STATISTICAL ANALYSIS PLAN

Study Title	Phase 3 Study of Sacituzumab Govitecan (IMMU-132) versus Treatment of Physician's Choice (TPC) in Subjects with Hormonal Receptor Positive (HR+) and Human Epidermal Growth Factor Receptor 2 Negative (HER2-) Metastatic Breast Cancer (MBC) Who Have Failed at least Two Prior Chemotherapy Regimens
Protocol Number:	IMMU-132-09
Protocol Version and Date:	21 December 2018 (Original release) 03 July 2019 (Amendment 1) 10 July 2019 (Amendment 2) 04 February 2020 (Amendment 3) 13 March 2020 (Amendment 4) 08 October 2020 (Amendment 5) 27 January 2021 (Amendment 6) 23 August 2021 (Amendment 7)
Investigational Product:	sacituzumab govitecan (Company Code: IMMU-132)
Phase:	Phase 3
IND #:	122694
EudraCT Number:	2018-004201-33
Methodology:	Two arms open-label study
Sponsor:	Gilead Sciences, Inc (Immunomedics, Inc. is now part of the Gilead group of companies) 333 Lakeside Drive Foster City, CA 94404
Author:	PPD . Associate Director, Biostatistics, Gilead Sciences, Inc.
Analysis Plan Version:	Version 5.0

CONFIDENTIAL AND PROPRIETARY INFORMATION

APPROVAL SIGNATURE PAGE

IMMU-132-09 STATISTICAL ANALYSIS PLAN

Protocol Title:	Phase 3 Study of Sacituzumab Govitecan (IMMU-132) versus Treatment of Physician's Choice (TPC) in Subjects with Hormonal Receptor Positive (HR+) and Human Epidermal Growth Factor Receptor 2 Negative (HER2-) Metastatic Breast Cancer (MBC) Who Have Failed at least Two Prior Chemotherapy Regimens
Protocol Number:	IMMU-132-09
Investigational Product:	sacituzumab govitecan (Company Code: IMMU-132)
Sponsor:	Gilead Sciences, Inc (Immunomedics, Inc. is now part of the Gilead group of companies) 333 Lakeside Drive Foster City, CA 94404

I confirm I have reviewed this SAP and find its content to be acceptable.

Head of Biostatistics Signatory:

PPD
Executive Director, Biostatistics

Signature: [See appended signature page]
Date: [See appended signature page]

Clinical Signatory:

PPD
Clinical Development

Signature: [See appended signature page]
Date: [See appended signature page]

Clinical Pharmacology Signatory:

PPD
Clinical Pharmacology

Signature: [See appended signature page]
Date: [See appended signature page]

REVISION HISTORY

Version Number	Version Date	Summary and Rational of Revision(s)
1.0	25JUN2020	Initial version
2.0	08OCT2020	Update sample size to align with Protocol Amendment 5. Clarify AEOSI definitions. Add sensitivity analysis for interim and for Clinical Benefit Rate (CBR)
3.0	03FEB2021	Section 1. Introduction: Update to reference the protocol amendment 6. Section 2.1. Primary Objective: Changed primary PFS definition from determine by LIR to BICR and moved ORR to Secondary Objective to align with Protocol Amendment 6. Section 3.3. Interim Analysis: Clarified interim analysis will not be conducted to align with Protocol Amendment 6. Section 3.4: Multiplicity Adjustment: Clarify alpha spent on PFS and OS to align with Protocol Amendment 6. Section 4.1: Primary Efficacy Endpoint: Update PFS as determined by BICR and moved ORR to Secondary Endpoint to align with Protocol Amendment 6. Table 2: added clarification on analyses and their analyses population to align with Protocol Amendment 6. Section 7.1.1. Progression-Free Survival: Update PFS as determined by BICR and added clarification to sensitivity analyses and censoring rules to align with Protocol Amendment 6. Added a row under "Continued scheduled response assessments until objective PD or death" in Table 3 to clarify censoring rules. Added clarification to following sections: Section 6.5.1. Demographics Section 6.5.2. Baseline Disease Characteristics Section 6.6 Breast Cancer History Section 6.7. Non-breast Cancer History Section 6.9. Prior Cancer Surgeries and Procedures Section 6.10 Prior Anti-cancer Therapy Section 6.11 Prior Radiation Therapy Section 7.3. Subgroup Analysis 9.2 Adverse Events 9.3. Adverse Events of Special Interest Section 11. Changes to Analysis Specified in Protocol: Update age categories to align with previous Sacituzumab Govitecan studies.
4.0	24Aug2021	• Section 2.2 Secondary Objectives and Section 2.3 CCI Objectives updated to align with Protocol Amendment 7. • Section 3.2 Determination of Sample Size updated to align with Protocol Amendment 7 adding clarification on removal of interim analysis of ORR in Protocol Amendment 6. • Section 3.3 Interim Analysis updated to align with protocol clarifying removal of interim analysis of ORR in Protocol Amendment 6 and adding two interim analyses for OS.

Version Number	Version Date	Summary and Rational of Revision(s)
		• Section 3.4 Multiplicity Adjustment updated to align with protocol detailing alpha allocation for OS. Hierarchical testing added to align with Protocol Amendment 7. • Section 4 Study Endpoints updated to align with Protocol Amendment 7 • Section 5 Analysis Population updated to remove Per-protocol population and Response Evaluable population; changed the Enrolled population to Screened population to be consistent with ASCENT study; add HRQoL-evaluable population for HRQoL related analysis; add PK population for PK related analysis. • Section 7.2.4.1 EQRTC-QLQ-C30 updated to remove QLQ-C30 Summary Score, remove MMRM analysis and add Time to deterioration analysis to align with Protocol Amendment 7. • Section 7.2.4.2 updated to remove scoring and MMRM analysis • Section 7.4.1 Remove PFS2 analysis since no much reliable data are collected after the 1st PD. • CCI [redacted] • CCI [redacted] • Section 10 Add the detailed description of missing data handling • Section 11 No change to the analysis specified in Protocol Amendment 7
5.0	07Feb2022	• Section 3 Updated the analysis plan to combine the primary PFS (final) analysis and OS first interim analysis. Rationale: As of 03Jan22, the targeted number of events required for the first interim OS analysis has been reached. At this time 329 PFS events for the final PFS analysis have been reached (actual number of events is subject to change due to ongoing data cleaning activities). Conducting the final PFS analysis with >90% of the 350 PFS events has negligible impact on the overall study power. • Section 5 Added EQ-5D-5L Evaluable Population for analyses of EQ-5D-5L endpoints since the specified population (HRQoL-Evaluable Population) in the previous version of SAP is not applicable; updated population for endpoints related to antidrug antibody (ADA) as Immunogenicity Analysis Population; updated definition of PK population to align with Gilead convention; analyses population of EORTC endpoints other than time to deterioration clarified. • Section 7.1 Updated censoring rule for primary PFS analysis to align with industry convention, which is due to an oversight in previous versions of SAP to miss the case of death occurs after the initiation of other anti-cancer therapy for censoring; Sensitivity analyses 2 updated to align with FDA guideline: earliest date of treatment discontinuation or initiation of new anti-cancer therapy is considered as progression event; Sensitivity analyses 4 for primary PFS analysis added to align with EMA guideline; Table 3 describing censoring

