing
Fatal	Outcome of an AE is death. "Fatal" should be used when death is at least possibly related to the AE
Unknown	Outcome of an AE is not known (e.g., a subject lost to follow-up)

AE = adverse event

The Investigator will ensure adequate medical care is provided to subjects for AEs. In addition, the Investigator will describe whether any treatment was given for the AE. "Yes" is used if any treatment was given in response to an AE and may include treatments such as other medications, hospitalization, radiation therapy, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an AE.

7.6.6.12. Investigator Notification to Local Institutional Review Boards

The Investigator must notify his/her local IRB/IEC about certain AEs, including SUSARs in accordance with the IRB/IEC's policies and procedures and GCP/ICH guidelines.

7.6.6.13. Sponsor Responsibilities

The Sponsor or designee will be responsible for reporting all AEs, SAEs, and SUSARs to the appropriate regulatory authorities, Investigators, and Central IRBs in accordance with all applicable regulations and guidance documents.

Events otherwise meeting the definition of SUSARs but related to TPC do not require reporting to regulatory authorities, Investigators, and Central IRBs, but will be reported by the Sponsor to the respective product manufacturers.

7.7. Immunogenicity

Serum samples for ADA testing will be collected from all subjects in the sacituzumab govitecan arm according to the Schedule of Assessments (see Appendix 4). ADA will be evaluated by the Sponsor's designee using a validated 3-tier (screen, confirm, titer) assay. Instructions for shipping these serum samples are provided in Appendix 3.

7.8. Pharmacokinetic Evaluations

Serum samples will be collected from all subjects in the sacituzumab govitecan arm for measurement of individual and mean concentration-time concentrations of total SN-38, free SN-38, total antibody (hRS7 IgG) and SN-38G. Samples are to be shipped to the Sponsor's designee who will perform these assays. Instructions for shipping these samples are provided in Appendix 3.

7.9. UGT1A1 Genotype

UGT1A1 genotype will be evaluated by the Sponsor's designee for all subjects in the sacituzumab govitecan arm from a blood sample collected at Baseline.

7.10. Blood Biomarker Evaluations

Blood samples for biomarker analysis will be collected according to the Schedule of Assessments (see Appendix 4) and will be retained for future analysis. Details of blood collection are provided in the Laboratory Manual. This research will be focused on identifying future marker(s) that can better predict response as well as to identify mechanisms of resistance that can provide a more accurate prognosis in subjects treated with sacituzumab govitecan.

Participation in the future use of specimens is optional and is not required in order to be eligible for the study. Subjects can withdraw consent for future use at any time by contacting their site.

Samples may be stored for testing for up to 15 years after the completion of the study or until the sample is gone. When the 15-year period ends, the samples will be destroyed. Samples will be retained for longer than 15 years if a Health Authority (or medicinal product approval agency) has active questions about the study, in which case, samples will be stored until the Health Authority's (or medicinal product approval agency's) questions have been addressed.

Specimens will be de-identified and coded only with a study identification number unique to the subject and will be stored in a limited access, secure facility. Only the Investigator will retain and have access to the code list that matches the study code to the subjects' identifying information.

Access to samples and/or results from the research will be limited to the Sponsor, their research partners, or laboratories contracted to perform work for the Sponsor.

8. SCHEDULE AND SEQUENCE OF PROCEDURES

Study-specific assessments are outlined in the Schedule of Assessments in Appendix 4. Unless otherwise specified, collection windows for study time points are within ±2 days for the treatment schedule and ±7 days for response assessments. Collection windows for PK samples are ±15 minutes on infusion days.

8.1. Pre-Randomization Phase

The Pre-randomization Phase will last no longer than 28 days and consists of the following two periods: Screening Period (Day -28 to Day -3) and Baseline Period (Day -3 to Day 1 prior to dosing). See Appendix 4 for the schedule of Screening and Baseline assessments.

8.2. Randomization Phase

The Randomization Phase will begin at the time of randomization of the first subject and will end on the data cut-off date for the final analysis of OS. The Randomization Phase consists of the following two periods: a Treatment Period and a Follow-up Period (see Section 8.2.1 and Section 8.2.2, respectively).

8.2.1. Treatment Period

The Treatment Period begins at the time of randomization and ends with the completion of the EOT visit, which will occur at least 30 days after the last dose of sacituzumab govitecan or TPC and before the start of other treatments or in the event of premature study termination.

Subjects will continue to receive study treatment until RECIST 1.1 disease progression by LIR, development of unacceptable toxicity, subject request, withdrawal of consent, Investigator decision, pregnancy, or study termination by the Sponsor.

All subjects will be permitted to continue treatment in the Treatment Period beyond initial RECIST 1.1 defined progression as long as the Investigator believes that the subject is still receiving clinical benefit and is clinically stable and tolerating study drug treatment. The assessment of clinical benefit should consider the potential efficacy benefit versus the safety risk of continuation of treatment. These subjects must continue tumor assessments at the same interval in the Treatment Period until further progression and/or loss of clinical benefit, as judged by the Investigator. At that time subjects discontinue study treatment, they will have their EOT visit and move to the Follow-Up Period.

Clinical stability is defined by the following criteria:

1) Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values, and

2) No decline in ECOG performance status, and

3) Absence of rapid progression of disease, and

4) Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent medical and/or surgical intervention

See Appendix 4 for the schedule of assessments during the Treatment Period.

8.2.2. Follow-up Period

The Follow-up Period begins the day after the EOT visit and continues as long as the subject is alive or until the data cut-off date of the final analysis of OS, unless the subject withdraws consent from the study or the Sponsor terminates the study. If a subject discontinues study treatment and does not consent to continued follow-up, the Investigator must not access confidential records that require the subject's consent. However, an Investigator may consult public records to establish survival status.

Subjects who enter the Follow-Up Period due to disease progression may be treated by the Investigator according to the local standard of care. Subjects will be followed every 12 weeks ±1 week for survival status and subsequent anticancer treatment received.

Subjects who enter the Follow-up Period prior to disease progression will continue to undergo tumor assessments every 12 weeks ±1 week until disease progression is documented or another anticancer therapy is initiated. At that time, these subjects will then be contacted for survival status and subsequent anticancer treatment received, unless the subject withdraws consent for the study.

See Appendix 4 for the schedule of assessments during the Follow-up Period.

8.3. End of Study

End of study is defined as the point in time when the number of death events required for the final OS analyses have been reached or if the Sponsor terminates the study, whichever comes first. At the end of study, in the event that the Investigator believes a subject is continuing to receive clinical benefit, the Sponsor will discuss options with the Investigator in order to ensure the potential for continuing supply of sacituzumab govitecan.

Subjects who are deriving benefit from sacituzumab govitecan after evaluating the primary and secondary efficacy outcome measures and safety data gathered in the study may continue to receive treatment in a rollover study, if such a study is available to the subject.

9. STATISTICAL CONSIDERATIONS

9.1. Determination of Sample Size

The sample size is estimated based on the primary end point of PFS, but also taking into consideration OS as the main secondary end point. An overall sample size of approximately 520 subjects were randomized in a 1:1 ratio to either sacituzumab govitecan (Investigational Arm A) or TPC (Control Arm B).