Version Number	Version Date	Summary and Rational of Revision(s)
		rules of primary and sensitivity analyses of PFS is also updated to align with all the changes. • Section 7.2.2 Removed BOR concordance analyses between LIR and BICR given ORR is no longer primary endpoint since Protocol Amendment 6. • Section 7.2.3 Updated censoring rule of DOR to align with the censoring rules of primary PFS analysis. • Section 7.2.5 Updated definition of time to deterioration (TTD) endpoints to include death as event to align with the approach in ASCENT trial; added sensitivity analysis without using death as events; clarified the analysis set of TTD further to include subjects with baseline value at risk only. • Section 8 Updated PK analyses to clarify the PK concentration and parameters to be summarized. • Section 9.3 Removed summary of reasons for dose reduction since it is covered in the summary of AE leading to dose reduction; Updated definition of AESI of Hypersensitivity+ to include not only infused treatments but also oral capecitabine. • Other minor updates for clarification or correction.

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN 1
APPROVAL SIGNATURE PAGE 2
REVISION HISTORY 3
TABLE OF CONTENTS 6
LIST OF IN-TEXT TABLES 7
LIST OF IN-TEXT FIGURES 7
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS 8
1. INTRODUCTION 10
2. STUDY OBJECTIVES 11
2.1. Primary Objective 11
2.2. Secondary Objectives 11
CCI [redacted]
3. STUDY OVERVIEW 13
3.1. Study Design 13
3.2. Determination of Sample Size 14
3.3. Interim Analysis 14
3.4. Multiplicity Adjustment 15
4. STUDY ENDPOINTS 17
4.1. Primary Efficacy Endpoints 17
4.2. Secondary Efficacy Endpoints 17
4.3. Safety Endpoints 17
CCI [redacted]
5. ANALYSIS POPULATIONS 19
6. STATISTICAL METHODS AND ANALYSIS 22
6.1. General Statistical Considerations 22
6.2. Patient Accrual and Eligibility 22
6.3. Subject Disposition 22
6.4. Important Protocol Deviations 23
6.5. Demographics and Baseline Disease Characteristics 23
6.5.1. Demographics 23
6.5.2. Baseline Disease Characteristics 23
6.6. Breast Cancer History 23
6.7. Non-breast Cancer History 23
6.8. Non-protocol Specific Procedures 24
6.9. Prior Cancer Surgeries and Procedures 24
6.10. Prior Anti-cancer Therapy 24
6.11. Prior Radiation Therapy 24
6.12. Prior, Concomitant Medications and Medical History Excluding Cancer 24
6.12.1. Prior and Concomitant Medications 24
6.12.2. Medical History Excluding Cancer 25
7. EFFICACY ANALYSES 26
7.1. Analysis of Primary Efficacy Endpoints 26
7.1.1. Progression-Free Survival (PFS) per BICR 26
7.2. Analysis of Secondary Efficacy Endpoints 30

7.2.1. Overall Survival (OS) 30
7.2.2. Objective Response Rate (ORR) and Clinical Benefit Rate (CBR) 30
7.2.3. Duration of Response (DOR) 31
7.2.4. Progression-Free Survival (PFS) per LIR 31
7.2.5. Patient Reported Outcomes (EORTC QLQ-C30) 32
7.3. Subgroup Analyses 34
CCI [redacted]
7.5. Other Analyses Related to Efficacy 35
8. PHARMACOKINETIC AND BIOMARKER ANALYSES 36
8.1. Pharmacokinetic Analyses 36
8.2. Biomarker Analyses 36
8.3. Immunogenicity (Anti-Drug Antibodies) Analysis 36
9. SAFETY ANALYSES 37
9.1. Exposure to Study Drug and Compliance 37
9.2. Adverse Events 38
9.3. Adverse Events of Special Interest (AESI) 39
9.4. Death 40
9.5. Clinical Laboratory 40
9.6. Vital Signs 41
9.7. Electrocardiograms 41
9.8. ECOG performance status 42
9.9. Physical Examination and Pregnancy Test 42
10. METHODS FOR HANDLING MISSING DATA 43
11. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL 45
12. REFERENCES 46

LIST OF IN-TEXT TABLES

Table 1. Overall Statistical Inference 16
Table 2. An Overview of Analyses and Analysis Populations 20
Table 3. Censoring Rules for the Endpoint of PFS 28
Table 4. Censoring Rules for the Endpoint of DOR 31
Table 5. Scoring the EORTC QLQ-C30 33
Table 6. Definitions of Adverse Events of Special Interest 40

LIST OF IN-TEXT FIGURES

Figure 1. Hierarchical Testing Procedures 16

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibody
ADaM	Analysis Data Model
AE	Adverse event
AEOSI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BICR	Blinded independent central review
BMI	Body mass index
BOR	Best overall response
BUN	Blood urea nitrogen
C1D1	Cycle 1 Day 1
CBR	Clinical benefit rate
CDK	Cyclin-dependent kinases
CI	Confidence interval
CR	Complete response
CRF	Case report form
CT	Computed tomography imaging
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EOT	End of treatment
FDA	Food and Drug Administration
HER2-	Human Epidermal Growth Factor Receptor 2 Negative
HR+	Hormonal receptor positive
HR-QOL	Health-Related Quality of Life
IND	Investigational New Drug Application
ITT	Intent to treat
KM	Kaplan Meier
LDH	Lactate dehydrogenase
LIR	Local Investigator Review
MBC	Metastatic Breast Cancer
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NE	Not Evaluable

ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PRO	Patient reported outcomes
PT	Preferred term
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors (version 1.1)
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SG	Sacituzumab govitecan
SMQ	Standard MedDRA Query
SOC	System organ class
TEAE	Treatment-emergent adverse event
TPC	Therapy of physician's choice
TTD	Time to deterioration
WHO	World Health Organization

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze, and report results for study IMMU-132-09: "Phase 3 Study of Sacituzumab Govitecan (IMMU-132) versus Treatment of Physician's Choice (TPC) in Subjects with Hormonal Receptor Positive (HR+) and Human Epidermal Growth Factor Receptor 2 Negative (HER2-) Metastatic Breast Cancer (MBC) Who Have Failed at least Two Prior Chemotherapy Regimens". This SAP incorporates Amendment 7 of the protocol, dated as 23 August 2021. The focus of this SAP is for the planned interim analysis and the final analysis specified in the study protocol.

This SAP provides a comprehensive and detailed description of the objectives, definitions of endpoints, statistical and analytical methods used to evaluate the specified efficacy and safety endpoints.

2. STUDY OBJECTIVES

2.1. 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 {Eisenhauer 2009} 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

2.2. 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 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/QOL, pain, and fatigue domains as measured by European Organization for the Research and Treatment of Cancer (EORTC) quality of life questionnaire version 3.0 (QLQ-C30)

- To assess and compare the overall safety and tolerability

[redacted] CCI [redacted]

[redacted]

3. STUDY OVERVIEW

3.1. 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

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.