For PFS, assuming a hazard ratio of 0.70 (medians of 5.3 months in Arm A and 3.7 months in Arm B), a total of 350 PFS events will be used to detect a statistically significant difference at a 2-sided alpha of 0.05 with 92% power. With an estimated average accrual rate of 22 subjects per month, a total of 520 subjects will provide 350 PFS events approximately 27 months after the first subject is randomized, after accounting for events being censored because of subjects missing tumor assessments or starting subsequent anti-cancer therapies (see primary end point PFS definition in Section 9.5.1). The recruitment rate is assumed to be non-uniform so that half of the subjects are recruited 55% of the way through the recruitment period of approximately 24 months, reflecting the change in sample size and actual recruitment rate that was affected by the global COVID-19 pandemic.

At PFS final analysis, OS will be summarized descriptively only. To be conservative, the nominal 2-sided alpha of 0.00001 will be spent even without formal hypothesis testing. For OS, assuming a hazard ratio of 0.73 (median of 16.5 months in Arm A and 12 months in Arm B), a total of 438 OS events are needed to detect a statistically significant difference with 86.7% power at a 2-sided alpha of 0.04999 based on a recruitment period of approximately 24 months and 52 months of survival follow-up from the first subject randomized.

The Sponsor will closely monitor the number of subjects randomized and discontinued, including subjects who refuse study treatment assigned. As the primary analysis is triggered by a targeted number of PFS events, subjects who prematurely discontinue from the study or whose events are censored do not count toward the targeted number. To compensate for such cases, an additional number of subjects is necessary to be enrolled to ensure the targeted number of events is reached within a reasonable timeframe. If required, the additional number of subjects will be determined by the Sponsor on the basis of the number and pattern of accumulated and censored events at the appropriate times as the study progresses.

9.2. Interim Analysis

An independent DSMC will be formed for the study. The function and membership of the DSMC will be described in a DSMC charter. Safety monitoring will be conducted by the DSMC according to the schedule defined in the DSMC charter.

A descriptive, non-comparative analysis of OS will be performed when the final primary analysis of PFS is performed. The purpose of this analysis is to examine the OS effect of sacituzumab govitecan, at the time when the primary end point PFS of this study is determined. It is estimated that 205 OS events will occur at this time of analysis; an administrative alpha of 0.00001 will be spent on this non-comparative analysis of OS.

The study is planned to have 2 superiority interim efficacy analyses of the main secondary end point, OS, performed when approximately a total of 272 (62% information fraction) and 350 (80% information fraction) death events have occurred, respectively. The method used to account for the multiplicity introduced by efficacy interim analyses is described in Section 9.3.

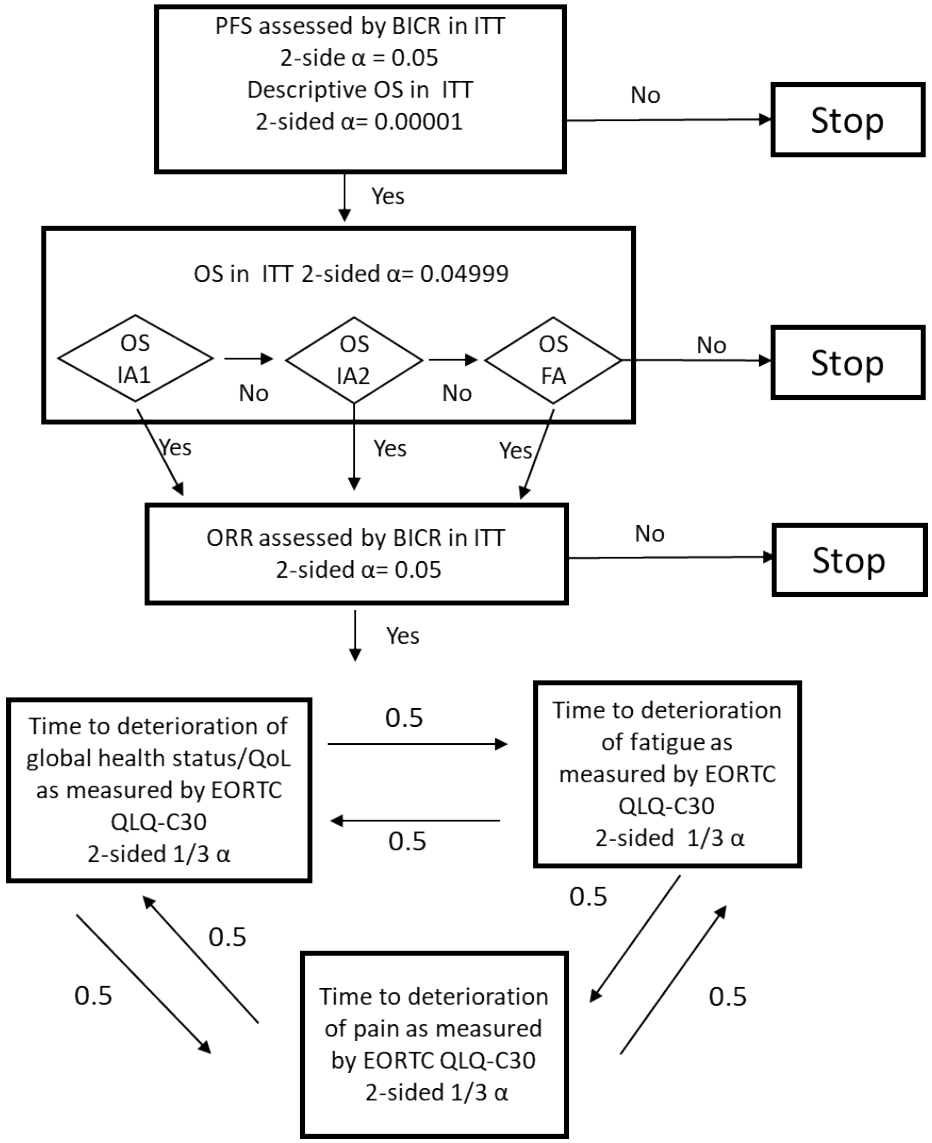
There is no planned interim analysis of PFS in this study.

9.3. Multiplicity

The overall type I error rate for this study is strictly controlled at a 2-sided alpha of 0.05. The primary end point analysis of PFS assessed by BICR will serve as the gatekeeper for the secondary end point analyses and be tested at the 2-sided alpha of 0.05. At PFS final analysis, OS will be summarized descriptively only. To be conservative, the nominal 2-sided alpha of 0.00001 will be spent even without formal hypothesis testing. If the primary PFS analysis is positive, analysis of the main secondary end point of OS will be formally tested sequentially at the 2-sided alpha of 0.04999, ORR (assessed by BICR) and analysis for QOL will be formally tested sequentially at the 2-sided alpha of 0.05, respectively, when the above hypotheses in the hierarchy are also statistically significant. For analysis of QOL, TTD of global health status/QOL, pain, and fatigue domains as measured by EORTC QLQ-C30 will be tested using graphical approach of Maurer and Bretz to control multiplicity {Maurer 2013}. According to this approach, the hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests. The arrows in Figure 4 show how the type I error allocated to a null hypothesis that is successfully rejected will be redistributed for the testing of the other hypotheses. Please note that the arrows do not necessarily indicate the testing order. A Bonferroni approach is used to control the type I error rate at 0.05 (2-sided) alpha for the 3 TTD hypothesis tests.

The Lan-DeMets alpha spending function that approximates a Pocock approach will be used to account for multiplicity introduced by including OS interim analyses for superiority. The first OS efficacy interim analysis will be tested at the 2-sided significance level of 0.0363 if 62% of the death events (272/438) is available at the time of the analysis. If the first OS interim analysis is not positive, the second OS efficacy interim analysis will be tested at the 2-sided significance level of 0.0206 if 80% of death events (350/438) is available at the time of the analysis. If neither of the interim analyses are positive, final analysis will be tested at the 2-sided significance level of 0.0195. Note that alpha levels for the OS interim and final analyses are based on the actual observed events and will be adjusted accordingly.