3.2. Determination of Sample Size

At the time of Protocol Amendment 6, the Sponsor decided to remove the interim analysis of ORR. Thus, the alpha originally allocated to ORR will be reverted back to the primary endpoint of PFS which will be tested at two-sided alpha of 0.05. In addition, two interim analyses of OS were added to accommodate the time gap between PFS final analysis and OS final analysis in Protocol Amendment 7.

The sample size is estimated based on the primary endpoint of PFS, but also takes into account OS as the main secondary endpoint. An overall sample size of approximately 520 subjects will be 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 are needed 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 approximately 350 PFS events around 27 months after the first subject is randomized, after accounting for events being censored because of subjects missing tumor assessments or starting subsequent anticancer therapies. 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. 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 86.7% power at a 2-sided alpha of 0.05, based on a recruitment period of 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 may be 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. Additionally, the projected time to reach analysis milestones and the duration of subjects' follow-up may be different from what are estimated due to differences of actual enrollment rates from the assumptions and the impact of COVID-19 pandemic.

3.3. Interim Analysis

The study is planned to have 2 superiority interim efficacy analyses of the secondary endpoint, 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 3.4.

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

As of 03Jan22, the targeted number of events required for the first interim OS analysis has been reached. At this time, 329 PFS events for the final PFS analysis have been reached (actual number of events is subject to change due to ongoing data cleaning activities). Conducting the final PFS analysis with >90% of the 350 PFS events has negligible impact on the overall study power (e.g., >90% power if the actual observed event number is 329). Therefore, the Sponsor plans to conduct the final (and only) analysis for PFS and the first interim superiority analysis for OS together. The prespecified PFS and OS analyses will be provided in a combined data package.

3.4. Multiplicity Adjustment

The overall type I error rate for this study is strictly controlled at a 2-sided alpha of 0.05. The primary endpoint analysis of PFS assessed by BICR will serve as the gatekeeper for the secondary endpoint analyses and be tested at the 2-sided alpha of 0.05. If the primary PFS analysis is positive, analysis of the main secondary endpoints of OS will be formally tested sequentially at the 2-sided alpha of 0.05, 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, time to deterioration (TTD) of global health status/QoL, pain, and fatigue domains as measured by EORTC QLQ-C30 will be tested using the 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 on the diagram 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 3 TTD hypothesis tests (see Figure 1).

The Lan DeMets alpha spending function that approximates a Pocock approach {Lan 1983} 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 0.0207 if 80% of death events (350/438) is available at the time of the analysis. If neither of interim analyses is positive, final analysis will be tested at the 2-sided significance level of 0.0196. Note that alpha levels for the OS interim and final analyses are based on the actual observed events and will be adjusted accordingly.

Statistical inferences in terms of nominal alpha-value for planned analyses are summarized in Table 1.

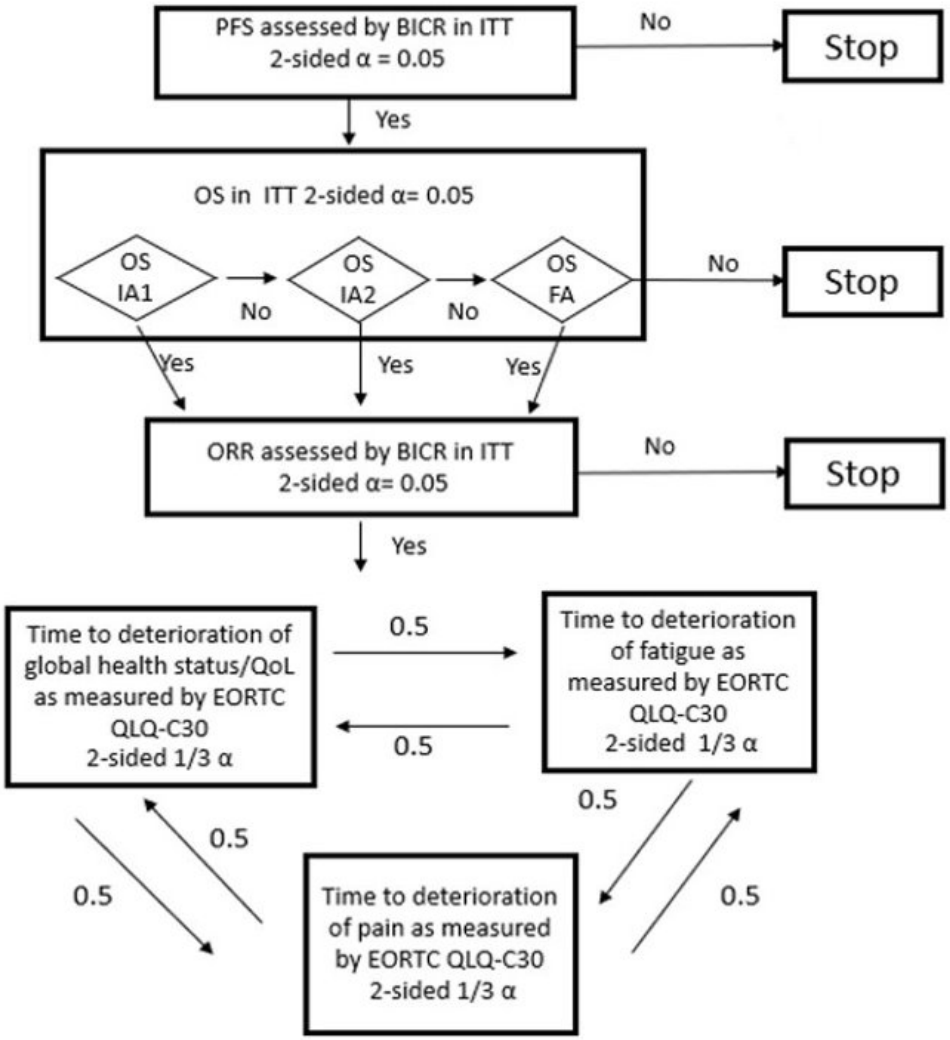
Table 1. Overall Statistical Inference

Description	Clinical cutoff	2-sided significance level
Primary PFS analysis (Final)	Approximately 350 primary endpoint PFS events†	0.05
OS 1st interim analysis	272 deaths	0.0363*
OS 2nd interim analysis	350 deaths	0.0207*
OS analysis (Final)	438 deaths	0.0196*

† Actual number of primary PFS events within +/- 10% of target 350 events is acceptable for the primary PFS analyses (final). Full alpha will be used at the final (and only) analysis for primary endpoint PFS.

* The boundary p-values at each analysis timepoint will be based on the actual observed events and adjusted by using the Lan DeMets alpha spending function that approximates a Pocock approach.

Figure 1. Hierarchical Testing Procedures



4. STUDY ENDPOINTS

4.1. Primary Efficacy Endpoints

- PFS as determined by BICR using RECIST 1.1

4.2. Secondary Efficacy Endpoints

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

4.3. Safety Endpoints

- Incidence of AEs and SAEs
- Clinical laboratory data (i.e. Hematology, Chemistry, Urinalysis)
- ECG
- ECOG performance status
- Vital signs (i.e. heart rate, systolic and diastolic blood pressure, respiratory rate, temperature)

The correlation between ADA and Safety will be addressed in Sections 4.4 and 8.3 and a separate analysis plan.


CCI

5. ANALYSIS POPULATIONS

The following analysis populations will be used for analyses:

- Screened Population: defined as 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.

- Intent-to-Treat (ITT) Population/Full Analysis Set: defined as all subjects who are randomized, regardless of whether they received study treatment or not. The efficacy analysis will be performed on the ITT population. Subjects will be analyzed according to the randomized treatment.

- Safety Population: defined as all ITT subjects who have received at least one dose of study drug. This is the analysis population for all safety analyses which will be based on the actual treatment received.

- HRQoL-Evaluable Population: defined as ITT population subjects who have 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.

- EQ-5D-5L Evaluable Population: defined as ITT population subjects who have an evaluable assessment of the EQ-5D-5L 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 5 dimensions or VAS score were non-missing at that scheduled assessment visit.

- PK Population: defined as Safety population subjects who had at least one dose of sacituzumab govitecan treatment and have at least one non-missing PK concentration of SG, total SN-38, free SN-38, or total antibody (hRS7 IgG).

- Immunogenicity Analysis Population: defined as Safety population subjects who had at least one dose of sacituzumab govitecan treatment and at least one blood sample for immunogenicity evaluation after sacituzumab govitecan administration.

- Analysis populations used for biomarker analyses will be defined in a separate analysis plan and not subject to the scope of this SAP.

An overview of the analyses and their analyses population are provided in Table 2.

Table 2. An Overview of Analyses and Analysis Populations

Analysis Category	Screened Population	Intent-to-Treat (ITT) Population	HRQoL/EQ-5D-5L Evaluable Populations	Safety Population	PK/Immunogenicity Analysis Populations
Enrollment and Eligibility	X				
Demographics		X		X	
Baseline Disease Characteristics		X			
Patient Disposition		X			
Breast and non-breast Cancer History		X			
Protocol Deviation		X			
Prior Anticancer Therapy, Prior Cancer Surgeries, Prior Radiation Therapy, Prior and Concomitant Medications, Medical History		X			
Exposure to Study Therapies				X	
Efficacy on primary endpoint (BICR assessed PFS)		X			
Secondary Efficacy endpoint (LIR assessed PFS)		X			
Secondary Efficacy endpoint ORR (BICR assessed)		X			
Secondary Efficacy endpoint ORR (LIR assessed)		X			
Secondary Efficacy endpoints (CBR, DOR, BICR and LIR assessed)		X			

Analysis Category	Screened Population	Intent-to-Treat (ITT) Population	HRQoL/EQ-5D-5L Evaluable Populations	Safety Population	PK/Immunogenicity Analysis Populations
Secondary Efficacy endpoints (OS, TTD in global health status/QoL, pain and fatigue)		X (OS)	X (Only TTD in global health status/QoL, pain and fatigue)		
CCI					
CCI					
Efficacy Subgroup Analyses		X			
Safety Analyses (AE, AESI, ECG, ECOG performance status, Vital Sign, Clinical Lab, Physical Exam and Pregnancy Test)				X	
Death				X	
PK analyses (C_{max}, T_{max}, and C_{trough})					X (PK Population)
Immunogenicity (Anti-drug antibody)					X (Immunogenicity Analysis Population)

6. STATISTICAL METHODS AND ANALYSIS

6.1. General Statistical Considerations

Endpoints and analyses pertaining to the study's primary, secondary and exploratory objectives will be conducted as prescribed in respective sections of this SAP. Any notable analyses, adjustments to analyses, or analyses not conducted due to lack of data (such as insufficient numbers of subjects in subgroups) or due to other technical constraints will be noted, if included in the clinical study report.

All efficacy analyses will be analyzed in the ITT population and all safety analyses will be analyzed in the safety population.

Continuous data will be summarized using descriptive statistics: n (number of subjects), mean, median, standard deviation, and range (minimum and maximum), unless otherwise specified. Categorical data will be summarized using counts and percentages. For summary statistics, the tables will be presented by treatment arm, and when warranted, may include an overall column. In general, individual subject listings will be provided to support the tables.

All calculations and analyses will be conducted using SAS version 9.2 or higher.

6.2. Patient Accrual and Eligibility

Number and percentage of subjects screened and randomized will be summarized and listed for the Screened Population.

Screen failures will be summarized for the Screened Population by the screen failure reasons as collected per CRF.

A by-subject listing will be provided for the screened population, including their Informed Consent dates, Protocol Amendment Number the subject is consented under, whether the subject is a screen failure, the primary reason for screen failure, and whether the subject is included in each of the analysis populations. Subjects who are randomized but never received treatment will be presented with the reason for not being treated, if known.

6.3. Subject Disposition

The numbers and percentages of subjects randomized, ongoing treatment, ongoing study, permanently discontinued from treatment and discontinued from study, and reasons for treatment or study discontinuation will be summarized for the ITT population. The numbers and percentages of subjects included in each analysis population will also be summarized by treatment arm. The percentage will be calculated relative to the number of subjects randomized.

By-subject listing will be provided to include the following: treatment status, treatment start/end date, reason for treatment discontinuation, study completion status, study end date and reason for study discontinuation.

6.4. Important Protocol Deviations

Important protocol deviation criteria are established and subjects with important protocol deviations will be identified and documented. Important protocol deviations will be summarized for the ITT population if warranted. Important protocol deviations will also be listed by subject.

6.5. Demographics and Baseline Disease Characteristics

Demographics for the ITT and safety populations will be summarized using descriptive statistics. Baseline Disease Characteristics will be summarized for the ITT population.

Individual subject listings will be provided to support the summary tables.

6.5.1. Demographics

Baseline demographic data summaries will include age (years), age by categories (< 65 or ≥ 65 years), sex, race, ethnicity.

6.5.2. Baseline Disease Characteristics

Baseline disease characteristics will include but are not limited to: stratification factors of prior chemotherapy regimens for treatment of metastatic disease (two versus three/four lines), visceral metastasis (Yes/No), and endocrine therapy in the metastatic setting for at least 6 months (Yes/No), ECOG at screening, UGT1A1 status.

By-subject listing will be generated according to information as collected from CRFs per each treatment arm.

6.6. Breast Cancer History

Breast cancer history will include: time from confirmed metastatic disease to randomization, current breast cancer tumor stage, current breast cancer node stage, current breast cancer metastasis stage, HER2 status, IHC/FISH results, estrogen receptor status, progesterone receptor status, BRCA1 mutation status, and BRCA2 mutation status. Breast cancer history will be summarized for the ITT population.

By-subject listing will be generated according to information as collected from CRFs per each treatment arm.

6.7. Non-breast Cancer History

Non-breast cancer history will include: time from initial diagnosis to randomization, cancer site, staging at initial diagnosis, histological type, disease classification, time from confirmed metastatic disease to randomization date and site of known metastases. Non-breast cancer history will be summarized for the ITT population.

By-subject listing will be generated according to information as collected from CRFs per each treatment arm.

6.8. Non-protocol Specific Procedures

By-subject listing will be generated according to information as collected from CRFs per each treatment arm.