Figure 4. Hierarchical Testing Procedures



BICR = blinded independent central review; EORTC QLQ-C30 = European Organization for Treatment of Cancer Quality of Life questionnaire version 3.0; FA = final analysis; IA = interim analysis; ITT = Intent-to-Treat; OS = overall survival; PFS = progression-free survival

9.4. Analysis Sets

The following analysis sets will be used as defined and used for analysis:

- **Screened Set** is the group of all subjects who have signed an informed consent and participated in screening procedures at the investigative site to assess eligibility. This analysis population is used for selected tables and listings pertaining to subjects' disposition and eligibility criteria.

- **Full Analysis Set (Intent-to-Treat Analysis [ITT] Population)** is the group of all randomized subjects. This is the primary analysis population for all efficacy analyses which will be based on the ITT principle, with subjects analyzed according to the randomized treatment assignment.

- **Safety Analysis Set** is the group of subjects who received at least 1 dose of study drug. This is the analysis population for all safety analyses which will be based on the actual treatment received.

- **HRQoL-Evaluable Set** is the all ITT population who had an evaluable assessment of the HRQoL at baseline and at least one evaluable assessment at post-baseline visits. An evaluable assessment at a given visit will be defined as at least one of the 15 domains/scales were non-missing at that scheduled assessment visit.

- **PK Set** is defined as Safety population subjects who have completed at least one cycle of sacituzumab govitecan treatment and have at least one non-missing PK concentration of total SN-38, free SN-38, total antibody (hRS7 IgG) and/or SN-38G

9.5. Efficacy Analyses

Primary analysis of PFS will be based on BICR assessments. PFS, ORR, CBR and DOR analyses will be produced for both BICR and LIR.

9.5.1. Primary Efficacy Analyses

PFS is defined as the time from the date of randomization to the date of the first documentation of disease progression or death (whichever occurs first) according to BICR using RECIST 1.1. Any subject who progresses or dies after more than one missed scheduled visit will be censored at the last date of radiographic assessment prior to the missed visit. Any subject who receives alternative anticancer treatment before documented PD will be censored at the last date of radiographic assessment prior to receiving alternative anticancer treatment. Otherwise, subjects who do not have progression and are alive will be censored at the last date of radiographic assessment without documented PD. Subjects who did not have any on study tumor assessments and did not die will be censored on their date of randomization.

The primary analysis of PFS will be carried out after approximately 350 subjects experience disease progression or death events according to the primary definition of PFS as assessed by BICR.

PFS will be described using Kaplan-Meier (K-M) estimates. The primary analysis of PFS for the comparison between treatment arms will be performed using a stratified log rank test with the stratification factors used in the randomization. Median PFS and its 95% CI as determined by the Brookmeyer and Crowley method with log-log transformation will be presented and the K-M estimates of PFS will be plotted over time. Hazard ratio of PFS and its 95% CI will be estimated using Cox proportional-hazards model stratified by the same stratification factors used in the randomization.

9.5.2. Secondary Efficacy Analyses

Secondary efficacy analyses include the following:

- **OS** is defined as the time from the date of randomization to the date of death from any cause. Subjects who are lost to follow-up and those who are alive at the date of data cut-off will be censored at the date the subject was last known alive or date of data cut-off, whichever occurs first.

- **ORR** is defined as the proportion of subjects who have a best overall response of either CR or PR that is confirmed ≥ 4 weeks later according to BICR using RECIST 1.1.

- **TTD** of global health status/QOL, pain, and fatigue domains of the EORTC QLQ-C30 is defined as the time between randomization and the time a subject experienced a deterioration (i.e., ≥ 10 points worsening from baseline in a given domain).

- **DOR** is defined as the time from the date a response was first documented until the date of the first documentation of disease progression or date of death (whichever occurs first). Subjects who neither progress nor die will be censored on the date of their last tumor assessment. DOR will be evaluated for responders (CR or PR) only.

- **CBR** is the proportion of subjects who have best overall response of CR or PR or durable SD (duration of SD ≥ 6 months after randomization).

At the time of primary analysis of PFS is performed, OS will be summarized descriptively. No other formal treatment comparison for OS will be performed at this time.

The analysis of OS will be described using K-M estimates. The primary analysis of OS for comparison between treatment arms will be performed using a stratified log rank test with the same stratification factors used in the randomization. Median OS and the associated 95% CI as determined by the Brookmeyer and Crowley method with log-log transformation will be presented. Hazard ratio and the associated 95% CI will be estimated using a Cox proportional-hazards model stratified by the same stratification factors used in the randomization.

ORR will be analyzed and compared between the treatment arms using the Cochran Mantel-Haenszel (CMH) test stratified by the stratification factors used in the randomization. The 2-sided 95% CIs will be calculated using the Clopper-Pearson exact method.

CBR will be calculated with exact 95% CIs using the method of Clopper and Pearson. CBR will be compared between treatment arms using a CMH test stratified by the stratification factors used in the randomization. The differences and odds ratios of these rates between treatment arms and 95% CIs will be calculated respectively.

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

Time to deterioration of global health status/QOL, pain, and fatigue domains as measured by EORTC QLQ-C30 will be analyzed similarly as the primary analysis of PFS.

A separate prespecified HRQOL analysis following Food and Drug Administration (FDA) and European Medicines Agency PRO Guidelines will be performed.

9.5.3. Sensitivity Analyses

The following sensitivity analyses will be conducted for the primary end point of PFS in order to evaluate the robustness of the results:

- Sensitivity Analysis 1 of PFS will use the same censoring rule of the primary PFS definition except that any subject who progresses or dies after more than one missed scheduled tumor assessment will not be censored at the last date of radiographic tumor assessment prior to the missed assessment.

- Sensitivity Analysis 2 of PFS will use the same censoring rule of the primary PFS definition except that it considers discontinuation of treatment or initiation of alternative anticancer treatment, whichever occurs later, to be a PD event for subjects without documented progression or death.

- Sensitivity Analysis 3 of PFS will use the same primary PFS definition, but for all treated subjects who received at least one dose of study drug.

All three sensitivity analyses will be conducted on both BICR and LIR assessments.

9.5.4. Subgroup Analyses

To evaluate whether the treatment effect is consistent across various subgroup populations, the estimate of the between-group treatment effect with a 95% CI for the primary and secondary end points will be estimated and plotted graphically for the following subgroups, including but not limited to:

1) Stratification factor of number of prior chemotherapy regimens for treatment of metastatic disease (two vs. three/four lines)

2) Stratification factor of visceral metastasis (Y/N)

3) Stratification factor of endocrine therapy in the metastatic setting for ≥ 6 months (Y/N)

4) Age group (< 65 years old or ≥ 65 years old)

5) Race (white, non-white)

6) Baseline ECOG status (0 vs 1)

7) Geographic region (North America, Europe, and elsewhere)

8) Prior CDK treatment duration (≤ 12 months or > 12 months)

9) Investigators' choice of chemotherapy (eribulin, capecitabine, gemcitabine, vinorelbine)

10) Early progressors (Y/N) (defined as progressing to metastatic disease within 1 year of neo/adjuvant therapy)

11) Baseline documented Target or Non-Target liver lesions per RECIST 1.1 (Y/N)

12) Chemotherapy in neo/adjuvant setting (Y/N)

CCI [redacted]

CCI [redacted]

9.6. Safety Analyses

Safety analyses will be based on the Safety Analysis Set. All safety analyses will be summarized by treatment arm. Treatment-emergent AEs and SAEs, laboratory test results, vital signs, and ECG results will be summarized. Safety data will be summarized using descriptive statistics. Categorical variables will be summarized by number and percentage. Continuous variables will be summarized using number of subjects, mean, standard deviation, median, upper and lower quartiles, and range (minimum and maximum), unless otherwise specified.