6.9. Prior Cancer Surgeries and Procedures

By-subject listing will be generated for all prior cancer surgeries and procedures according to information as collected from CRFs.

6.10. Prior Anti-cancer Therapy

Prior anti-cancer therapy will include the following: number of subjects with different regimens, reason for administration (neoadjuvant, adjuvant, advanced/metastatic, unknown and other), best response for the last therapy before entering study and time from last disease progression to randomization date.

Prior anti-cancer therapy will be coded using the World Health Organization (WHO) Drug Dictionary and summarized by Preferred Drug Name for ITT population.

By-subject listing will be generated according to information as collected from CRFs.

6.11. Prior Radiation Therapy

Prior radiation therapy will include anatomical site, duration of therapy, time from last therapy to randomization date, and best response in the last therapy before study. The last therapy refers to the therapy whose end date is the last before randomization date.

By-subject listing will be generated according to information as collected from CRFs.

6.12. Prior, Concomitant Medications and Medical History Excluding Cancer

6.12.1. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Prior medications include medication with a start and end date prior to first administration of study drug. Concomitant medications are those medications that were taken at any time while on study treatment, including medication that were started before first dose of study therapy but were ongoing at the time of first dose of study drug or that were initiated after first dose but prior to 30 days after last dose. If an end date is missing or the medication is ongoing during study treatment, the medication will be included as concomitant medications. Prior and concomitant medications will be summarized separately for the ITT population by following the WHO Drug Anatomical Therapeutic Chemical (ATC) Classification, and listed for the ITT population.

6.12.2. Medical History Excluding Cancer

Medical history excluding cancer will be summarized for the ITT population and listed by subject for each treatment arm. Medical history will be summarized by system organ class (SOC) and preferred term (PT) and sorted by frequency in SOC and by decreasing frequency in PT.

7. EFFICACY ANALYSES

Efficacy analyses will be performed on the ITT population.

7.1. Analysis of Primary Efficacy Endpoints

7.1.1. Progression-Free Survival (PFS) per BICR

PFS is defined as the time from date of randomization to the first observation of documented disease progression based on RECISIT 1.1 or death due to any cause, whichever comes first. Primary analysis of PFS will be based on BICR for ITT population.

The following censoring rules will be applied to the primary analysis of PFS:

A) A patient who dies during follow-up period for survival without documented progressive disease will be considered to have an event for PFS analysis.

B) Patients who do not have progression and are alive will be censored at last date of radiographic assessment without documented progressive disease.

C) Patients that progress or die following more than one missed scheduled visit of scheduled assessment interval, as defined in the protocol, will be censored at the last date of radiographic assessment without documented progressive disease prior to the missed assessment.

D) Patients who receive alternative anticancer treatment before documented progressive disease or death will be censored at the last date of radiographic assessment without documented progressive disease prior to receiving alternative anticancer treatment.

E) Patients without baseline tumor assessments or without additional follow-up data will be censored at the date of randomization. However, if these patients die without initiation of alternative anti-cancer treatment and no later than the time of the second scheduled assessment as defined in the protocol, these patients will be considered to have an event at the date of death.

In order to evaluate the robustness of the primary PFS analysis, several sensitivity analyses will be performed using the following modified definitions of PFS:

- **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 earlier, to be a PD event.

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

- **Sensitivity Analysis 4** of PFS will use the same censoring rule of the primary PFS definition except that any subject who initiates other anti-cancer treatment prior to disease progression or death or who progresses or dies after more than one missed scheduled tumor assessment will not be censored.

Calculation and censoring rules of PFS are described in Table 3.

Table 3. Censoring Rules for the Endpoint of PFS

Case	Outcome	Date of Event/Censoring[1]			
		Primary Analysis	**Sensitivity analysis 1**	**Sensitivity analysis 2**	**Sensitivity analysis 4**
No adequate response assessment after randomization					
No baseline tumor assessment or alive	Censored	Randomization date	Randomization date	Randomization date	Randomization date
Died prior to second scheduled assessment without initiation of other anti-cancer therapy	Death	Date of death	Date of death	Date of death	Date of death
Died after missing 2 or more scheduled successive assessments	Primary analysis and Sensitivity analysis 2: Censored Sensitivity analysis 1 and 4: Death	Randomization date	Date of death	Randomization date	Date of death
Continued scheduled response assessments until PD or death					
PD prior to missing 2 or more scheduled successive assessments	PD	Date of PD	Date of PD	Date of PD	Date of PD
Death prior to missing 2 or more scheduled successive assessments	Death	Date of death	Date of death	Date of death	Date of death
PD or death after missing 2 or more scheduled successive assessments	Primary analysis and Sensitivity analysis 2: Censored Sensitivity analysis 1 and 4: PD or death	Date of last adequate response assessment before missed ones	Date of PD or Death, whichever occurs first	Date of last adequate response assessment before missed ones	Date of PD or Death whichever occurs earlier

Case	Outcome	Date of Event/Censoring[1]			
		Primary Analysis	**Sensitivity analysis 1**	**Sensitivity analysis 2**	**Sensitivity analysis 4**
Treatment Discontinuation (for sensitivity analysis 2 only) or initiated other anti-cancer treatment prior to PD or death	Primary analysis and Sensitivity analysis 1: Censored Sensitivity analysis 2: PD Sensitivity analysis 4: PD or death	Date of last adequate response assessment without documented progression prior to starting other anti-cancer treatment	Date of last adequate response assessment without documented progression prior to starting other anti-cancer treatment	Date of discontinuation of treatment or start date of anti-cancer therapy whichever occurs earlier.	Date of PD or Death whichever occurs earlier
Continued scheduled response assessments without PD or death					
Treatment discontinuation (for sensitivity analysis 2 only) or initiated other anti-cancer treatment	Primary analysis and Sensitivity analysis 1 and 4: Censored Sensitivity analysis 2: PD	Date of last adequate response assessment without documented progression prior to starting other anti-cancer treatment	Date of last adequate response assessment without documented progression prior to starting other anti-cancer treatment	Date of discontinuation of treatment or start date of anti-cancer therapy whichever occurs earlier.	Date of last adequate response assessment regardless of the starting of other anti-cancer treatment
No PD or death	Censored	Date of last adequate response assessment	Date of last adequate response assessment	Date of last adequate response assessment	Date of last adequate response assessment

1. Adequate response assessment was defined as a response assessment other than 'not assessed' or 'not evaluable'. If progression was based on the sum of target lesion measurements at different time points, the last measurement date was to be used as the date of progression. For progression based on new or non-target lesions considered unequivocal progression, the earliest date when progression was detected was to be used as the date of progression.

The primary analysis of PFS in the ITT Population for comparison between sacituzumab govetican and the control TPC arm will be performed using a stratified log-rank test stratified by randomization factors as employed in the randomization. Estimate of hazard ratio and its 95% confidence interval will be based on stratified Cox proportional-hazards model with treatment arm as the only covariate, stratified by the same stratification factors employed in the randomization. The test comparing the treatment groups will be performed using a 2-sided alpha level of 0.05. PFS will be plotted over time using Kaplan-Meier (K-M) curves, median PFS will be derived by Kaplan-Meier estimates and its associated 95% CIs are calculated by the Brookmeyer and Crowley method with log-log transformation {Brookmeyer 1982}. Milestone PFS rates at time points including 6 months, 9 months, and 12 months will be derived from KM estimates.

7.2. Analysis of Secondary Efficacy Endpoints

7.2.1. Overall Survival (OS)

OS is defined as the time from randomization into study to death from any cause. Patients without documentation of death are censored on the date they were last known to be alive.

OS will be analyzed by the same method as the primary PFS analysis. Analysis of OS will be performed on ITT population.

Milestone OS rates at time points including 12 months, 18 months and 24 months will be derived from the KM estimates.

7.2.2. Objective Response Rate (ORR) and Clinical Benefit Rate (CBR)

Objective Response Rate (ORR) is defined as the proportion of subjects who have a best overall response of either complete response (CR) or partial response (PR) that is confirmed ≥ 4 weeks later according to blinded independent clinical review (BICR) using RECIST 1.1.

Clinical Benefit Rate (CBR is defined as the proportion of subjects who have best overall response of CR, PR or durable SD (duration of SD ≥ 6 months after randomization).

The ORR and CBR will be analyzed and compared between the treatment arms using the Cochran-Mantel-Haenszel method stratified by the stratification factors used in the randomization. The 2-sided 95% CIs will be calculated by the Clopper-Pearson exact method{Clopper 1934}. ORR and CBR will be analyzed based on both BICR and LIR assessments.

Number and percentage of subjects with a best overall response of complete response (CR), Partial response (PR), Stable Disease (SD), Progressive Disease (PD), and Not Evaluable (NE) will be summarized based on LIR and BICR assessments.

7.2.3. Duration of Response (DOR)

For subjects experiencing response (a best overall response of CR or PR), DOR will be calculated based on the time between the first date showing a documented response of CR or PR and the date of progression or death (whichever occurs first). Subjects who do not progress or die after response will be censored, and the censoring rules as described in the following Table 4 will apply. DOR will be analyzed based on both BICR and LIR assessments.

Table 4. Censoring Rules for the Endpoint of DOR

Case	Outcome	Date of Event/Censoring[1]
Subsequent PD or death after response		
PD prior to missing 2 scheduled successive assessments	DOR ended	Date of PD
Death prior to missing 2 scheduled successive assessments	DOR ended	Date of death
PD or death after missing 2 or more scheduled successive assessments	Censor	Date of last adequate response assessment before missing ones
Initiated other anti-cancer treatment prior to PD or Death	Censor	Date of last adequate response assessment without documented progression prior to starting other anti-cancer treatment
Response without subsequent PD or death		
Initiated other anti-cancer treatment	Censor	Date of last adequate response assessment without documented progression prior to starting other anti-cancer treatment
No PD or death	Censor	Date of last adequate response assessment

1 Adequate response assessment was defined as a response assessment other than 'not assessed' or 'not evaluable'. If progression was based on the sum of target lesion measurements at different time points, the last measurement date was to be used as the date of progression. For progression based on new or non-target lesions considered unequivocal progression, the earliest date when progression was detected was to be used as the date of progression.

A Kaplan-Meier analysis will be performed for DOR. Median DOR will be derived by Kaplan-Meier estimates and 95% confidence will be calculated based on Brookmeyer and Crowley method with log-log transformation {Brookmeyer 1982}. The milestone DOR rate at 3 months, 6 months, 9 months, and 12 months will be derived from the KM curve.

7.2.4. Progression-Free Survival (PFS) per LIR

The analysis of PFS based on LIR assessment will be conducted by using the same method as the primary analysis of PFS per BICR in Section 7.1.1.

7.2.5. Patient Reported Outcomes (EORTC QLQ-C30)

European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life of Cancer Patients, core questionnaire, version 3.0 (QLQ-C30), will be used to assess and compare the impact of treatment on Health-Related Quality of Life (HRQOL) between treatment arms. Subjects in the HRQoL-Evaluable Population will be included in the analysis.

A separate prespecified QOL analysis following FDA and European Medicines Agency Patient-Reported Outcome Guidelines will be performed.

7.2.5.1. EORTC QLQ-C30

EORTC QLQ-C30 Scoring

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items.

Principals for scoring these scales:

1) Derive raw score by averaging the items that contribute to the scale.

2) Standardize the raw score by applying a linear transformation so that the scores range from 0 to 100. A higher score presents a higher ("better") level of functioning, or higher ("worse") level of symptoms.

Raw Score

Raw Score = RS = $(I_1 + I_2 + \ldots + I_n)/n$; where I_1, I_2, … I_n are items included in a scale

Linear transformation

Apply linear transformation to 0-100 to obtain the score S.

Functional scales: $S = \left(1 - \frac{(RS-1)}{range}\right)x100$

Symptom scales: $S = \left(\frac{(RS-1)}{range}\right)x100$

Global health status / QoL: $S = \left(\frac{(RS-1)}{range}\right)x100$

Range is the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Item numbers and item ranges for each scale is presented in Table 5.

Scores for these scales will be computed only if at least half of the items contributing to the scale are not missing. Otherwise the score will be set to missing. If the response is missing for single-item measures, score will be set to missing.

Table 5. Scoring the EORTC QLQ-C30

	Scale	Number of items	Item range*	Version 3.0 Item numbers
Global health status / QoL				
Global health status/QoL	QL	2	6	29, 30
Functional scales				
Physical functioning	PF	5	3	1 to 5
Role functioning	RF	2	3	6, 7
Emotional functioning	EF	4	3	21 to 24
Cognitive functioning	CF	2	3	20, 25
Social functioning	SF	2	3	26, 27
Symptom scales / items				
Fatigue	FA	3	3	10, 12, 18
Nausea and vomiting	NV	2	3	14, 15
Pain	PA	2	3	9, 19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhoea	DI	1	3	17
Financial difficulties	FI	1	3	28

* Item range is the difference between the possible maximum and the minimum response to individual items

Absolute values and change from baseline values of EORTC QLQ-C30 functional scales, symptom scales and global health status QoL will be summarized descriptively.

Time to deterioration of Global health status/QoL, Pain, and Fatigue domains

Time to deterioration will be analyzed for Global health status/QoL, Pain and Fatigue domains. Time to deterioration is defined as the time from randomization to the first date a subject achieves 10-point deterioration from baseline or death due to any cause, whichever occurs first. Subjects who have not experienced 10-point deterioration at the time of analysis will be censored on the last non-missing assessment date. Subjects without baseline or post baseline PRO assessments will be censored at randomization date. Subject with baseline value at risk (defined as ≥ 10 in Global health status/QoL or ≤ 90 in Pain and Fatigue domains) will be included for analyses. The distribution of time to deterioration will be estimated using the Kaplan-Meier

method and compared between two treatment groups using stratified log-rank test. A stratified Cox proportional-hazards model will provide estimates of hazard ratios with 95% confidence intervals. A sensitivity analysis without considering death as an event will also be conducted.