10. TREATMENT COMPLIANCE

Sacituzumab govitecan will be administered at scheduled study centers under the supervision of the Investigator or sub-Investigator(s). The pharmacist will maintain records of study drug receipt, preparation, and dispensing, including the applicable lot numbers, subject's height, weight and total drug administered in milligrams. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents and on appropriate CRF.

11. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor has ethical, legal and scientific obligations to follow this study carefully in a detailed and orderly manner in accordance with established research principles and applicable regulations. Monitoring visits to the study site will be conducted periodically during the study to ensure that GCP and all aspects of the protocol are followed. The trial site may also be subject to review by the IRB/IEC, to quality assurance audits performed by the Sponsor's designee and/or to inspection by appropriate regulatory authorities. Investigator(s) and their relevant personnel must agree to be available and participate with visits conducted at a reasonable time in a reasonable manner, and the Investigator/Institution must guarantee direct access to source documents by the Sponsor and its designee, and appropriate regulatory authorities.

Regulatory authorities worldwide may also audit the Investigator during or after the study. The Investigator should contact the Sponsor's designated contact immediately if this occurs and must fully cooperate with regulatory authority audits conducted at a reasonable time in a reasonable manner.

12. DATA HANDLING AND RECORD KEEPING

12.1. Electronic Case Report Forms

An eCRF is required and must be completed for each enrolled subject. The completed original eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate regulatory authorities, without written permission from the Sponsor.

It is the Investigator's responsibility to ensure completion and to review and approve all eCRFs. eCRFs must be signed by the Investigator or by an authorized staff member. These signatures serve to attest that the information contained on the eCRFs is true. At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the eCRFs. Subject source documents are the physician's subject records maintained at the study site. In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital or the physician's chart, the information collected on the eCRFs must match those charts.

12.2. Record Retention

Records and documents pertaining to the conduct of this study, including eCRFs, source documents, consent forms, laboratory test results, and medication inventory records must be retained by the Investigator for at least 15 years. No study records shall be destroyed without prior authorization from the Sponsor. For studies conducted outside the US under a US Investigational New Drug (IND), the Investigator must also comply with US FDA IND regulations, ICH guidelines, and with the regulations of the relevant national and local health authorities.

12.3. Good Clinical Practice

The study will be conducted in accordance with the ICH for GCP and the appropriate local and national regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study medications as described in the protocol and Investigator’s Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files for this study should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

12.4. Ethical Considerations

This study is planned to be conducted in North America, Europe, and potentially elsewhere. European regulatory agencies require that the study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The trial will be performed in accordance with ICH GCP guidelines, the Declaration of Helsinki, 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions (as mandated for European trials), and applicable local regulatory requirements and laws. In the US, ethical protection is provided by compliance with GCPs as described in ICH and 21 CRF 50 (Protection of Human Subjects).

The IRB and the IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The Investigator is responsible for providing their IRB/IEC with any required study documents, progress reports and safety updates and is responsible for notifying the IRB/IEC promptly of all SAEs occurring at the site.

All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to the Sponsor or the designee.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the Investigator must notify the IRB/IEC and the Sponsor or its designee in writing within 5 working days after the implementation**.**

12.5. Subject Information and Consent

It is the responsibility of the Investigator to give each subject (or the subject's acceptable representative) full and adequate verbal and written information regarding the objective and procedures of the trial including the possible risks and benefits involved. Written subject information, approved by the IRB/IEC, must be given to each subject before any trial-related procedure is undertaken. During the consent process, the subject must be informed about their right to withdraw from the trial at any time. The subject must also be given ample time to read the written ICF and have all study-related questions answered to the satisfaction of the subject (or the subject's legally acceptable representative). It is the responsibility of the Investigator to obtain a signature from each subject, the subject's legally acceptable representative (if applicable), and from the persons conducting the informed consent discussion prior to undertaking any trial-related procedure. The subject (or the subject's legally acceptable representative) must be given a copy of the signed and dated ICF. The Investigator is also responsible for providing the subject (or the subject's legally acceptable representative) with any clinical trial updates that may affect the subject's willingness to continue participation in the study. The informed consent process must be documented in the subject's medical or source chart.

The written subject information must not be changed without prior approval of the IRB/IEC.

Per ICH E6 4.3.3, it is recommended that the Investigator notify the subject's primary care physician of the subject's participation in the trial if the subject agrees to the Investigator informing the primary care physician.

In a case in which a subject is allowed to continue treatment after progression, the subject will be required to sign another ICF to ensure awareness that the subject will be foregoing other therapies, including other clinical trial which may be available.

12.6. Protocol Compliance

The Investigator will conduct the study in compliance with the protocol provided by the Sponsor or its designee and given approval by the IRB/IEC and the appropriate regulatory authorities. Changes to the protocol will require written IRB/IEC approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to the subject. The IRB/IEC may provide, if applicable, expedited review and approval for minor change(s) in ongoing studies that have the approval of the IRB/IEC. The Sponsor's designee will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor's designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the subject's eCRF and source documentation.

12.7. Site Monitoring and On-Site Audits

Monitoring and auditing procedures developed by the Sponsor or its designee will be followed, in order to comply with ICH/GCP; FDA and all applicable guidelines. Review of subject's eCRFs, EMR or paper source documentation for completeness, and accuracy will be required as well as a review of all applicable regulatory documents will be performed. All available source documents should be obtained by the Investigator and provided to the Sponsor's designee at each monitoring visit.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications.

Off-site monitoring visits and remote source data verification are allowed (if permitted by local regulation) when restrictions due to the COVID-19 pandemic prevent on site visits (e.g., monitors may not be able to access the sites in a timely manner). (Appendix 10). Should this occur, it should be documented and the reasons be available for review by the Sponsor and during inspections by any Regulatory Authorities. Remote monitoring should be focused on review of critical study site documentation and source data and the monitoring activities, including remote review of source documents, should be documented in the same level of detail as on-site monitoring activities. Any resulting actions to address issues identified from the remote source document review should be consistent with procedures and processes described in the study monitoring plan.

Regulatory authorities, the IRB/IEC, and/or the Sponsor's clinical quality assurance group or designee may request access to all source documents, subject's eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must cooperate and provide support at all times for these activities.

12.8. Subject Data Protection

Privacy Act Compliance. Information collected in this clinical trial is subject to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) as described in 45 Code of Federal Regulations (CFR) 160, 45 and 164. The study Investigator is responsible for informing subjects of their rights under HIPAA and obtaining any necessary HIPAA authorizations. Any clinical study information referred to in this section is understood to be compliant with the provisions of the Privacy Act.

Handling of all personal data will be in compliance with the EU General Data Protection Regulation.

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. Information obtained during the conduct of this study will be used by the Sponsor or designee in connection with the development of the study drug. The study Investigator is obliged to provide the Sponsor or designee with complete test results and all data developed in this study. This information may be disclosed to other physicians participating in the study, to the FDA, or to national and local health authorities. To ensure compliance with all current Federal Regulations and the ICH/GCP guidelines, data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, the Sponsor or its designee and the IRB/IEC for each study site.

12.9. Financial Disclosure

In accordance with 21 CFR Part 54, FDA requires that certain financial interests and arrangements between sponsors of clinical investigations be disclosed in marketing applications. Since the results of this study may eventually be used in a marketing application, compliance with this Federal statute is essential. In order to comply with the provisions of this regulation, the Sponsor requests that every Investigator and sub-Investigator mentioned on FDA Form 1572 fill out a financial disclosure form. Under the provisions of 21 CFR Part 54, the term clinical Investigator includes the spouse and each dependent child of the Investigator.

The provisions of 21 CFR Part 54 specify disclosure of significant equity interests in the Sponsor that exceed $50,000, or significant payments of other sorts made by the Sponsor to the Investigator that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study or other clinical studies (e.g., grants to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation), during the time the clinical Investigator is carrying out the study or for 1 year following the completion of the study. If a change in financial interest occurs throughout the study, the Investigator is obligated to notify the Sponsor.

To assist the Sponsor or its designee in providing the FDA with the required information, please complete the financial disclosure form and return a signed copy. All information provided in the financial disclosure form will be regarded as strictly confidential and will only be disclosed to the FDA.

12.10. Sponsor Discontinuation Criteria

The Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of subjects. After such a decision, the Investigator must contact all participating subjects within a time period set by the Sponsor. In the unlikely event of premature termination or discontinuation of the study, in the event the Investigator believes a subject is continuing to receive clinical benefit, the Sponsor will discuss options with the Investigator in order to ensure continuing supply of sacituzumab govitecan.

As directed by the Sponsor's designee, all study materials will be collected and all eCRFs completed to the greatest extent possible.

13. DISSEMINATION AND PUBLICATION OF RESULTS

The conditions regulating dissemination of the information derived from this clinical study are described in the Clinical Trial Agreement.

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15. APPENDICES

Appendix 1. Signature Page

GILEAD SCIENCES, INC.
(IMMUNOMEDICS, INC. IS NOW PART OF THE GILEAD GROUP OF COMPANIES)
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGMENT

Product: **IMMU-132 (sacituzumab govitecan)**

Protocol Number: **IMMU-132-09**

Protocol Title: **Phase 3 Study of Sacituzumab Govitecan (IMMU-132) Versus Treatment of Physician's Choice (TPC) in subjects with Hormonal Receptor-Positive (HR+) Human Epidermal Growth Factor Receptor 2 (HER2) Negative Metastatic Breast Cancer (MBC) who have failed at least two prior chemotherapy regimens**

IND #: 122694

EudraCT Number: 2018-004201-33

Approval Signature

Medical Monitor

Senior Director, Clinical Development

PPD

Appendix 2. ECOG Performance Status Evaluation

ECOG PERFORMANCE STATUS
0 - Fully active, able to carry on all pre-disease performance without restriction
1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2 - 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 - Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4 - Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5 - Dead

Appendix 3. Procedure for Collection, Storage, and Shipment of Blood and Tissue Samples

Instructions for collection, storage, and shipping of samples to be provided in a separate Eurofins laboratory instruction manual and Flow Chart prepared for this study. Samples being referred to are as follows:

- Serum samples for PK
- Serum samples for immunogenicity/ADA
- Blood samples for UGT1A1 genotyping
- Archived biopsy/surgical tissue sample tumor block or a minimum of 6 freshly sectioned unstained slides (at a thickness of 5 microns)
- Blood samples for biomarker analysis

Appendix 4. Schedule of Procedures/Assessments

Phase	**Pre-randomization Phase**		**Randomization Phase**					
Period			**Treatment Period**					**F/U Period**
	Screening	**Baseline** [w]	**Cycle 1**		**Cycle 2+ through last cycle**		**End of Treatment (EOT)**	**Follow-up**[v]
Day	**-28 to -3**	**-3 to Day 1**	**Day 1**	**Day 8** [j]	**Day 1**	**Day 8** [j]	**+30 days of final treatment**	**Every 12 wks ±1wk**
Assessments [a]								
Informed consent	X							
Inclusion/exclusion criteria	X							
Demographics /Reproductive Status	X							
Medical/surgical history	X							
Prior anticancer therapy	X							
Prior radiation therapy	X							
Histology review to confirm HR+/HER2- (local)	X							
Tissue sample[b]	X							
ECOG	X		X		X		X	
Vital signs [c]	X	X	X	X	X	X	X	
Serum pregnancy test[d]	X	X					X	
Weight				X		X		
Physical examination [e]	X	X	X		X		X	
ECG [f]		X	X					
Hematology [g]	X	X	X	X	X	X	X	

Phase	**Pre-randomization Phase**		**Randomization Phase**					
Period			**Treatment Period**					**F/U Period**
	Screening	**Baseline** [w]	**Cycle 1**		**Cycle 2+ through last cycle**		**End of Treatment (EOT)**	**Follow-up**[v]
Day	**-28 to -3**	**-3 to Day 1**	**Day 1**	**Day 8** [j]	**Day 1**	**Day 8** [j]	**+30 days of final treatment**	**Every 12 wks ±1wk**
Chemistry [g]	X	X	X		X		X	
Uracil level [h]	X							
Urinalysis [i]	X							
Hepatitis B surface antigen, Hepatitis C antibody tests	X							
IMMU-132 Only UGT1A1 sample		X						
Biomarker samples [k]		X			X		X	
PK samples [l]			X		X		X	
Immunogenicity/ADA samples [m]			X		X		X	
QOL assessments [n]		X			X		X [o]	
Randomization [p]			X					
Sacituzumab govitecan administration [q]			X	X	X	X		
TPC administration [r]			As per standard of care					
CT or MRI tumor assessments [s]	X		Every 6 weeks for 54 weeks, then every 12 weeks				X[x]	X[r]
CT or MRI of brain if known or suspected brain metastases	X		As clinically indicated or to confirm CR				X[x]	
Bone scan or 18F-NaF/FDG PET scan [t]	X							

Phase	**Pre-randomization Phase**		**Randomization Phase**					
Period			**Treatment Period**					**F/U Period**
	Screening	**Baseline** [w]	**Cycle 1**		**Cycle 2+ through last cycle**		**End of Treatment (EOT)**	**Follow-up**[v]
Day	**-28 to -3**	**-3 to Day 1**	**Day 1**	**Day 8** [j]	**Day 1**	**Day 8** [j]	**+30 days of final treatment**	**Every 12 wks ±1wk**
AEs/SAEs [u]	X	X	X	X	X	X	X	
Prior medications	X	X						
Concomitant medications			X	X	X	X	X	
Survival								X

ADA = antidrug antibodies; AE = adverse event; ANC = absolute neutrophil count; C1D1 = cycle 1 day 1; C2D1 = cycle 2 day 1; CR = complete remission; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin fixed paraffin embedded; F/U = follow-up; HER2- = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; IV = intraveneous; MRI = magnetic resonance imagining; PD = progressive disease; PET = positron emission tomography; PK = pharmacokinetics; PRO-CTCAE™ = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QOL = quality of life; SAE = serious adverse event; TPC = treatment of physician's choice.

a Assessments and visit schedule here are specific for Investigational Arm A. For subjects in Control Arm B, please follow TPC specific visit schedule footnotes.