7.3. 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 endpoints 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 (Yes/No)

3) Stratification factor of endocrine therapy in the metastatic setting for ≥6 months (Yes/No)

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

5) Race (white, non-white)

6) Screening 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, each of which to compare with sacituzumab govitecan)

10) Early relapse (Yes/No)

    (defined as relapse to metastatic disease within one year of the end of neo/adjuvant chemotherapy)

11) Baseline documented Target or Non-target liver lesions per RECIST1.1 per LIR (Yes/No)

12) Chemotherapy in neo/adjuvant setting (Yes/No)

CCI [redacted]

[redacted]

[redacted]


CCI

8. PHARMACOKINETIC AND BIOMARKER ANALYSES

8.1. Pharmacokinetic Analyses

Descriptive summary of PK concentration (SG, total SN-38, free SN-38 and total antibody - hRS7 IgG) and PK parameters including C_{max} (maximum drug concentration), T_{max} (time to maximum drug concentration) and C_{trough} (pre-dose drug concentration) will be summarized by visits. A listing of PK concentrations will also be provided. Subjects in the PK population will be included for analyses.

Analyses, including non-compartmental pharmacokinetics (if adequate data available) and population pharmacokinetics (PopPK), will be described in separate analyses plans and not in scope for this SAP.

8.2. Biomarker Analyses

See Section 7.4.4 for biomarker analyses.

8.3. Immunogenicity (Anti-Drug Antibodies) Analysis

Data on anti-drug antibody (ADA) results will be listed and may be summarized by number and frequency of results according to positivity of results when the prerequisite data for this analysis becomes available by a designated vendor. Subjects in immunogenicity analysis population will be included for analyses. The correlative analyses assessing the impact of ADA on PK, efficacy and safety endpoints will be described in separate analyses plan and not in the scope for this SAP.

9. SAFETY ANALYSES

Safety analyses will be conducted in the safety population.

Safety data will be presented in terms of study drug exposure, AEs, clinical laboratory data, ECG data, and vital signs.

9.1. Exposure to Study Drug and Compliance

Treatment exposure will be summarized for the safety population using the following measures:

- Number of doses administered
- Descriptive statistics of duration of treatment (months), along with number of subjects with treatment duration longer than or equal to 3 months, 6 months, 12 months, and 24 months; Duration of treatment (in days) will be calculated as (date of the last dose - date of the first dose + 1) and converted to months by dividing by 30.4375
- Number of treatment cycles
- Number and percentage of subjects with dose reduction according to percentage of dose reduction
- Descriptive statistics of time to first dose reduction.
- Number and percentage of subjects with dose delays
- Number and percentage of subjects with infusion interruptions
- Descriptive statistics of duration of interruptions
- Relative dose intensity will be calculated as described below and summarized. Cumulative dosage and relative dose intensity will be summarized by descriptive statistics, and relative dose intensity will be additionally summarized by the category of < 70%, 70% to <90%, 90% to <110%, >=110%.

Delivered dose (mg) for each infusion is calculated per CRF form from ("Dose calculated for this subject" x "Total volume administered"/"Total volume prior to administration").

Delivered dosage (mg/kg) of each infusion in a cycle is calculated by dividing the delivered dose (in mg) by body weight (in kg) at the beginning of the cycle (the body weight according to which the prescribed dose is calculated and prepared per the Protocol).

Cumulative dosage (mg/kg) received for each subject is defined as the sum of all delivered dosages (mg/kg) of all infusions the subject received in the study.

Total assigned dosage (mg/kg) for each subject is defined as the product of the assigned dose of sacituzumab govitecan (10 mg/kg) and number of doses the subject was scheduled to receive during the subject's treatment period (number of infusions actually received by the subject plus the number of infusions the subject missed between the first and last infusion).

Relative dose intensity (in %) for each subject is calculated: dividing the subject's cumulative dosage received (in mg/kg) by the total assigned dosage (in mg/kg) as defined above.

9.2. Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AEs that begin or worsen on or after the start of study drug through 30 days after the last dose of study drug. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). The severity will be graded based on the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Only TEAEs will be summarized and will be referred to as AEs hereafter.

The frequency and severity of AEs, classified by MedDRA, will be summarized using MedDRA Preferred Term (PT) and System Organ Class (SOC). An AE that occurs more than once within each subject will be counted only once in the summaries, *i.e.*, where a subject has the same adverse event, based on preferred terminology, reported multiple times, the subject will only be counted once at the preferred terminology level in adverse event summary tables. Where a subject has multiple adverse events within the same system organ class, the subject will be counted only once at the system organ class level in adverse event summary tables. When reporting adverse events by CTC grade, summary tables will be provided using the worst NCI-CTCAE grade.

The following AE summary tables and listings will be provided:

- **Overall Summary** of Treatment-Emergent Adverse Events
- Summary of Treatment-Emergent Adverse Events by SOC and PT
- Summary of Treatment-Emergent Adverse Events Reported **by ≥10%** Subjects in Any Treatment Arm by Preferred Term
- Summary of **Treatment-related** Treatment-Emergent Adverse Events by SOC and PT
- Summary of Treatment-Emergent **Serious** Adverse Events by SOC and PT
- Summary of Treatment-Emergent **Serious** Adverse Events Reported by **≥2% Subjects** in Any Treatment Arm by Preferred Term
- Summary of **Treatment-related** Treatment-Emergent **Serious** Adverse Events by SOC and PT
- Summary of Treatment-Emergent Adverse Events by **Worst CTCAE Grade**, SOC and PT

- Summary of **Treatment-related** Treatment-Emergent Adverse Events by **Worst CTCAE Grade**, SOC and PT
- Summary of **NCI-CTCAE Grade 3 or Higher** Treatment-Emergent Adverse Events by SOC and PT
- Summary of **NCI-CTCAE Grade 3 or Higher** Treatment-Emergent Adverse Events Reported by **≥5% Subjects** in Any Treatment Arm by Preferred Term
- Summary of **Treatment-related** Treatment-Emergent Adverse Events with **NCI-CTCAE Grade 3 or Higher** by SOC and PT
- Summary of Treatment-Emergent Adverse Events **Leading to Study Drug Discontinuation** by SOC and PT
- Summary of Treatment-Emergent Adverse Events **Leading to Death** by SOC and PT
- Summary of Treatment-Emergent Adverse Events **Leading to Study Drug Interruption** by SOC and PT
- Summary of Treatment-Emergent Adverse Events **Leading to Study Dose Reduction** by SOC and PT

The following AE listings will be provided:

- Listing of All Adverse Events
- Listing of Serious Adverse Events
- Listing of Adverse Events with NCI-CTCAE Grade 3 or Higher
- Listing of Adverse Events Leading to Study Drug Discontinuation
- Listing of Adverse Events Leading to Dose Reduction
- Listing of Adverse Events Leading to Study Drug Interruption
- Listing of Adverse Events Leading to Death

9.3. Adverse Events of Special Interest (AESI)

In addition to analyses of AEs, adverse events of special interest (AESI) will be assessed. Definitions of AESI, as currently defined, are provided in Table 6. For AESI, frequency tables will include overall summary of AESI, Summary of AESI by category and PT, Serious AESI by category and PT, AESI leading to study drug discontinuation by category and PT, AESI leading to study drug interruption by category and PT, Grade 3 or higher AESI by category and PT, and treatment-related AESI (by a worst CTCAE grade of 3, 4, or 5, >=3 and any grade) by category and PT. Corresponding listings will also be produced.