b Archival tumor tissue FFPE block preferably within 12 months prior to consent or newly acquired biopsy (FFPE block) from a metastatic site. Note: Bone biopsies are not allowed. Tumor tissue must be submitted to the Sponsor's central laboratory by Cycle 2 Day 1, but analysis results are not required from the central laboratory prior to enrollment.

c Vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature) For sacituzumab govitecan arm, required at baseline and on C1D1: prior to infusion, 30 minutes after initiation and 30 minutes after completion of infusion. All future visits will require vital signs to be obtained 5-10 min. prior to initiation and at the end of the infusion. For subjects receiving TPC, required prior to, once during, and at the end of each infusion, or if administered PO, once at each study visit; otherwise as per local standard of care. For TPC infusions less than 10 minutes, vital signs may be obtained before and after infusion. Time points can be ±15 minutes

d A serum β-hCG test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months.

e Physical examination including weight required on Day 1 of all cycles for sacituzumab govitecan and at start of each cycle for TPC. Sacituzumab govitecan dosing is based on subject's body weight on Day 1 of each cycle or at each dosing day if change in body weight is > 10% from last measurement or if required by institutional policy. Dose modifications for changes in body weight ≤ 10% may be made according to local institutional guidelines. TPC dosing is based upon body surface area as per local standard of care. Post-screening physical examinations may be targeted based on findings present at screening or subject complaints.

f A 12-lead ECG will be obtained at baseline for all subjects. For Arm A only, additional ECGs obtained at C1D1 prior to infusion and 3 hours post finalization of infusion ±15 minutes. Abnormal findings should be evaluated as clinically indicated, including repeated ECGs. ECGs may be done for all subjects at other time points during the study if clinically indicated.

g Hematology/chemistry laboratory assessments drawn at Screening and Baseline on all subjects. For subjects receiving sacituzumab govitecan, complete blood count (CBC) will be obtained each treatment day. For subjects receiving TPC, CBC and serum chemistries will be obtained at least on the first treatment day of each cycle and as per standard of care on other treatment days or study visits (blood draws at anticipated nadir). To be obtained more frequently at the discretion of the managing physician. Results must be reviewed prior to every cycle. See Section 7.6.4 for a list of assessments. Assessments must be reviewed prior to dosing and may be performed within 48 hours before the scheduled visit. Hematology laboratory assessment includes CBC and differential.

h Drawn at screening on all subjects eligible to be randomized to the TPC capecitabine arm. If required per local guidelines (please refer to https://www.has-sante.fr/portail/upload/docs/application/pdf/2019-01/inahta_brief_dpd_5fu.pdf)

i Urinalysis will be assessed at the Screening Visit. Urinalysis will include glucose, ketones, pH, protein, white blood cells, hemoglobin (or red blood cells), specific gravity, and microscopy. Microscopic examination to be performed only if there are positive findings for blood, protein, leukocytes, or nitrite on the dipstick analysis. If urinalysis suggests a urinary tract infection or if clinically indicated, culture and sensitivity should be performed at the institution's laboratory.

j If Day 15 is administered, follow Day 8 assessments.

k Blood samples for biomarkers will be collected at Baseline, pre-dose on C2D1, and at the End of Treatment (EOT)

l Sactituzumab govitecan only: serum samples for PK will be collected pre-dose and 30 minutes post end of infusion ±15 minutes on Day 1 of Cycles 1, 3, 5, 7, 9, 11 and every 3 cycles thereafter (e.g., 14, 17, etc.), and at EOT visit and at 3hr post end of infusion on C1D1 ±15 minutes.

m Sactituzumab govitecan only: serum samples for immunogenicity/ADA analysis will be collected pre-dose on Day 1 of Cycles 1, 3, 5, 7, 9, 11 and every 3 cycles thereafter (e.g., 14, 17, etc.), and at EOT visit.

n QOL assessments include: EORTC QLQ-C30 and EuroQOL EQ-5D-5L instruments, and 9 questions from the PRO-CTCAE™ item library.

o QOL assessments are to be evaluated at the End of Treatment visit prior to telling subjects that they are being withdrawn from the study treatment.

p Randomization must occur on or before C1D1, such that dosing commences within 5 days after randomization.

q Sacituzumab govitecan administered on Day 1 and Day 8 of a 21-day cycle (window of ±2 days from the scheduled cycle day). See Section 6.1.7.2.3 for when sacituzumab govitecan should be administered based on ANC.

r For TPC agents: Recommended doses and schedules as per local package insert or NCCN guidelines with dose/schedule modifications per institutional dosing practices.

s Screening tumor assessments using CT/MRI of the chest, abdomen, and pelvis and other areas of known disease or newly suspected disease should be performed within 28 days prior to C1D1. (Historical CT/MRI scans performed within 28 days before C1D1 may be used as screening scans to demonstrate eligibility by local radiology review as long as they meet minimum standards as separately defined by the central imaging vendor). Scans of the abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast. Tumor assessments of the chest, abdomen, and pelvis and other areas where scans were performed at screening or newly suspected disease should be performed every 6 weeks ±1 week after the start of study treatment (or sooner if there is evidence of PD) through 54 weeks, then every 12 weeks ±1 week until the occurrence of progression of disease and should use the same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as were used for the screening assessments. Objective responses must be confirmed ≥ 4 weeks later (e.g., generally at the next tumor assessment time point). Subjects who discontinue treatment prior to progression will move to the Follow-up Period and continue with radiologic response assessments every 12 weeks (± 1 week) , until progression of disease or initiation of new therapy. During the Treatment Period, CT/MRI of the brain will be performed if clinically indicated, and within a target of 1 week after a subject achieves a CR. For subjects with history of treated brain metastases, brain scans will be performed at tumor assessment time points if clinically indicated. The same methodology and scan acquisition techniques used at Screening should be used throughout the study to ensure comparability.

t 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 prior to C1D1 (historical scans are acceptable). In subjects whose body CT/MRI scans indicate CR has been achieved, a bone scan or 18F-NaF/FDG PET will be required at confirmation of CR to exclude new bone metastases or if clinically indicated and within a target of 1 week, but no more than 2 weeks following a CR as assessed by the Investigator. The same methodology and acquisition techniques used at Screening should be used throughout the study to ensure comparability. Lesions detected on bone scans must be followed with cross-sectional imaging.

u The safety reporting period begins when the subject signs the informed consent and continues until 30 days after the last dose of study drug. During the period after informed consent has been obtained and before the first dose of study drug has been administered, only SAEs caused by a protocol-mandated intervention (e.g., biopsy) should be reported. Any SAE that occurs after the safety reporting period and is assessed as possibly related to study drug must be reported according to the instructions in Section 7.6.6. All SAEs should be followed to resolution or, if resolution is unlikely, to stabilization.

v Subjects will enter the Follow-up Period after completing the EOT Visit. During the Follow-up Period, subjects may be treated according to local standard of care. Subjects will be contacted every 12 weeks (±1 week) for survival status and subsequent anticancer treatment received. Subjects who discontinue study treatment prior to disease progression will have EOT visit and continue in the Follow-Up Period with radiologic response assessments every 12 weeks (±1 week) until disease progression or initiation of new therapy. At that time these subjects will then be contacted for survival status and subsequent anticancer treatment received.

w Baseline assessment must be completed prior to C1D1 dosing

x Only to be performed if radiologic progression has not been already confirmed by RECIST 1.1.

Appendix 5. Quality of Life Questionnaires

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: □□□□
Your birthdate (Day, Month, Year): □□□□□□□□
Today's date (Day, Month, Year): □□□□□□□□

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:				
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4

	1	2	3	4
	1	2	3	4
	1	2	3	4
	1	2	3	4
	1	2	3	4
	1	2	3	4
	1	2	3	4
	1	2	3	4
	1	2	3	4
	1	2	3	4
	1	2	3	4
	1	2	3	4
	1	2	3	4
	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

_____

1 2 3 4 5 6 7

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EuroQoL EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g., work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐

I am slightly anxious or depressed ☐

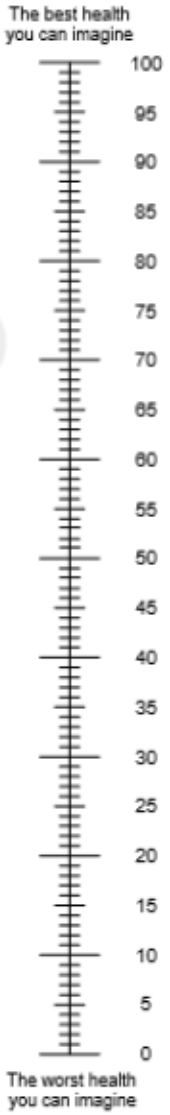
I am moderately anxious or depressed ☐

I am severely anxious or depressed ☐

I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine. 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

Form created on 20 November 2018

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days.

1.	**In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?**				
	○ **None**	○ **Mild**	○ **Moderate**	○ **Severe**	○ **Very severe**
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ **Not at all**	○ **A little bit**	○ **Somewhat**	○ **Quite a bit**	○ **Very much**
2.	**In the last 7 days, how OFTEN did you have NAUSEA?**				
	○ **Never**	○ **Rarely**	○ **Occasionally**	○ **Frequently**	**Almost constantly**
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ **None**	○ **Mild**	○ **Moderate**	○ **Severe**	○ **Very severe**
3.	**In the last 7 days, how OFTEN did you have VOMITING?**				
	○ **Never**	○ **Rarely**	○ **Occasionally**	○ **Frequently**	**Almost constantly**
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ **None**	○ **Mild**	○ **Moderate**	○ **Severe**	○ **Very severe**
4.	**In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?**				
	○ **None**	○ **Mild**	○ **Moderate**	○ **Severe**	○ **Very severe**
5.	**In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?**				
	○ **Never**	○ **Rarely**	○ **Occasionally**	○ **Frequently**	**Almost constantly**
6.	**In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?**				
	○ **Never**	○ **Rarely**	○ **Occasionally**	○ **Frequently**	**Almost constantly**
	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	○ **None**	○ **Mild**	○ **Moderate**	○ **Severe**	○ **Very severe**
	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	○ **Not at all**	○ **A little bit**	○ **Somewhat**	○ **Quite a bit**	○ **Very much**
7.	**In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?**				
	○ **None**	○ **Mild**	○ **Moderate**	○ **Severe**	○ **Very severe**

	In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
	○ **Not at all**	○ **A little bit**	○ **Somewhat**	○ **Quite a bit**	○ **Very much**
8.	**In the last 7 days, did you have any HAIR LOSS?**				
	○ **Not at all**	○ **A little bit**	○ **Somewhat**	○ **Quite a bit**	○ **Very much**
9.	**In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?**				
	○ **None**	○ **Mild**	○ **Moderate**	○ **Severe**	○ **Very severe**
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ **Not at all**	○ **A little bit**	○ **Somewhat**	○ **Quite a bit**	○ **Very much**

Appendix 6. RECIST 1.1

New RECIST: Revised RECIST criteria 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 one 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 exam (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable) • 20 mm by chest X-ray. Malignant LNs: To be considered pathologically enlarged and measurable, a LN 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.
Non-Measurable	All other lesions, including small lesions (longest diameter <10 mm or pathological LNs 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 examination that is not measurable by reproducible imaging techniques.

Source: https://recist.eortc.org/recist-1-1-2/
LN = lymph node

Special considerations regarding lesion measurability

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

- Bone lesions:
  - — Bone scan, (99m-technetium polyphosphonate scintigraphy, whole body bone MRI, or 18F-NaF / FDG PET) 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 MRI, 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 subject, 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.

Note: 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 (LD) 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 the LD of target lesions and a 5 mm absolute increase, taking as reference the smallest sum LD recorded since the baseline assessment or the appearance of one or more new lesions.
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; PD=progressive disease; PR=partial response; SD=stable disease

Non-Target Lesions

Non-target 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 non-target lesions to treatment is evaluated on the basis of their presence or absence as follows:

Evaluation Criteria Used for Categorizing Treatment Response of Non-Target Lesions	
Response Category	**Definition**
CR	Disappearance of all non-target lesions and normalization of tumor marker levels initially above upper limits of normal
PD	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
Incomplete Response/SD	Persistence of one or more non-target 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

Overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed ≥ 4 weeks later according to BICR using RECIST 1.1 after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once with a minimum interval of at least 6-8 weeks from randomization.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR*
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD**
Any	PD	Yes or No	PD**
Any	Any	Yes	PD**

*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.
**Subjects 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.

DOR

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). SD 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. Child-Pugh Score in Subjects with Hepatic Impairment

Modified Child-Pugh Score			
Manifestation	**One point**	**Two points**	**Three points**
Encephalopathy[a]	None	Grade I–II	Grade III–IV
Ascites	Absent	Nontense	Tense
Bilirubin (mg/dl)			
Noncholestatic	< 2	2–3	> 3
Cholestatic	< 4	4–10	> 10
Albumin (g/dl)	> 3.5	2.8–3.5	< 2.8
INR (International normalized ratio)	< 1.7	1.7–2.3	> 2.3

a Encephalopathy: I, mild confusion or slowing, no asterixis; II, drowsy, asterixis present; III, marked confusion, somnolence, asterixis present; IV, unresponsive or responsive only to painful stimuli, no asterixis.

Class A, 5– 6 points
Class B, 7–9 points
Class C, >10 points

Table adapted from Superfin D, Iannucci AA, Davies AM. Commentary: Oncologic drugs in patients with organ dysfunction: A summary. The Oncologist 2007;12:1070-1083.