Table 6. Definitions of Adverse Events of Special Interest

Adverse Event of Special Interest	Definition
Diarrhea	Preferred term: diarrhoea
Neutropenia+	Preferred terms: neutropenia, neutrophil count decreased, and febrile neutropenia
Febrile neutropenia	Preferred term: febrile neutropenia
Infections	SOC: infections and infestations
Neuropathy+	Preferred terms: gait disturbance, hypoaesthesia, muscular weakness, neuropathy peripheral, paraesthesia, and peripheral sensory neuropathy
Hypersensitivity+*	Hypersensitivity SMQ (broad and narrow) and Anaphylactic Reactions SMQ (broad and narrow)*
Pulmonary events+	Interstitial lung disease SMQ (narrow)

All definitions based on MedDRA vs 24.0 or higher, SMQ=Standard MedDRA Query
+ Grouped AE terms
* For the category of Hypersensitivity+, only events whose onset dates are on the day of or 1 day after study drug administration are included.

9.4. Death

All-cause deaths will be summarized (including presentation of causes of death), and deaths within 30 days of the last dose of study drug will be summarized by treatment arm. A listing of all death information will be generated.

9.5. Clinical Laboratory

Routine safety laboratories, based on hematology and routine serum chemistry data (including but not limited to glucose, BUN, total bilirubin, AST, ALT, LDH, alkaline phosphatase, serum albumin, total protein, Na, K, calcium, Cl, magnesium, and phosphate), will be summarized using values at each visit and change from baseline using descriptive statistics. Laboratory test results for lab parameter including but not limited to platelets, neutrophils, white blood count, lymphocytes, and hemoglobin will be graded according to NCI-CTCAE v5.0 severity grade. Shift tables from baseline to the worst NCI-CTCAE grade observed on-treatment will be tabulated for each lab parameter. For parameters whose CTCAE scales do not exist, the proportion of subjects with abnormal values will be summarized by treatment arm.

Clinical laboratory data results will be reported in standard international units. Baseline is defined as the last observation occurring prior to the first treatment administration of study drug.

If a lab value is reported using a non-numeric qualifier (eg, less than [<] a certain value, or greater than [>] a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier. Any other manipulation related to lab data not documented here will be specified in the ADaM specification.

9.6. Vital Signs

Both actual and change-from-baseline data on vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature) will be summarized using descriptive statistics by treatment group for each study time-point.

All the collected information will be presented for each subject in a by-subject data listing.

9.7. Electrocardiograms

Descriptive statistics for the actual values and changes from baseline over time will be summarized for the ECG parameters including Heart Rate, QT, PR, QRS and QTcF correction.

The proportion of patients with maximum post-baseline absolute QTcF intervals who fall into the following categories will be presented:

- ≤ 450 msec
- > 450 msec
- > 450 to ≤ 480 msec
- > 480 msec
- > 480 to ≤ 500 msec
- > 500 msec

The proportion of patients who have a maximum post-baseline increase from baseline in QTcF intervals of the following categories will be presented:

- ≤ 30 msec
- > 30 msec
- >30 to ≤ 60 msec
- > 60 msec

The shift table of overall interpretation ('Normal,' 'Abnormal, not clinically significant,' and 'Abnormal, clinically significant') from baseline to post-baseline evaluation will also be provided by treatment arm and by overall.

A listing will be produced for ECG parameters along with any investigator comments that may be provided.

9.8. ECOG performance status

Shift tables from screening to best post-baseline value will be displayed by treatment arm for the safety population. A listing for ECOG grades will be provided as well.

9.9. Physical Examination and Pregnancy Test

A by-subject listing for each treatment arm will be generated according to the body system and presented for any clinically significant findings from physical examination.

The pregnancy test results will be listed for each treatment arm, by subject, indicating the cycle, the date of the test, the test results, and the reason for not performing the test.

10. METHODS FOR HANDLING MISSING DATA

Missing normal ranges for laboratory parameters

When either the lower limit of normal, the upper limit of normal or both are missing or are not machine readable, a standardized reference range will be used.

Missing Data Imputation for Adverse Event/Concomitant Medication Start Dates

1) Missing day only

   - If the month and year of the AE/the concomitant medication are the same as the month and year of the first IMMU-132 dose date, the first dose date day will be used.
   - If the month and year are before the month and year of the first dose date, the first day of the month will be assigned to the missing day.
   - If the month and year are after the month and year of the first dose date, the first day of the month will be assigned to the missing day.

2) Missing day and month

   - If the year is the same as the year of the first dose date, the first dose date day and month will be used.
   - If the year is prior to the year of the first dose date, December 31 will be assigned to the missing fields.
   - If the year is after the year of the first dose date, January 1 will be assigned to the missing fields.

3) Missing day, month, and year

   - The first dose date will be used.

The imputed start date should be prior or equal to the end date of the AE or medication.

Missing Data Imputation for Missing Adverse Event/Concomitant Medication Stop Date

4) Missing day only

   - The month and year are the same as the month and year of the first dose date: use the last date of the month.
   - The month and year are before the month and year of the first dose date: use the last date of the month.
   - The month and year are after the month and year of the first dose date: use the last date of the month.

5) Missing day and month

- The year is the same as the year of the first dose date: use December 31.

6) Missing year

Uncertain: unable to impute.

7) Missing month

- The year is the same as the year of the first dose date: use December.
- The year is before the year of the first dose date: use December.
- The year is after the year of the first dose date: use December.

8) Missing month and year

Uncertain: unable to impute

9) Missing day and year

Uncertain: unable to impute

10) Missing day, month, year

This event is ongoing.

If the death date is available and the imputed end date is after the death date, the death date will be used.

If the imputed end date is before the start date of the AE or medication, then make end date equals to start date.

11. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

In the protocol, at the time of the primary PFS (final) analysis, OS will only be summarized descriptively, while the OS 1st interim analysis was estimated to occur after the primary PFS (final) analysis. However, as of 03Jan22, the targeted number of events required for the first interim OS analysis has been reached. At this time, 329 events for the final PFS analysis have been reached. Therefore in this SAP, the Sponsor plans to conduct the final (and only) analysis for PFS and the first interim superiority analysis for OS together. The prespecified PFS and OS analyses will be provided in a combined data package.

The PFS per LIR is a planned analysis as described in Section 9.5 of the protocol, but it is not included as an endpoint in protocol Section 4.3.1. PFS per LIR is added as secondary endpoint in Section 4.2 of this SAP.

The sensitivity analyses for PFS per LIR is included in Section 9.5.3 in the protocol. Since sensitivity analyses are only required for primary endpoint of PFS per BICR and PFS per LIR is a secondary endpoint, sensitivity analyses for PFS per LIR are not planned in the SAP.

12. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

Clopper CJ, Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika 1934;26 (4):404-13.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). Eur J Cancer 2009;45 (2):228-47.

Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70 (3):659-63.

Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. Statistics in biopharmaceutical research 2013;5 (4):311-20.