Appendix 8. Medications Affecting QT Interval

Medications Affecting QT Interval			
Abarelix (PR)	Dexmedetomidine (PR)	Lacidipine (PR)	Piperacillin/Tazobactam (CR)
Aclarubicin (KR)	Dextromethorphan/Quinidine (PR)	Lansoprazole (CR)	Posaconazole (CR)
Alfuzosin (PR)	Diphenhydramine (CR)	Lapatinib (PR)	Primaquine phosphate (PR)
Alimemazine (trimeprazine) (PR)	Disopyramide (KR)	Lenvatinib (PR)	Probucol (KR)
Amantadine (CR)	Dofetilide (KR)	Leuprolide (Leuprorelin) (PR)	Procainamide (KR)
Amiodarone (KR)	Dolasetron (PR)	Levofloxacin (KR)	Promethazine (PR)
Amisulpride (CR)	Domperidone (KR)	Levomepromazine (methotrimeprazine) (KR)	Propafenone (CR)
Amitriptyline (CR)	Donepezil (KR)	Levomethadyl acetate (KR)	Propofol (KR)
Amphotericin B (CR)	Doxepin (CR)	Levosulpiride (KR)	Prothipendyl (PR)
Amsacrine (acridinyl anisidide) (CR)	Dronedarone (KR)	Lithium (PR)	Quetiapine (CR)
Anagrelide (KR)	Droperidol (KR)	Lofexidine (PR)	Quinidine (KR)
Apalutamide (PR)	Efavirenz (PR)	Loperamide (CR)	Quinine sulfate (CR)
Apomorphine (PR)	Eliglustat (PR)	Lopinavir and ritonavir (PR)	Ranolazine (CR)
Aripiprazole (PR)	Encorafenib (PR)	Maprotiline (PR)	Ribociclib (PR)
Arsenic trioxide (KR)	Eperisone (CR)	Melperone (PR)	Rilpivirine (PR)
Artemether + Lumefantrine (PR)	Epirubicin (PR)	Memantine (PR)	Risperidone (PR)
Artenimol+piperaquine (PR)	Eribulin mesylate (PR)	Namenda XR	Romidepsin (PR)
Asenapine (PR)	Erythromycin (KR)	Mesoridazine (KR)	Roxithromycin (KR)
Astemizole (KR)	Escitalopram (KR)	Methadone (KR)	Saquinavir (PR)
Atazanavir (CR)	Esomeprazole (CR)	Metoclopramide (CR)	Sertindole (PR)
Atomoxetine (PR)	Ezogabine (Retigabine) (PR)	Metolazone (CR)	Sertraline (CR)
Azithromycin (KR)	Famotidine (CR)	Metronidazole (CR)	Sevoflurane (KR)
Bedaquiline (PR)	Felbamate (PR)	Mianserin (PR)	Siponimod (PR)
Bendamustine (PR)	Fingolimod (PR)	Midostaurin (PR)	Solifenacin (CR)
Bendroflumethiazide or bendrofluazide (CR)	Flecainide (KR)	Mifepristone (PR)	Sorafenib (PR)
Benperidol (PR)	Fluconazole (KR)	Mirabegron (PR)	Sotalol (KR)
Bepridil (KR)	Fluorouracil (5-FU) (PR)	Mirtazapine (PR)	Sparfloxacin (KR)
Betrixaban (PR)	Fluoxetine (CR)	Moexipril/HCTZ (PR)	Sulpiride (KR)
Bortezomib (PR)	Flupentixol (PR)	Moxifloxacin (KR)	Sultopride (KR)
Bosutinib (PR)	Fluvoxamine (CR)	Necitumumab (PR)	Sunitinib (PR)
Buprenorphine (PR)	Furosemide (frusemide) (CR)	Nelfinavir (CR)	Tacrolimus (PR)
Cabozantinib (PR)	Galantamine (CR)	Nicardipine (PR)	Tamoxifen (PR)
Capecitabine (PR)	Garenoxacin (CR)	Nilotinib (PR)	Telaprevir (CR)
Ceritinib (PR)	Gatifloxacin (KR)	Norfloxacin (PR)	Telavancin (PR)
Chloral hydrate (CR)	Gemifloxacin (PR)	Nortriptyline (PR)	Telithromycin (PR)
	Gilteritinib (PR)		Terfenadine (KR)
	Glasdegib (PR)		Terlipressin (KR)
	Granisetron (PR)		Terodiline (KR)

Medications Affecting QT Interval			
Chloroquine (KR)	Grepafloxacin (KR)	Nusinersen (PR)	Tetrabenazine (PR)
Chlorpromazine (KR)	Halofantrine (KR)	Ofloxacin (PR)	Thioridazine (KR)
Cilostazol (KR)	Haloperidol (KR)	Olanzapine (CR)	Tiapride (PR)
Cimetidine (CR)	Hydrochlorothiazide (CR)	Omeprazole (CR)	Tipiracil and Trifluridine (PR)
Ciprofloxacin (KR)	Hydrocodone - ER (PR)	Ondansetron (KR)	Tizanidine (PR)
Cisapride (KR)	Hydroquinidine, dihydroquinidine (KR)	Osimertinib (PR)	Tolterodine (PR)
Citalopram (KR)	Hydroxychloroquine (CR)	Oxaliplatin (KR)	Toremifene (PR)
Clarithromycin (KR)	Hydroxyzine (CR)	Oxytocin (PR)	torsemide (torasemide) (CR)
Clofazimine (PR)	Ibogaine (KR)	Paliperidone (PR)	Tramadol (PR)
Clomipramine (PR)	Ibutilide (KR)	Palonosetron (PR)	Trazodone (CR)
Clotiapine (PR)	Iloperidone (PR)	Panobinostat (PR)	Trimipramine (PR)
Clozapine (PR)	Imipramine (melipramine) (PR)	Pantoprazole (CR)	Tropisetron (PR)
Cobimetinib (PR)	Indapamide (CR)	Papaverine HCl (Intracoronary) (KR)	Valbenazine (PR)
Cocaine (KR)	Inotuzumab ozogamicin (PR)	Paroxetine (CR)	Vandetanib (KR)
Crizotinib (PR)	Isradipine (PR)	Pasireotide (PR)	Vardenafil (PR)
Cyamemazine (cyamepromazine) (PR)	Itraconazole (CR)	Pazopanib (PR)	Vemurafenib (PR)
Dabrafenib (PR)	Ivabradine (CR)	Pentamidine (KR)	Venlafaxine (PR)
Dasatinib (PR)	Ivosidenib (PR)	Perflutren lipid microspheres (PR)	Voriconazole (CR)
Degarelix (PR)	Ketanserin (PR)	Perphenazine (PR)	Vorinostat (PR)
Delamanid (PR)	Ketoconazole (CR)	Pilsicainide (PR)	Ziprasidone (CR)
Desipramine (PR)		Pimavanserin (PR)	Zotepine (PR)
Deutetrabenazine (PR)		Pimozide (KR)	Zuclopenthixol, Zuclopentixol (PR)
		Pipamperone (PR)	

26-Jun-19website at www.crediblemeds.org as of 26-Jun-19. CredibleMeds® has reviewed available evidence for the drugs on the following list and place them in one of three designated categories: Known Risk of TdP (KR), Possible Risk of TdP (PR) or have a Conditional Risk of TdP (CR).

Appendix 9. UGT1A1 Inducers and Inhibitors

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 10. 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: Study drug supplies may be provided to the patient from the site without a clinic visit, once it is confirmed that the patient may safely continue on study drug as determined by the principal investigator. A remote study visit, via phone or video conferencing, must be performed before remote study drug resupply. 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 utilized to ship the study drug from sites to study patients if permitted by the local ethics committee/institutional review board/regulatory authority as applicable and with Sponsor's approval.

    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 investigational site for their scheduled study visits as required per protocol.

    Mitigation plan: For patients who may be unable or unwilling to visit the investigational 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.

iii) If applicable, confirm electronic diary questionnaires and patient-reported outcomes have been completed and transmitted.

iv) If applicable, confirm the patient's study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed, it will be provided as described above in (1).

v) If applicable, remind the patient to maintain current dosing.

b) Patients may be unable or unwilling to travel to the site for planned assessments (e.g., 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 ethics committee/institutional review board and national laws and regulations. Remote consent will be allowed if it has been approved by the local ethics committee/institutional review board. 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 sacituzumab govitecan (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 scheduled visits cannot be conducted as planned per protocol.

      Mitigation plan: If it is not possible to complete a required procedure, an unscheduled 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 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 underreporting 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 (e.g., 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 safety data regarding the concurrent administration of the COVID-19 vaccine and SG. 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 electronic case report form (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.